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Fatigue outcomes following COVID-19: A systematic review and meta-analysis

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Title **Fatigue outcomes following COVID-19: A systematic review and meta-analysis**

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ABSTRACT

Objectives

Fatigue is a pervasive clinical symptom in coronaviruses and may continue beyond the acute phase, lasting for several months or years. This systematic review and meta-analysis aimed to incorporate the current evidence for post-infection fatigue among survivors of SARS-CoV-2 and investigate associated factors.

Methods

Embase, PsyINFO, Medline, CINAHL, CDSR, Open Grey, BioRxiv and MedRxiv were systematically searched from January 2019 to December 2021. Eligible records included all study designs in English. Outcomes were fatigue or vitality in adults with a confirmed diagnosis of SARS-CoV-2 measured at $\geq$ 30 days post-infection. Non-confirmed cases were excluded. CASP risk of bias was assessed by 2 reviewers. Random-effects model was used for the pooled proportion with 95% CIs. A mixed-effects meta-regression of 36 prospective articles calculated change in fatigue overtime. Subgroup analyses explored specific group characteristics of study methodology. Heterogeneity was assessed using Cochran's Q and I^2 statistic. Egger's tests for publication bias.

Results

Database searches returned 14262 records. Following deduplication and screening, 178 records were identified. 147 (n=49032 participants) were included for the meta-analyses. Pooled prevalence was 41% (95% CI: 36-45%, k=147, I^2=98.6%). Fatigue significantly reduced over time (-0.059, 95% CI: -0.011- -0.107, k=36, I^2=99.4%, p=0.05). A higher proportion of fatigue was found in studies using a valid scale (51%, 95% CI: 43- 58%, k=36,$!^2$=97.6%, p=.03) and cross-sectional methodology (45%, 95% CI: 39-52%, k=68, I^2=98.2%, p=0.04). Egger's test indicated publication bias for all analyses. CASP assessments indicated 4% at low risk of bias, 78% at moderate risk and 17% at high risk. Frequently reported associations were female gender, age, physical functioning, breathlessness and psychological distress.

Conclusion This study revealed that a significant proportion of survivors experienced fatigue following SARS-CoV-2 and their fatigue reduced overtime. Non-modifiable factors and psychological morbidity may contribute to ongoing fatigue and impede recovery.

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Strengths &Limitations

- This review and meta-analysis was conducted using a significant sample size from a comprehensive search of the literature, including only confirmed cases;
- Substantial unexplained heterogeneity between studies limits generalisability of our findings;
- Only one reviewer screened and extracted the data from each study leaving the potential for missing articles and selection errors;
- Outcome measures of fatigue were unvalidated in the majority of studies, limiting confidence in our estimates;
- Total point-prevalence was likely impacted by predominance of hospitalised patients with potentially more severe disease.

INTRODUCTION

Fatigue may be characterised as tiredness or exhaustion as a result of physical or mental exertion or as a result of an illness or disease.[1] The experience of fatigue is common and is usually short-lived but, for a small number of people, it can become long-lasting, associated with a number of impairments in daily living and quality of life.[1] It is one of the most common presenting symptoms of coronaviruses.[2] The current pandemic has also revealed a considerable burden of lasting symptoms with approximately 1 in 4 people experiencing fatigue by one estimate.[3] Systematic reviews indicate a pooled-prevalence of post-COVID-19 fatigue to vary between 45% [4], 52% [5] and 64%.[6] In previous epidemics, fatigue was enduring. In a follow-up of 90 SARS survivors 30 months post-illness, for instance, 1 study found significantly lower vitality scores compared to Hong Kong population norms.[7] A small study of Middle East Respiratory Syndrome patients, revealed 32.7% had clinically relevant chronic fatigue, according to their FSS scores, at 18 months follow-up.[8] Likewise, for a considerable number of COVID-19 patients, tiredness symptoms extend beyond 3 months and represent a larger burden of post-infection symptomology.[9–30]. A large study of 1,142 hospitalised patients found that 61% had fatigue 7 months post-COVID-19.[31] Similarly, those who perceived themselves as experiencing 'poor recovery' had lower vitality on the 15D instrument, compared to those making a 'full recovery' ($p<.001$) 1 year post-illness.[32]

More severe disease, associated with being hospitalised or ICU admission, has been related to post-illness fatigue.[33–40]. In a small cohort of 55 people, 30 days post-discharge for COVID-19, each additional day of hospitalisation increased fatigue by 1.2.[41] Apart from hospitalised patients, among non-hospitalised or those treated for milder disease, fatigue is persistent.[42–49] In 359 patients 63.4% reported significant fatigue up to 12 months post-infection and were more likely than admitted patients to require referral for fatigue symptomology.[50]

Determinants of post-illness fatigue include female gender, [51–55] and older age, although the latter relationship was not consistent. Being over 50 years was associated with fatigue severity in some studies,[41,56,57] but not in others.[58–60] Exercise impairments are a common feature of post-Covid sequelae.[61–66] Poorer performance on the six-minute walk test (6MWT) was associated with fatigue and lower vitality at 6 months despite no concomitant impairments in pulmonary functions.[67] Indeed, impairments in lung functions have not thus far fully explained worse fatigue in COVID-19 [67–70] Nevertheless, patients often report persistent dyspnoea, which was consistently related to their fatigue, [71–74] suggestive of multi-dimensional functional consequences. For instance, quality of life,[75] functional status[76] and an increased risk for post-infection healthcare needs [77] were all related to fatigue. Anxiety, post-traumatic stress and depressive symptoms are prevalent in survivors of respiratory viral infections.[74,78–82] A meta-analysis of 36 COVID-19 articles found high rates of anxiety (29%) and depressive symptoms (23%) 4-12 weeks post-illness.[83] The relationship between mental health outcomes and fatigue is consistent among convalescing COVID-19 patients. Depressive symptoms for example were associated with lower vitality [84] and fatigue.[68,85] In a retrospective study of 55 patients, baseline anxiety was related to higher fatigue 30 days after hospitalisation.[41] Moreover, these relationships can be present at 12 months follow-up. Mazza et al. (2021) found depression ($r=0.56$, $q=0.05$) and PTSD ($r=0.52$, $q=0.05$) were related to fatigue severity in 402 post-Covid patients. Neuropsychiatric symptoms comprising anxiety, mood swings, irritability and depression and others, predicted chronic fatigue 9 months later for those with mild/moderate disease ($p=0.01$).[86]

Summary and aims

For the majority of patients acute fatigue diminishes during the course of a virus, but current evidence suggests some experience longer lasting symptoms, and these affect functional and psychological recovery. Furthermore, fatigue is reported as the most prominent factor of post-infection symptomology indicative of its importance in understanding recovery. Therefore, the objectives of this systematic review were to a) investigate the prevalence of persistent fatigue among survivors of

COVID-19; b) integrate the findings by conducting a meta-analysis and c) investigate current evidence for factors associated with fatigue outcomes in this context.

METHODS

Search strategy

The protocol and PICO framework for this study (supplementary file 1) was developed utilising the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[87] Embase, PsyINFO, Medline, CINAHL, Cochrane Database of Systematic Reviews, Open Grey, MedRxiv and BioRxiv were systematically searched from January 2019 to 31 December 2021. Search terms: severe acute respiratory syndrome or severe acute respiratory adj2 syndrome or coronavirus or corona virus or corona adj1 virus or COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV or nCoV19 or nCoV2 or covid19 or covid-19 or covid and "chronic fatigue" or fatigue or tired or exhaust or quality adj2 life or QoL or health related quality) adj2 life or HRQoL. We incorporated 'health related quality of life' into our search terms in order to capture 'vitality', which we used as proxy for fatigue. Reference lists of the review studies were manually searched for additional articles. Full search protocols for each database are available in supplementary file 2. Duplicate references were removed electronically and imported into Rayyan [88] for screening and inclusion decisions.

Inclusion and exclusion criteria

Included were original articles with primary data, published in English between 2019-2022. Adult patients ($\geq$18 years) must have had a diagnosis of SARS-CoV-2 confirmed by RT-PCR, IgM/IgG serology or clinical assessment (e.g. chest X-ray, CT scan). 'Probable' or self-reported cases were excluded. All study designs were incorporated except qualitative and case reports. Main outcomes were fatigue/vitality reported as 'post-discharge', 'post-hospitalisation', 'post-acute', 'post-illness' or 'post-onset'. Outcomes were included if measured at a median/mean time of $\geq$ 30 days post-infection as defined. All associations with fatigue/vitality were included if reported/quantified (e.g. anxiety, dyspnoea). We excluded pandemic fatigue (defined as 'worn out' by pandemic warnings, government safety instructions, media coverage or compliance requirements), healthcare worker fatigue in the context of their work (e.g. burnout, compassion fatigue), comorbid physical disease or pregnant populations. We excluded 'muscle fatigue', 'leg fatigue' and fatigue combined with 'malaise' or 'muscle weakness'. Protocols, vaccination studies, newspaper articles, conference papers, commentaries, opinions or editorials were also omitted.

Data extraction

Titles and abstracts were screened by 1 reviewer (KPW). Full texts were screened by KPW. A data spreadsheet was created to record extracted data from the included studies. Spreadsheet variables were citation, population, sample size, control group, location, virus type and diagnostic method, follow-up period, study design, inclusion/exclusion criteria, objectives, outcome variable of interest (e.g. fatigue, vitality), associated variables (e.g. PTSD, dyspnoea), scales/measures employed, results, power calculation (Y/N). The senior researcher (TC) reviewed 10% of the final included studies. Discrepancies were resolved via discussion and consensus. A PRISMA flow diagram is available in Figure 1.

Figure 1. PRISMA 2020 flow diagram

Quality Assessments

Risk of bias was assessed by the Critical Appraisal Skills Programme (CASP) (2019). Each study design had an appropriate checklist (e.g. cohort) comprising 12 items designed to systematically assess a study. We adapted the cohort checklist for cross-sectional/retrospective designs by excluding item 7 "Was the follow up of participants complete enough?" Item 9 was changed from "how precise are the results?" to a Y/N/? response. Checklist items demanded a "yes", "no" or "can't tell". For the purposes of this study, an overall assessment was made by assigning a grade of 1, 2 or 3 representing 'low' risk, 'moderate' risk and 'high' risk of bias respectively. Two researchers (KPW, OS) independently graded 49%/51% each of the total articles and, for the purposes of interrater estimation, both researchers graded the same 23% of the articles. Interrater agreement was assessed by Cohen's kappa, which indicated moderate agreement (k=0.516, p=.002).

Statistical analysis

We computed pooled mean prevalence for fatigue outcomes with 95% confidence intervals using a random effects model as high heterogeneity was anticipated. A number of studies investigated fatigue across multiple time points. Therefore, in order to maintain the independence of observations for the pooled prevalence, we selected 1 time-point with accompanying prevalence from each study using 1 of 3 methods: (a) fatigue reported at the stated mean/median time of the follow-up assessment, e.g. 127 days post-illness, (b) fatigue at the 3-month follow-up (being the mode for all 147 studies), or (c) for studies investigating fatigue > 4 months, we selected the shortest timepoint. Studies with missing data were excluded from analyses. Where studies investigated both 'fatigue' and CFS outcomes, we incorporated the 'fatigue' data only. This was because a confirmed diagnosis of CFS could not be established. To determine the trend for fatigue, 36 prospective studies, with available data for $\geq$ 2 follow-up times, were included in a meta-regression using the mixed-effects framework for meta-analyses developed by Sera et al. (2019). Meta-regression coefficients were estimated using a Restricted Maximum Likelihood (REML) estimator. To determine the proportion of fatigued participants by study design, and to increase the power, we categorised studies into 2: 'cross-sectional' and 'prospective'. The latter included longitudinal and retrospective designs. The cross-sectional category comprised the remaining designs. Two categories were used to investigate proportions for 'ongoing symptomatic COVID-19'(1-3 months) and 'post-Covid-19 syndrome' (>3 months) following NICE guidelines (nice.org.uk). The robustness of the main pooled prevalence was checked by controlling for the presence of outliers. Studies with 95% confidence intervals falling outside the 95% confidence interval of the total pooled effect were defined as 'outliers. Sensitivity analysis was performed on the mean pooled prevalence by excluding high risk of bias studies. Meta-analyses were conducted using R Studio, Version 1.3.1073 (2020) using packages meta, metafor, dmetar, metareg and mixmeta. SPSS Version 26 (IBM, 2019) was used for the Cohen's kappa statistic. Heterogeneity was assessed using Cochran Q statistic. We obtained the I^2 statistic with the degree of heterogeneity categorised as 'not important' (0-40%), 'moderate' (30-60%), 'substantial' (50-90%) and 'considerable' (75-100%) (Higgins, 2003). We conducted Egger's tests and produced funnel plots to explore potential publication bias for all proportional analyses. For 'vitality' outcomes, lack of comparable controls and missing data precluded a means difference analysis.

Patient and public involvement: No patient was involved in this study.

RESULTS

Search results

A total of 14,262 articles were identified using the database search protocols. Following the removal of duplicates 13,210 articles remained for title and abstract screening. Of these a total of 3,222 were selected for full text screening producing a final total of 178 studies and 22 systematic reviews. We identified 147 as eligible for a quantitative analysis. A summary of the 147 included articles is available as supplementary Table 1. The studies are tabulated according to categorical and continuous fatigue outcome measures. Summary table of systematic reviews is available in supplementary file 3.

Study characteristics

A total of 178 articles comprising 53,567 participants and 22 systematic reviews were included.[3–6,80,83,89–104] 14(8%) were pre-prints, 30(17%) used a fatigue scale and 27(15%) used a validated measure with a fatigue item(s). 13(7%) utilised the 'vitality' subscale of the SF-36 and 108(61%) employed a questionnaire, interview or health records. The most common countries were Italy with 25 studies and USA with 22 studies. UK had 19 studies and China 15 studies. Spain had 12 and France had 9 studies. Germany had 8 and Switzerland had 7 studies. The Netherlands and Turkey had 6 studies each and India had 5. Iran had 4 studies. Bangladesh, Denmark, Egypt and Pakistan had 3 studies each. Brazil, Chile, Israel, Mexico, Norway and Sweden all had 2 studies. Austria, Australia, Belgium, Canada, Colombia, Finland, Ireland, Hungary, Japan, Lithuania, Mexico, Nepal, Poland, Russia, Saudi Arabia and Zambia each had 1 study. There were 78 prospective and 11 retrospective cohort deigns. Six longitudinal studies, 27 cross-sectional, 8 case-controls, 3 case series, 42 cohort, 3 randomised-controlled trials and 22 systematic reviews. The most frequent follow-up times were 3 months (45 studies), 6 months (21 studies), 1 month (20 studies), 12 months (12 studies) and 2 months (12 studies). All other time-points had $\leq$ 8 studies. CASP quality assessments resulted in most studies receiving a moderate rating. Full ratings are available as supplementary file 4. In summary, 30 were assigned a 'high' risk of bias, 140 received a 'moderate' risk assessment and only 8 were considered 'low' risk. Lower grades were assigned for selection bias, lack of adequate control groups, small samples, study design and methodological bias (employment of unvalidated/unreliable scales).

Meta-analyses

A total of 49,032 participants were included for the meta-analysis of proportions using a random-effects model. A pooled prevalence from 147 studies was found to be 41% (95% CI: 36-45%, I^2 =98.6%). A forest plot of this analysis is available in Figure 2. Fatigue was present between 1 month to 1-year post-infection with a medium time of 3 months (IQR=2-6). An Egger's test was conducted to assess possible publication bias for our proportional analysis. The results indicated funnel plot asymmetry (bias=3.19, p=0.002) (supplementary file 5).

Figure 2 Forest plot for proportion of fatigued

To explore potential origins of heterogeneity and to test the robustness of our pooled prevalence, outliers were controlled for. A 1% difference was found once n=84 outlier studies were removed 42% (95% CI: 40-44%, I^2= 67%), although heterogeneity was reduced to 'substantial'. Given the range of post-infection assessment periods, the effect of time on fatigue was investigated by a linear mixed-effects model meta-regression. The outcome variable was the proportion of individuals reporting fatigue, with 'Months' (number of months since infection) and 'Hospitalisation' (whether someone was hospitalised) as predictors. 36 studies with available fatigue data and multiple time points ($\geq$ 2 follow-ups) were included. We found an effect of time, with the proportion of fatigued participants decreasing by 5.9% per month (95% CI: 1-10%, p=0.05). There was no effect of Hospitalisation and no interaction between Hospitalisation and time (Table 1).

Table 1 Results of linear mixed-effect meta-regression of time and hospitalisation

Parameter	*Estimate*	*SE*	*AIC*	*p*	*95% CI*	
					Lower	*Upper*
Months	-0.0593	0.0238	501.335	.005	-0.1059	-0.0128
Hospitalisation	-0.0871	0.1088	-	.423	-0.3003	0.1261
Months: Hospitalised	0.0303	0.0663	505.062	.647	-0.0997	0.1603

AIC Akaike Information Criterion

We conducted 2 subgroup analyses to explore the origins of heterogeneity arising from study methodology and investigate between group differences. A significant difference in fatigue was found between n=67 cross-sectional studies (45%, CI: 39-52%,I^2=98.2%) and n=80 prospective studies (37%, CI: 31-43%, I^2=98.8%), p=0.04.

A higher proportion of fatigued participants was found in n=36 studies using a scale (51%, 95% CI: 43-58%,I^2= 97.6%) compared to n=111 studies using an unvalidated questionnaire (37%, 95% CI: 32-43%, I^2=98.7%), p=0.006. To assess fatigue occurring at (a) 1-3 months ('ongoing symptomatic COVID-19') and (b) > 3 months ('post-COVID-19 syndrome'), 2 random effects subgroup analyses were conducted. Between 1-3 months the proportion of fatigued was 40% (95% CI: 35-46%, k=87, I^2=98.6%). At > 3 months, the proportion was 39% (95% CI: 33-46%, k=66, I^2= 98.8%). Sensitivity analysis was performed by excluding n=25 high risk of bias assessments (graded '3'). Results found the pooled prevalence to be 40% (95% CI: 35-44%, I^2 =98.6%) indicating little impact on the main results. Egger's tests indicated publication bias for both time categories and sensitivity. Plots available in supplementary files 6-11.

Factors associated with fatigue

Not all studies investigated or reported factors associated with fatigue. For some, the available data for each risk factor were too few to conduct a quantified analysis. Studies also used diverse outcome measures or non-validated scales. In addition, some risk factors were reported but not accompanied by quantified data making comparisons between studies problematic. Consequently, reported associations were arranged in tabular form illustrating the direction of the association with fatigue (Table 2). A positive symbol (+) indicated a positive association, a negative symbol (-) indicated a negative association and a zero (0) indicated no significant association between the investigated variable and fatigue.[105] Associations with fatigue measured in prospective cohort designs were demonstrated by superscript figures contained within parentheses, representing the time period the relationships were examined. Where a risk factor was examined with another (e.g. ICU admission with age), one set of results was included. Full details of the associations are available in supplementary material (file 12).

Table 2. Variables associated with fatigue

Factor	Cross-sectional		Prospective Cohort	
	Bivariate	*Multivariate*	*Bivariate*	*Multivariate*
PTSD ↑	+ +		+ +	
Anxiety symptoms ↑	+ 0 +	0	+	
Depression ↑	+ + + + + +	0 0	+ (0^{6} $+^{12}$)	+
Psychiatric morbidity ↑			+	
Physical comorbidities	0 0 0	+	0	+ + + + + + +
Psychological distress			0	
Somatisation				0
Pulmonary functions	+ 0 0			0
Pneumonia (CXR)		+		

1:

Disease Severity ↑	+ 0 - + 0 0 0 0	+	+ 0 + 0 0 0 + 0 0 0 0 + + + 0 0	0 0
Age ↑	0 - 0 + - 0 0 -	- + 0 0 0 +	0 0 + 0 0 0 0 0 0 --	+ 0 – + 0 +
ICU Admission	0 0 + + + +	0 0	+ 0	
Female gender	+ + + 0 + + + + + + 0 + + + + 0 + + + +	+ + + +	+ + 0 + 0 + + 0 + 0 0 + +	+ + + + 0 0
Ethnicity	0 0			
Marital status			0	
Rural/Urban habitat			0	
Occupation type			0	
BMI/obesity/weight↑	0 + + 0	0 0 +	0 0	0
Returned to work	+	+	0	
Employed				+
Retired				-
Exercise capacity <	+ + +			0 0
Intubated/IMV	+		+	+ +
Serum troponin-1 (TN1)			+	
Nucleic-acid test (> 14 days, 46-69 years old)	+	+		
Reduction of serum NfL levels			0	
Blood (e.g. lymphocytes10⁹/L, IgG)	0 + +	+	0	0
SpO²				0
Gut microbiota	+			
% Predicted VO2			0	
Mean consecutive difference (MCD) in extensor digitorum communis (EDC)	+			
Alcohol consumption	0	0		
Smoking history	0 0 0 0	0 0		0 0
Response to follow-up <				
Length of stay (LOS) >	0 + + 0 0	+	0	
Hospital readmission				+
Education ↑	0	0		
Physical health ↓	0 +			+
Post functional status/daily functioning ↓	+ + +			
Frailty ↑			+	
Sleep (quality & quantity)	+ +		+	
Steroid treatment	0 0			
Days since onset ↑	0	+		
Cognitive problems ↑	+ + +		+	
Breathlessness/Dyspnoea ↑	+ 0	+	+ +	+

Post Covid-19 functioning↓			±	±

Non-modifiable factors

Older age was reported in 31 studies with mixed results. Six reported an association with, or an increased likelihood of fatigue (OR=1.02) in participants >50.[34,41,54,56,57,106] Two reported higher fatigue in > 60 year olds [107] and > 40-year olds.[72] Some, however, reported that younger age related to fatigue [108–111] or no difference in fatigue severity between <65 and >65 year olds.[112] The remaining 18 studies did not find a relationship to fatigue.[33,58,59,68,69,73,74,84,86,112–120]. However, studies reporting non-significant results had small to modest sample sizes and were therefore potentially underpowered. Gender was investigated by 43 studies. Twenty-six reported a significant association with fatigue or found higher fatigue in women.[31,34,41,51–54,57,84,86,107,112,115,117,119–131] Females (54.3%) reported more severe/moderate fatigue than males (29.6%),[75,111] and had significantly lower vitality scores (M=81.80) compared to men (M=83.25).[106] However, 16 utilised an unvalidated instrument potentially affecting results. Those finding no association [33,59,68,72,73,113,114,118,119,132,133] had small sample sizes and only 3 used a fatigue scale.

Physical factors

The key physical factors associated with fatigue were dyspnoea, pulmonary functions, exercise capacity, comorbidities and ICU admission. Positive correlations between breathlessness and fatigue were found in 7 studies.[68,71–74,111,134] At ≥ 6 months post-infection 2 did not find a relationship,[69,84] suggestive of improvements over time. Although Staudt et al. (2022) found that 'respiratory symptoms' on the SGRQ were related to fatigue in multivariate analyses at 10 months post-infection (OR=1.06, p=0.05). However, only 2 used a dyspnoea scale or a fatigue scale. All had small sample sizes, therefore potentially underpowered. Pulmonary functions were reported in 4 studies. FEV_1 related to higher vitality in 1 (r=.0.23, p<.05),[67] but non-significant in the others.[68,69,134] These studies assessed survivors > 3 months, suggesting results are indicative of functional improvements overtime. Exercise capacity was generally poor in survivors[135] and 7 studies examined its relationship with fatigue, with mixed results. Better exercise performance was associated with vitality (r = 0.526, p<.001)[67] but not with 4-meter gait speed test [74] or 6MWT.[68] Two others found improved fatigue following a physical rehabilitation programme.[85,136] At 3 months post-infection, fatigue was cited as the reason for halting a cardiopulmonary performance test or limiting exercise in 3 studies.[137–139] Myopathy was associated with fatigue in another small study of 20 people [140] suggestive of poor conditioning contributing to limited capacity. Generally, fatigue had an inverse relationship with exercise capacity in the early months. Where the relationship remained beyond 3 months,[67] patients were overweight/obese, which possibly affected performance. Also all studies had small sample sizes limiting generalisability.

Physical comorbidities such as hypertension, asthma and diabetes were related to fatigue in 8 studies.[51,57,108,110,117,128,130,141] Four found no relationship.[114,115,118,129]. A large study of 4,755 participants found hypertension increased the likelihood (OR=1.27, p=0.05) of persistent fatigue > 6 months.[130] Yomogida et al. (2021) reported that having at least 1 comorbidity increased the risk for fatigue (aOR=4.39, p<.001). Moreover, worse physical health and its effects of daily living were related to an increased likelihood of fatigue (OR = 10.48) in 3 studies,[142–144] implying general poorer functioning among survivors.

For those admitted to ICU, some experienced high fatigue (8 studies),[111,113,141] and lower vitality,[145,146] or had an increased likelihood for fatigue (OR=4.63).[41,110,147] While 4 found no association between ICU admission and worse fatigue or vitality.[31,134,148,149] Patients who received mechanical ventilation had lower vitality (M=50, 95% CI: 44- 57) than a sex and age matched group (M=68, 95% CI: 67-69).[150] Similarly, more intubated patients had fatigue (38.1%) than non-intubated(29.9%).[151] One study found the proportion of fatigued was higher in the ward group (74%) compared to ICU (33%).[125] Disease severity also had an inconsistent impact on fatigue, with most studies finding no association with severe acute disease.[60,75,82,112,117,118,133,152–158] Five studies found a significant association with critical illness.[33,34,159–161] Two studies found a relationship between severity of acute illness and vitality,[35,36] although both had small samples and were single-centre designs. Interestingly, moderately severe COVID-19 related to fatigue (OR=2.1) in 2 studies.[160,162] Even after a longer hospital stay, the relationship with fatigue was inconsistent with 2 finding significance,[41,106] while 4 did not.[58,118,120,163] Taken together these results indicate an uncertain contribution of critical illness to fatigue, although the non-significant results chiefly occurred > 6 months. However, the classification of disease severity varied between studies and countries making comparisons difficult.

Psychological factors

A relationship with anxiety was found up to 6 months post-infection in 6 studies.[41,72,163,164] The fatigued had higher anxiety (56.3%) compared to non-fatigued (24.6%, p<.001)[72,163] In contrast, no significant interaction between anxiety and fatigue at 1 month related to later fatigue.[165] Similar results were found for depression. Previous depression was associated with lower vitality (-12.05, p=0.005) in 1 study.[84] and a higher proportion of fatigued had depressive symptoms in 2 other studies (p =.004).[72,79] Other studies found consistently moderate positive correlations (r=0.470).[120,166,167] or increased likelihood of fatigue (OR=0.24, p=0.05) in those with depressive symptoms.[41] The relationship continued up until 12 months.[68,120] Four studies found that those with PTSD symptoms reported higher fatigue [79,111] and PTSD was associated with fatigue at 6 and 12 months after infection.[120] Barizien et al. (2021) found higher scores on the PCL-5 (PTSD Checklist for DSM-5) in those with fatigue (M=31, IQR=18) compared to those without fatigue (M=18, IQR=19, p<.001). Generalisability of these results, however, are likely limited due to modest sample sizes and single-centre designs. In addition only 3 studies used a valid fatigue scale.

DISCUSSION

This review investigated the prevalence of persistent fatigue in survivors who had a confirmed diagnosis of SARS-CoV-2, using a mean of ≥ 30 days post-infection. We found a considerable proportion of patients continued to experience fatigue up to 12 months after their initial illness, which was associated with some non-modifiable factors including gender, age and modifiable factors such as anxiety, depression and post-traumatic stress. Our findings support other research indicating that fatigue is an important symptom in persistent post-acute sequelae.[4,92,168–171]. Rates of fatigue may depend on when it was measured and, in this respect, we found overall rates of fatigue decreased by 6% per month. Fatgue did not differ by hospitalisation status, indicating that the contribution of severe disease was not related to fatigue recovery for most people. This is consistent with previous reviews, which did not find support for the effects of critical illness on fatigue outcomes.[97,172]. Respiratory impairments, a key clinical indicator, were associated with worse vitality ($r=0.290$, $p=0.026$) post-recovery, [67] although at 10 months, FEV_1 was not associated[68] implying that, as lung function improved, fatigue diminished. Indeed, rehabilitation aimed at improving functioning by incorporating aerobic exercises, improved vitality scores.[85,146,173] Some survivors, however, continued to experience dyspnoea, which was associated with their fatigue,[71–74] despite normal pulmonary tests.[69,138] Similarly, reduced exercise capacity, as a result of critical illness, is thought to contribute to reduced HRQoL and fatigue outcomes in recovered patients.[174] However, our review did not find a consistent relationship between exercise performance and worse fatigue in those who had more severe disease. It is possible that these limitations are related to diminished muscle function [174] and deconditioning as rehabilitation programmes have led to improved vitality [136,173] and lower fatigue.[85,136] In a 9-week telerehabilitation study of 115 participants, incorporating 2/3 aerobic exercises per week to improve physical capacity, reported significantly increased vitality scores from pre = 40.7(SD=21.7)to post = 58.5(SD=21.2), p=0.001.[146] While deconditioning could explain fatigue, persistent fatigue may be related to other variables including psychological factors.

Depression and anxiety were found to be correlated with fatigue in our review [41,164,166]. Moreover, these relationships were found some distance from the initial infection.[120,134] In a prospective study of 402 participants using a fatigue scale, Mazza et al. (2021) found that both anxiety (r=0.48) and PTSD (r=0.52) were moderately correlated with fatigue at 6 and 12 months, post-illness. These findings accord with critical illness studies[175] and systematic reviews suggesting that symptoms of depression, anxiety, PTSD and fatigue persist long after discharge.[172] For COVID-19, we cannot be certain of the longevity of psychological factors or their relationship to fatigue because the body of evidence is too small, but current literature indicates the relationship remains up to 6 months later.[72,114,164]. This fits with previous coronavirus research indicating those with chronic fatigue were more likely to have psychiatric morbidity 4 years following a SARS infection.[176] Similarly, those with psychiatric illness reported higher fatigue than those without ($p<.05$) in survivors of SARS.[177]

Theoretical implications

Our results found that persistent fatigue was associated with physical functioning several months after the initial infection. The origins of fatigue persistence are multidimensional, likely linked to physical factors in the shorter term and psychological factors in the long term. Both possibly as a result of stress and distress resulting from the pandemic or infection.[178,179] These factors, alongside other mechanisms such as skeletal muscle deficits[180], could lead to poorer global functioning and lower engagement in activities or exercise thus prolonging fatigue. We have illustrated diagrammatically our findings post-coronavirus fatigue (Figure 3).

Figure 3 Diagram of post-COVID-19 fatigue findings

Practical implications

Our review suggests post-coronavirus fatigue is complex, affecting multiple domains of physical and psychological well-being. While there were small improvements in fatigue over time, our review indicates that fatigue remains a significant problem for patients beyond their anticipated recovery time.[181] Pulmonary and exercise programmes have shown promise.[85,146,173] Our results also suggest that psychological interventions may benefit some survivors. Given fatigue is one of a number of post-Covid symptoms,[182–185] an integrated management approach has been suggested.[186] Care pathways should identify those most at risk for long-term symptoms such as women and older people with comorbidities.

Future directions

Few studies have examined correlates between fatigue, physical and pulmonary functioning, psychological and social functioning in hospitalised and outpatients. Some research concerns symptom 'clusters' or 'post-covid syndrome'[187–190] limiting understanding of fatigue processes. Future studies should interrogate risk factors further to help inform the development of clinical interventions to address persistent fatigue. Furthermore, fatigue is the principal symptom for post-illness patients, but there is little research into what mechanisms may ameliorate distress resulting from infection, and thus protect against long symptoms. Severity of the illness, for instance, was not conclusive in our study and nor was length of stay pointing to the importance of individual differences.

Limitations

The generalisability of our results should be applied with caution due to a number of limitations. Firstly, the considerable and unexplained between-study heterogeneity. Measurement error was not found to explain the inconsistency. However, diverse tools were used to measure fatigue in different populations. Non-validated questionnaires were unlikely to capture fatigue dimensions accurately given most had 1-2 fatigue-related items. Moreover, scoring and cut-offs were underreported, contributing to variability. Some studies used particular populations, including older age or only those admitted to ICU, meaning they were not representative. Furthermore, our sample comprised primarily of hospitalised patients with potentially more severe disease. This was complicated by different admission and discharge protocols across countries, with some admitting all confirmed patients regardless of disease severity, explaining why there was no difference between hospitalised and non-hospitalised survivors. We also encountered missing data, which reduced the reliability of our results. Moreover, Egger's tests suggested all analyses were asymmetric representing a high likelihood of publication bias. Small study effects were likely to affect precision. Larger studies, with more precise confidence intervals are likely to be a more reliable indicator of fatigue proportions. Moreover, sample bias probably occurred due to recruitment from single-centre post-covid clinics[191–193] for persistent symptoms and therefore could be expected to have higher fatigue than controls or population norms. Different admission and discharge protocols and lung function reference ranges vary between countries.[194] Our results, therefore, should be viewed with this in mind. Methodologically, our study had only one reviewer for screening and data extraction and we did not contact authors for missing data meaning our study was at higher risk for excluding relevant data. Other limitations include the inclusion of non-peer reviewed articles (n=10) and those limited to English. For the meta-analysis, given the multiple assessment times, we incorporated one median follow-up time obtained from each study, which may not denote actual fatigue prevalence. Despite these limitations, we incorporated as substantial sample size likely to be a reasonable estimate of fatigue in this population.

CONCLUSION

This large review provides a broad illustration of fatigue outcomes and complements the growing body of information for persistent symptoms in those recovering from COVID-19. We report that fatigue decreases over time, but recovery pathways are potentially impeded by a number of risk factors, independent of disease severity or hospitalisation. Our study indicates the need for long-term clinical and psychological rehabilitation support for survivors of COVID-19.

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TC is the author of several self-help books on chronic fatigue for which she has received royalties. TC(KCL) has received ad hoc payments for workshops carried out in long-term conditions. TC acknowledges financial support from NIHR. She has a patent background IP with a software company for which she receives fees for work unrelated to fatigue. There are no other relationships or activities that could have influenced submitted work.

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References

1 Dittner A., Wessely S., Brown R. The assessment of fatigue. *J Psychosom Res* 2004;**56**:157–

70. doi:10.1016/S0022-3999(03)00371-4

2 Grant MC, Geoghegan L, Arbyn M, *et al.* The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. *PLoS One* 2020;**15**:e0234765. doi:http://dx.doi.org/10.1371/journal.pone.0234765

3 Badenoch JB, Rengasamy ER, Watson CJ, *et al.* Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.30.21256413. doi:10.1101/2021.04.30.21256413

4 Hoshijima H, Mihara T, Seki H, *et al.* Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. *medRxiv* 2021;:2021.04.08.21255109. doi:10.1101/2021.04.08.21255109

5 Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, *et al.* Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chron Respir Dis* 2021;**18**:147997312110022. doi:10.1177/14799731211002240

6 Malik P, Patel K, Pinto C, *et al.* Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* Published Online First: 2021. doi:https://dx.doi.org/10.1002/jmv.27309

7 Mak IWC, Chu CM, Pan PC, *et al.* Long-term psychiatric morbidities among SARS survivors. *Gen Hosp Psychiatry* 2009;**31**:318–26. doi:10.1016/j.genhosppsych.2009.03.001

8 Lee SH, Shin H-S, Park HY, *et al.* Depression as a Mediator of Chronic Fatigue and Post-Traumatic Stress Symptoms in Middle East Respiratory Syndrome Survivors. *Psychiatry Investig* 2019;**16**:59–64. doi:10.30773/pi.2018.10.22.3

9 Becker C, Beck K, Zumbrunn S, *et al.* Long COVID 1 year after hospitalisation for COVID-19: a prospective bicentric cohort study. *Swiss Med Wkly* 2021;**151**:w30091. doi:https://dx.doi.org/10.4414/smw.2021.w30091

10 Khalaf M, Bazeed SE, Abdel-Gawad M, *et al.* Prevalence and Predictors of Persistent

Symptoms after Clearance of SARS-CoV-2 Infection: A Report from Egypt. *SSRN Electron J* Published Online First: 2020. doi:10.2139/ssrn.3727954

11 Arnold DT, Hamilton FWFW, Morley MA, *et al.* Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. *medRxiv* 2020;:2020.08.12.20173526. doi:10.1101/2020.08.12.20173526

12 Bozzetti S, Ferrari S, Zanzoni S, *et al.* Neurological symptoms and axonal damage in COVID-19 survivors: are there sequelae? *Immunol Res* Published Online First: 7 August 2021. doi:10.1007/s12026-021-09220-5

13 Steinbeis F, Thibeault C, Doellinger F, *et al.* Severity of respiratory failure and computed chest tomography in acute COVID-19 correlates with pulmonary function and respiratory symptoms after infection with SARS-CoV-2: An observational longitudinal study over 12 months. *Respir Med* 2021;**191**:106709. doi:https://dx.doi.org/10.1016/j.rmed.2021.106709

14 Tleyjeh IM, Saddik B, AlSwaidan N, *et al.* Prevalence and predictors of Post-Acute COVID-19 Syndrome (PACS) after hospital discharge: A cohort study with 4 months median follow-up. *PLoS One* 2021;**16**:e0260568. doi:https://dx.doi.org/10.1371/journal.pone.0260568

15 van Veenendaal N, van der Meulen IC, Onrust M, *et al.* Six-Month Outcomes in COVID-19 ICU Patients and Their Family Members: A Prospective Cohort Study. Healthc. . 2021;**9**. doi:10.3390/healthcare9070865

16 Wu Q, Li H, Guo J, *et al.* A Follow-Up Study of Lung Function and Chest Computed Tomography at 6 Months after Discharge in Patients with Coronavirus Disease 2019. *Can Respir J* 2021;**2021**:6692409. doi:http://dx.doi.org/10.1155/2021/6692409

17 Zayet S, Zahra H, Royer P-YY, *et al.* Post-COVID-19 Syndrome: Nine Months after SARS-CoV-2 Infection in a Cohort of 354 Patients: Data from the First Wave of COVID-19 in Nord Franche-Comte Hospital, France. *Microorganisms* 2021;**9**. doi:https://dx.doi.org/10.3390/microorganisms9081719

18 Evans RA, McAuley H, Harrison EM, *et al.* Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study.

Lancet Respir Med Published Online First: 2021. doi:https://dx.doi.org/10.1016/S2213-2600(21)00383-0

19 Kayaaslan B, Eser F, Kalem AK, *et al.* Post-COVID syndrome: A single-center questionnaire study on 1007 participants recovered from COVID-19. *J Med Virol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/jmv.27198

20 Fatima G, Bhatt D, Idrees J, *et al.* Elucidating Post-COVID-19 manifestations in India. *medRxiv* 2021;:2021.07.06.21260115. doi:10.1101/2021.07.06.21260115

21 Catalan IP, Marti CR, Sota DP de la, *et al.* Corticosteroids for COVID-19 symptoms and quality of life at 1 year from admission. *J Med Virol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/jmv.27296

22 Scherlinger M, Felten R, Gallais F, *et al.* Refining "Long-COVID" by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection. *Infect Dis Ther* 2021;**10**:1747–63. doi:10.1007/s40121-021-00484-w

23 Poyraz BÇ, Poyraz CA, Olgun Y, *et al.* Psychiatric morbidity and protracted symptoms after COVID-19. *Psychiatry Res* 2021;**295**:113604. doi:10.1016/j.psychres.2020.113604

24 Eloy P, Tardivon C, Martin-Blondel G, *et al.* Severity of self-reported symptoms and psychological burden 6-months after hospital admission for COVID-19: a prospective cohort study. *Int J Infect Dis* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.ijid.2021.09.011

25 Fortini A, Torrigiani A, Sbaragli S, *et al.* COVID-19: persistence of symptoms and lung alterations after 3-6 months from hospital discharge. *Infection* 2021;**49**:1007–15. doi:http://dx.doi.org/10.1007/s15010-021-01638-1

26 García-Abellán J, Padilla S, Fernández-González M, *et al.* Antibody Response to SARS-CoV-2 is Associated with Long-term Clinical Outcome in Patients with COVID-19: a Longitudinal Study. *J Clin Immunol* 2021;**41**:1490–501. doi:10.1007/s10875-021-01083-7

27 Mahmud R, Rassel MA, Rahman MM, *et al.* Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. *PLoS*

One 2021;**16**:e0249644. doi:http://dx.doi.org/10.1371/journal.pone.0249644

28 Moreno-Perez O, Merino E, Boix V, *et al.* Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect* 2021;**82**:378–83. doi:http://dx.doi.org/10.1016/j.jinf.2021.01.004

29 Righi E, Mirandola M, Mazzaferri F, *et al.* Long-Term Patient-Centred Follow-up in a Prospective Cohort of Patients with COVID-19. *Infect Dis Ther* 2021;**10**:1579–90. doi:http://dx.doi.org/10.1007/s40121-021-00461-3

30 Seesle J, Hippchen T, Lim A, *et al.* Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. *Clin Infect Dis* Published Online First: 2021. doi:http://dx.doi.org/10.1093/cid/ciab611

31 Fernandez-De-Las-Penas C, Palacios-Cena D, Palacios-Cena M, *et al.* Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously Hospitalized Patients: Related Functional Limitations and Disability. *Respiration* Published Online First: 2021. doi:http://dx.doi.org/10.1159/000518854

32 Gamberini L, Mazzoli CA, Prediletto I, *et al.* Health-related quality of life profiles, trajectories, persistent symptoms and pulmonary function one year after ICU discharge in invasively ventilated COVID-19 patients, a prospective follow-up study. *Respir Med* 2021;**189**:106665. doi:10.1016/j.rmed.2021.106665

33 Rauch B, Kern-Matschilles S, Haschka SJ, *et al.* COVID-19-related symptoms 6 months after the infection - Update on a prospective cohort study in Germany. *medRxiv* 2021;:2021.02.12.21251619. doi:10.1101/2021.02.12.21251619

34 Zhang X, Wang F, Shen Y, *et al.* Symptoms and Health Outcomes among Survivors of COVID-19 Infection 1 Year after Discharge from Hospitals in Wuhan, China. *JAMA Netw Open* 2021;**4**:e2127403. doi:http://dx.doi.org/10.1001/jamanetworkopen.2021.27403

35 Van Den Borst B, Van Hees HWH, Van Helvoort H, *et al.* Comprehensive Health Assessment 3 Months after Recovery from Acute Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis* 2021;**73**:E1089–98. doi:http://dx.doi.org/10.1093/cid/ciaa1750

36 van der Sar - van der Brugge S, Talman S, de Mol M, *et al.* Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respir Med* 2021;**176**:106272. doi:https://dx.doi.org/10.1016/j.rmed.2020.106272

37 Boari GEM, Bonetti S, Braglia-Orlandini F, *et al.* Short-Term Consequences of SARS-CoV-2-Related Pneumonia: A Follow Up Study. *High Blood Press Cardiovasc Prev* 2021;**28**:373–81. doi:https://dx.doi.org/10.1007/s40292-021-00454-w

38 Creamer AW, Alaee S, Iftikhar H, *et al.* Clinico-radiological recovery following Severe covid-19 pneumonia. *Thorax* 2021;**76**:A185. doi:http://dx.doi.org/10.1136/thorax-2020-BTSabstracts.320

39 Horwitz LI, Garry K, Prete AM, *et al.* Six-Month Outcomes in Patients Hospitalized with Severe COVID-19. *J Gen Intern Med* Published Online First: 2021. doi:https://dx.doi.org/10.1007/s11606-021-07032-9

40 Naik S, Haldar SN, Soneja M, *et al.* Post COVID-19 sequelae: A prospective observational study from Northern India. *Drug Discov Ther* 2021;**15**:254–60. doi:10.5582/DDT.2021.01093

41 Qin ES, Gold LS, Hough CL, *et al.* Patient-Reported Functional Outcomes Thirty Days after Hospitalization for COVID-19. *PM R* Published Online First: 2021. doi:https://dx.doi.org/10.1002/pmrj.12716

42 Bell ML, Catalfamo CJ, Farland L V, *et al.* Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT. *medRxiv* 2021;:2021.03.29.21254588. doi:10.1101/2021.03.29.21254588

43 Carvalho-Schneider C, Laurent E, Lemaignen A, *et al.* Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021;**27**:258–63. doi:10.1016/j.cmi.2020.09.052

44 Castro VM, Rosand J, Giacino JT, *et al.* Case-control study of neuropsychiatric symptoms following COVID-19 hospitalization in 2 academic health systems. *medRxiv* 2021;:2021.07.09.21252353. doi:10.1101/2021.07.09.21252353

45 Graham EL, Clark JR, Orban ZS, *et al.* Persistent neurologic symptoms and cognitive

dysfunction in non-hospitalized Covid-19 'long haulers'. *Ann Clin Transl Neurol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/acn3.51350

46 Savarraj JPJ, Burkett AB, Hinds SN, *et al.* Three-month outcomes in hospitalized COVID-19 patients. *medRxiv* 2020;:2020.10.16.20211029. doi:10.1101/2020.10.16.20211029

47 Senjam SS, Balhara YPS, Kumar P, *et al.* Assessment of Post COVID-19 Health Problems and its Determinants in North India: A descriptive cross section study. *medRxiv* 2021;:2021.10.03.21264490. doi:10.1101/2021.10.03.21264490

48 Boscolo-Rizzo P, Guida F, Polesel J, *et al.* Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol* 2021;**11**:1685–8. doi:10.1002/alr.22832

49 Bliddal S, Banasik K, Pedersen OB, *et al.* Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. *Sci Rep* 2021;**11**:13153. doi:10.1038/s41598-021-92045-x

50 Heightman M, Prashar J, Hillman TE, *et al.* Post-COVID assessment in a specialist clinical service: a 12-month, single-centre analysis of symptoms and healthcare needs in 1325 individuals. *medRxiv* 2021;:2021.05.25.21257730. doi:10.1101/2021.05.25.21257730

51 Amin-Chowdhury Z, Harris RJ, Aiano F, *et al.* Characterising post-COVID syndrome more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. *medRxiv* 2021;:2021.03.18.21253633. doi:10.1101/2021.03.18.21253633

52 Bai F, Tomasoni D, Falcinella C, *et al.* Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.cmi.2021.11.002

53 Hellemons ME, Huijts S, Bek L, *et al.* Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for SARS-CoV-2; A Longitudinal Study of Respiratory, Physical and Psychological Outcomes. *Ann Am Thorac Soc* Published Online First: 2021. doi:https://dx.doi.org/10.1513/AnnalsATS.202103-340OC

54 Lombardo MDM, Foppiani A, Peretti GM, *et al.* Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. *Open forum*

Infect Dis 2021;**8**:ofab384. doi:https://dx.doi.org/10.1093/ofid/ofab384

55 Augustin M, Schommers P, Stecher M, *et al.* Recovered not restored: Long-term health consequences after mild COVID-19 in non-hospitalized patients. *medRxiv* 2021;:2021.03.11.21253207. doi:10.1101/2021.03.11.21253207

56 Daugherty SE, Guo Y, Heath K, *et al.* Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021;**373**:n1098. doi:https://dx.doi.org/10.1136/bmj.n1098

57 Yomogida K, Zhu S, Rubino F, *et al.* Post-Acute Sequelae of SARS-CoV-2 Infection Among Adults Aged ≥18 Years — Long Beach, California, April 1–December 10, 2020. *MMWR Morb Mortal Wkly Rep* 2021;**70**:1274–7. doi:10.15585/mmwr.mm7037a2

58 Karaarslan F, Demircioğlu Güneri F, Kardeş S. Postdischarge rheumatic and musculoskeletal symptoms following hospitalization for COVID-19: prospective follow-up by phone interviews. *Rheumatol Int* 2021;**41**:1263–71. doi:10.1007/s00296-021-04882-8

59 Hossain MA, Hossain KMA, Saunders K, *et al.* Prevalence of Long COVID symptoms in Bangladesh: a prospective Inception Cohort Study of COVID-19 survivors. *BMJ Glob Heal* 2021;**6**. doi:https://dx.doi.org/10.1136/bmjgh-2021-006838

60 Zhao Y, Yang C, An X, *et al.* Follow-up study on COVID-19 survivors one year after discharge from hospital. *Int J Infect Dis* 2021;**112**:173–82. doi:https://dx.doi.org/10.1016/j.ijid.2021.09.017

61 Cao J, Chen X, Zheng X, *et al.* Three-month outcomes of recovered COVID-19 patients: prospective observational study. *Ther Adv Respir Dis* 2021;**15**. doi:http://dx.doi.org/10.1177/17534666211009410

62 Aranda J, Oriol I, Martín M, *et al.* Long-term impact of COVID-19 associated acute respiratory distress syndrome. *J Infect* Published Online First: August 2021. doi:10.1016/j.jinf.2021.08.018

63 Szekely Y, Lichter Y, Sadon S, *et al.* Cardiorespiratory Abnormalities in Patients Recovering from Coronavirus Disease 2019. *J Am Soc Echocardiogr* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.echo.2021.08.022

64 Wang SY, Adejumo P, See C, *et al.* Characteristics of Patients Referred to a Cardiovascular Disease Clinic for Post-Acute Sequelae of SARS-CoV-2 Infection. *medRxiv* 2021;:2021.12.04.21267294. doi:10.1101/2021.12.04.21267294

65 Donaghy M, McKeegan D, Walker J, *et al.* Follow up for COVID-19 in Belfast City Hospital. *Ulster Med J* 2021;**90**:157–61.http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med19&NEWS=N&AN=34815594

66 Chudzik M, Kapusta J, Burzyńska M. Use of 1-MNA to Improve Exercise Tolerance and Fatigue in Patients After COVID-19. *medRxiv* 2021;:2021.07.14.21259081. doi:10.1101/2021.07.14.21259081

67 Bardakci MI, Ozkarafakili MA, Ozturk EN, *et al.* Evaluation of long-term radiological findings, pulmonary functions, and health-related quality of life in survivors of severe COVID-19. *J Med Virol* 2021;**93**:5574–81. doi:http://dx.doi.org/10.1002/jmv.27101

68 Staudt A, Jorres RA, Hinterberger T, *et al.* Associations of Post-Acute COVID syndrome with physiological and clinical measures 10 months after hospitalization in patients of the first wave. *Eur J Intern Med* 2022;**95**:50–60. doi:https://dx.doi.org/10.1016/j.ejim.2021.10.031

69 Froidure A, Mahsouli A, Liistro G, *et al.* Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. *Respir Med* 2021;**181**:106383. doi:10.1016/j.rmed.2021.106383

70 Smet J, Stylemans D, Hanon S, *et al.* Clinical status and lung function 10 weeks after severe SARS-CoV-2 infection. *Respir Med* 2021;**176**:106276. doi:10.1016/j.rmed.2020.106276

71 Aparisi A, Ybarra-Falcon C, Garcia-Gomez M, *et al.* Exercise Ventilatory Inefficiency in Post-COVID-19 Syndrome: Insights from a Prospective Evaluation. *J Clin Med* 2021;**10**. doi:https://dx.doi.org/10.3390/jcm10122591

72 Gonzalez-Hermosillo JA, Martinez-Lopez JP, Carrillo-Lampon SA, *et al.* Post-Acute COVID-19 Symptoms, a Potential Link with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A 6-Month Survey in a Mexican Cohort. *Brain Sci* 2021;**11**.

doi:https://dx.doi.org/10.3390/brainsci11060760

73 Shendy W, Elsherif AA, Ezzat MM, *et al.* Prevalence of fatigue in patients post Covid-19. *Eur J Mol Clin Med* 2021;**8**:1330–40.https://www.ejmcm.com/article_9929_c759b7fc62d11f801d43514cb73388c6.pdf

74 D'cruz RF, Waller MD, Perrin F, *et al.* Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res* 2020;**7**:00655–2020. doi:10.1183/23120541.00655-2020

75 Andrade Barreto AP, Duarte LC, Cerqueira-Silva T, *et al.* Post-Acute COVID Syndrome, the Aftermath of Mild to Severe COVID-19 in Brazilian Patients. *medRxiv* 2021;:2021.06.07.21258520. doi:10.1101/2021.06.07.21258520

76 Taboada M, Moreno E, Cariñena A, *et al.* Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. *Br J Anaesth* 2021;**126**:e110–3. doi:10.1016/j.bja.2020.12.007

77 Taylor RR, Trivedi B, Patel N, *et al.* Post-COVID symptoms reported at asynchronous virtual review and stratified follow-up after COVID-19 pneumonia. *Clin Med J R Coll Physicians London* 2021;**21**. doi:http://dx.doi.org/10.7861/CLINMED.2021-0037

78 Daher A, Balfanz P, Cornelissen C, *et al.* Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020;**174**:106197. doi:http://dx.doi.org/10.1016/j.rmed.2020.106197

79 Liyanage-Don NA, Cornelius T, Sanchez JE, *et al.* Psychological Distress, Persistent Physical Symptoms, and Perceived Recovery After COVID-19 Illness. *J Gen Intern Med* 2021;**36**:2525–7. doi:10.1007/s11606-021-06855-w

80 Rogers JP, Chesney E, Oliver D, *et al.* Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry* 2020;**7**:611–27. doi:10.1016/S2215-0366(20)30203-0

81 Suarez-Robles M, Iguaran-Bermudez MDR, Garcia-Klepizg JL, *et al.* Ninety days post-

hospitalization evaluation of residual covid-19 symptoms through a phone call check list. *Pan Afr Med J* 2020;**37**:1–4. doi:http://dx.doi.org/10.11604/pamj.2020.37.289.27110

82 Voruz P, Allali G, Benzakour L, *et al.* Long COVID neuropsychological deficits after severe, moderate or mild infection. *medRxiv* 2021;:2021.02.24.21252329. doi:10.1101/2021.02.24.21252329

83 Domingo FR, Waddell LA, Cheung AM, *et al.* Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review. *medRxiv* 2021;:2021.06.03.21258317. doi:10.1101/2021.06.03.21258317

84 Stavem K, Einvik G, Ghanima W, *et al.* Prevalence and determinants of fatigue after covid-19 in non-hospitalized subjects: A population-based study. *Int J Environ Res Public Health* 2021;**18**:1–11. doi:http://dx.doi.org/10.3390/ijerph18042030

85 Daynes E, Gerlis C, Chaplin E, *et al.* Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort study. *Chron Respir Dis* 2021;**18**:14799731211015692. doi:https://dx.doi.org/10.1177/14799731211015691

86 Mirfazeli FS, Sarabi-Jamab A, kordi A, *et al.* Acute phase clinical manifestation of COVID-19 is linked to long-COVID symptoms; A 9-month follow-up study. *medRxiv* 2021;:2021.07.13.21260482. doi:10.1101/2021.07.13.21260482

87 Page MJ, Moher D, Bossuyt PM, *et al.* PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;:n160. doi:10.1136/bmj.n160

88 Ouzzani M, Hammady H, Fedorowicz Z, *et al.* Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;**5**:1–10. doi:10.1186/S13643-016-0384-4/FIGURES/6

89 Chen C, Haupert SR, Shi X, *et al.* Global prevalence of post-acute sequelae of COVID-19 (PASC) or long COVID: A meta-analysis and systematic review. *medRxiv* Published Online First: 2021. doi:https://dx.doi.org/10.1101/2021.11.15.21266377

90 Fernandez-de-Las-Penas C, Palacios-Cena D, Gomez-Mayordomo V, *et al.* Prevalence of

post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021;**92**:55–70. doi:https://dx.doi.org/10.1016/j.ejim.2021.06.009

91 Garg M, Maralakunte M, Bhatia V, *et al.* The conundrum of 'long-covid-19': A narrative review. *Int J Gen Med* 2021;**14**:2491–506. doi:http://dx.doi.org/10.2147/IJGM.S316708

92 Jennings G, Monaghan A, Xue F, *et al.* A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: Ongoing symptomatic phase vs. post-COVID-19 syndrome. *medRxiv* 2021;:2021.06.25.21259372. doi:10.1101/2021.06.25.21259372

93 Gavriatopoulou M, Ntanasis-Stathopoulos I, Kastritis E, *et al.* Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. *J Infect* 2021;**83**:1–16. doi:http://dx.doi.org/10.1016/j.jinf.2021.05.004

94 Long Q, Li J, Hu X, *et al.* Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis. *Front Med* 2021;**8**. doi:10.3389/fmed.2021.702635

95 Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw open* 2021;**4**:e2111417. doi:https://dx.doi.org/10.1001/jamanetworkopen.2021.11417

96 Poudel AN, Zhu S, Cooper N, *et al.* Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One* 2021;**16**:e0259164. doi:https://dx.doi.org/10.1371/journal.pone.0259164

97 Rao S, Benzouak T, Gunpat S, *et al.* Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.23.21256006. doi:10.1101/2021.04.23.21256006

98 Sanchez-Ramirez DC, Normand K, Zhaoyun Y, *et al.* Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis. *Biomedicines* 2021;**9**. doi:https://dx.doi.org/10.3390/biomedicines9080900

99 Shanbehzadeh S, Tavahomi M, Ebrahimi-Takamjani I, *et al.* Physical and mental health complications post-COVID-19: Scoping review. *J Psychosom Res* 2021;**147**:110525. doi:http://dx.doi.org/10.1016/j.jpsychores.2021.110525

100 Wong TL, Weitzer DJ. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-A Systemic Review and Comparison of Clinical Presentation and Symptomatology. *Medicina (Kaunas)* 2021;**57**. doi:http://dx.doi.org/10.3390/medicina57050418

101 Aiyegbusi OL, Hughes SE, Turner G, *et al.* Symptoms, complications and management of long COVID: a review. *J R Soc Med* 2021;**114**:428–42. doi:10.1177/01410768211032850

102 Falk RS, Amdal CD, Pe M, *et al.* Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review. *Qual Life Res* Published Online First: 2021. doi:http://dx.doi.org/10.1007/s11136-021-02908-z

103 Cabrera Martimbianco AL, Pacheco RL, Bagattini AM, *et al.* Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. *Int J Clin Pract* 2021;**75**:e14357. doi:http://dx.doi.org/10.1111/ijcp.14357

104 Cha C, Baek G. Symptoms and management of long COVID: A scoping review. *J Clin Nurs* 2021;:No-Specified. doi:https://dx.doi.org/10.1111/jocn.16150

105 Matcham F, Ali S, Hotopf M, *et al.* Psychological correlates of fatigue in rheumatoid arthritis: A systematic review. Clin. Psychol. Rev. 2015;**39**:16–29. doi:10.1016/j.cpr.2015.03.004

106 Chen Y, Li T, Gong FH, *et al.* Predictors of Health-Related Quality of Life and Influencing Factors for COVID-19 Patients, a Follow-Up at One Month. *Front Psychiatry* 2020;**11**:668. doi:http://dx.doi.org/10.3389/fpsyt.2020.00668

107 Nehme M, Braillard O, Chappuis F, *et al.* Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in an Outpatient Setting. *Ann Intern Med* 2021;**174**:1252–60. doi:http://dx.doi.org/10.7326/M21-0878

108 Pauley E, Drake TM, Griffith DM, *et al.* Recovery from Covid-19 critical illness: a secondary analysis of the ISARIC4C CCP-UK cohort study and the RECOVER trial. *medRxiv* 2021;:2021.06.15.21258879. doi:10.1101/2021.06.15.21258879

109 Henneghan AM, Lewis KA, Gill E, *et al.* Describing cognitive function and psychosocial outcomes of COVID-19 survivors: A cross-sectional analysis. *J Am Assoc Nurse Pract* Published Online First: 2021. doi:http://dx.doi.org/10.1097/JXX.0000000000000647

110 Menges D, Ballouz T, Anagnostopoulos A, *et al.* Burden of Post-COVID-19 Syndrome and Implications for Healthcare Service Planning: A Population-based Cohort Study. *medRxiv* 2021;:2021.02.27.21252572. doi:10.1101/2021.02.27.21252572

111 Halpin SJ, McIvor C, Whyatt G, *et al.* Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;**93**:1013–22. doi:10.1002/jmv.26368

112 Shang YF, Liu T, Yu JN, *et al.* Half-year follow-up of patients recovering from severe COVID-19: Analysis of symptoms and their risk factors. *J Intern Med* 2021;**290**:444–50. doi:https://dx.doi.org/10.1111/joim.13284

113 Aul DR, Gates DJ, Draper DA, *et al.* Complications after discharge with COVID-19 infection and risk factors associated with development of post-COVID pulmonary fibrosis. *Respir Med* 2021;**188**:106602. doi:http://dx.doi.org/10.1016/j.rmed.2021.106602

114 Barizien N, Le Guen M, Russel S, *et al.* Clinical characterization of dysautonomia in long COVID-19 patients. *Sci Rep* 2021;**11**:14042. doi:http://dx.doi.org/10.1038/s41598-021-93546-5

115 Desgranges F, Tadini E, Munting A, *et al.* Post-COVID-19 syndrome in outpatients: a cohort study. *medRxiv* 2021;:2021.04.19.21255742. doi:10.1101/2021.04.19.21255742

116 Molnar T, Varnai R, Schranz D, *et al.* Severe Fatigue and Memory Impairment Are Associated with Lower Serum Level of Anti-SARS-CoV-2 Antibodies in Patients with Post-COVID Symptoms. *J Clin Med* 2021;**10**. doi:https://dx.doi.org/10.3390/jcm10194337

117 Sigfrid L, Drake TM, Pauley E, *et al.* Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *medRxiv* 2021;:2021.03.18.21253888. doi:10.1101/2021.03.18.21253888

118 Elkan M, Dvir A, Zaidenstein R, *et al.* Patient-Reported Outcome Measures After Hospitalization During the COVID-19 Pandemic: A Survey Among COVID-19 and Non-COVID-19 Patients. *Int J Gen Med* 2021;**14**:4829–36. doi:https://dx.doi.org/10.2147/IJGM.S323316

119 Guo L, Lin J, Ying W, *et al.* Correlation Study of Short-Term Mental Health in Patients Discharged After Coronavirus Disease 2019 (COVID-19) Infection without Comorbidities: A Prospective Study. *Neuropsychiatr Dis Treat* 2020;**Volume 16**:2661–7. doi:10.2147/NDT.S278245

120 Mazza MG, Palladini M, De Lorenzo R, *et al.* One-year mental health outcomes in a cohort of COVID-19 survivors. *J Psychiatr Res* 2021;**145**:118–24. doi:https://dx.doi.org/10.1016/j.jpsychires.2021.11.031

121 Aydin S, Unver E, Karavas E, *et al.* Computed tomography at every step: Long coronavirus disease. *Respir Investig* 2021;**59**:622–7. doi:https://dx.doi.org/10.1016/j.resinv.2021.05.014

122 Lindahl A, Aro M, Reijula J, *et al.* Women report more symptoms and impaired quality of life: a survey of Finnish COVID-19 survivors. *Infect Dis (Auckl)* Published Online First: 2021. doi:http://dx.doi.org/10.1080/23744235.2021.1965210

123 Pérez-González A, Araújo-Ameijeiras A, Fernández-Villar A, *et al.* Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a prospective cohort study. *medRxiv* 2021;:2021.08.05.21261634. doi:10.1101/2021.08.05.21261634

124 Romero-Duarte Á, Rivera-Izquierdo M, Guerrero-Fernández de Alba I, *et al.* Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med* 2021;**19**. doi:10.1186/s12916-021-02003-7

125 Sykes DL, Holdsworth L, Jawad N, *et al.* Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It? *Lung* 2021;**199**:113–9. doi:10.1007/s00408-021-00423-z

126 Boesl F, Audebert H, Endres M, *et al.* A Neurological Outpatient Clinic for Patients With Post-COVID-19 Syndrome — A Report on the Clinical Presentations of the First 100 Patients. *Front Neurol* 2021;**12**:738405. doi:10.3389/fneur.2021.738405

127 Iqbal A, Iqbal K, Ali SA, *et al.* The COVID-19 Sequelae: A Cross-Sectional Evaluation of Post-recovery Symptoms and the Need for Rehabilitation of COVID-19 Survivors. *CUREUS* 2021;**13**. doi:10.7759/cureus.13080

128 Bek LM, Berentschot JC, Heijenbrok-Kal MH, *et al.* Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study. *medRxiv* 2021;:2021.12.11.21267652. doi:10.1101/2021.12.11.21267652

129 Kashif A, Chaudhry M, Fayyaz T, *et al.* Follow-up of COVID-19 recovered patients with mild disease. *Sci Rep* 2021;**11**:13414. doi:https://dx.doi.org/10.1038/s41598-021-92717-8

130 Munblit D, Bobkova P, Spiridonova E, *et al.* Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin Exp Allergy* 2021;**51**:1107–20. doi:10.1111/cea.13997

131 Maamar M, Artime A, Pariente E, *et al.* POST-COVID-19 SYNDROME, INFLAMMATORY MARKERS AND SEX DIFFERENCES. *medRxiv* 2021;:2021.07.07.21260092. doi:10.1101/2021.07.07.21260092

132 Gebhard CE, Sütsch C, Bengs S, *et al.* Sex- and Gender-specific Risk Factors of Post-COVID-19 Syndrome: A Population-based Cohort Study in Switzerland. *medRxiv* 2021;:2021.06.30.21259757. doi:10.1101/2021.06.30.21259757

133 Sathyamurthy P, Madhavan S, Pandurangan V. Prevalence, Pattern and Functional Outcome of Post COVID-19 Syndrome in Older Adults. *Cureus* 2021;**13**:e17189. doi:https://dx.doi.org/10.7759/cureus.17189

134 Mantovani E, Mariotto S, Gabbiani D, *et al.* Chronic fatigue syndrome: an emerging sequela in COVID-19 survivors?. *J Neurovirol* 2021;**27**:631–7. doi:https://dx.doi.org/10.1007/s13365-021-01002-x

135 Latronico N, Peli E, Calza S, *et al.* Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax* 2021;:thoraxjnl-2021-218064. doi:10.1136/thoraxjnl-2021-218064

136 Ferraro F, Calafiore D, Dambruoso F, *et al.* COVID-19 related fatigue: Which role for

rehabilitation in post-COVID-19 patients? A case series. *J Med Virol* 2020;:jmv.26717. doi:10.1002/jmv.26717

137 Clavario P, Marzo V De, Lotti R, *et al.* Assessment of functional capacity with cardiopulmonary exercise testing in non-severe COVID-19 patients at three months follow-up. *ERJ Open Res* 2020;**7**:2020.11.15.20231985. doi:10.1101/2020.11.15.20231985

138 Mancini DM, Brunjes DL, Lala A, *et al.* Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post-Coronavirus Disease. *JACC Heart Fail* 2021;**9**:927–37. doi:https://dx.doi.org/10.1016/j.jchf.2021.10.002

139 Raman B, Cassar MP, Tunnicliffe EM, *et al.* Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine* 2021;**31**:100683. doi:https://dx.doi.org/10.1016/j.eclinm.2020.100683

140 Agergaard J, Ostergaard L, Leth S, *et al.* Myopathic changes in patients with long-term fatigue after COVID-19. *Clin Neurophysiol* 2021;**132**:1974–81. doi:http://dx.doi.org/10.1016/j.clinph.2021.04.009

141 Chen X, Li Y, Shao T-R, *et al.* Some characteristics of clinical sequelae of COVID-19 survivors from Wuhan, China: A multi-center longitudinal study. *Influenza Other Respi Viruses* Published Online First: 2021. doi:https://dx.doi.org/10.1111/irv.12943

142 O'Keefe JB, Minton HC, Morrow M, *et al.* Postacute Sequelae of SARS-CoV-2 Infection and Impact on Quality of Life 1-6 Months After Illness and Association With Initial Symptom Severity. *Open forum Infect Dis* 2021;**8**:ofab352. doi:https://dx.doi.org/10.1093/ofid/ofab352

143 Dini M, Poletti B, Tagini S, *et al.* Resilience, Psychological Well-Being and Daily Functioning Following Hospitalization for Respiratory Distress Due to SARS-CoV-2 Infection. *Healthc (Basel, Switzerland)* 2021;**9**. doi:https://dx.doi.org/10.3390/healthcare9091161

144 Jacobs LG, Gupta A, Rasouli L, *et al.* Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS One* 2020;**15**:e0243882. doi:http://dx.doi.org/10.1371/journal.pone.0243882

145 Valent A, Dudoignon E, Ressaire Q, *et al.* Three-month quality of life in survivors of ARDS due to COVID-19: A preliminary report from a French academic centre. *Anaesth Crit Care Pain Med* 2020;**39**:740–1. doi:10.1016/j.accpm.2020.10.001

146 Dalbosco-Salas M, Torres-Castro R, Leyton AR, *et al.* Effectiveness of a primary care telerehabilitation program for post-covid-19 patients: A feasibility study. *J Clin Med* 2021;**10**:4428. doi:http://dx.doi.org/10.3390/jcm10194428

147 Nune A, Durkowski V, Titman A, *et al.* Incidence and risk factors of long COVID in the UK: a single-centre observational study. *J R Coll Physicians Edinb* 2021;**51**:338–43. doi:https://dx.doi.org/10.4997/JRCPE.2021.405

148 Garrigues E, Janvier P, Kherabi Y, *et al.* Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;**81**:e4–6. doi:10.1016/j.jinf.2020.08.029

149 Yildirim S, Ediboglu O, Kirakli C, *et al.* Do Covid-19 patients needing ICU admission have worse 6 months follow up outcomes when compared with hospitalized non-ICU patients? A prospective cohort study. *Intensive Care Med Exp* 2021;**9**. doi:http://dx.doi.org/10.1186/s40635-021-00415-6

150 Schandl A, Hedman A, Lynga P, *et al.* Long-term consequences in critically ill COVID-19 patients: A prospective cohort study. *Acta Anaesthesiol Scand* 2021;**65**:1285–92. doi:https://dx.doi.org/10.1111/aas.13939

151 Morin L, Savale L, Montani D, *et al.* Four-Month Clinical Status of a Cohort of Patients after Hospitalization for COVID-19. *JAMA - J Am Med Assoc* Published Online First: 2021. doi:http://dx.doi.org/10.1001/jama.2021.3331

152 Kanberg N, Simrén J, Edén A, *et al.* Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. *EBioMedicine* 2021;**70**:103512. doi:10.1016/j.ebiom.2021.103512

153 Noviello D, Costantino A, Muscatello A, *et al.* Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: A controlled cohort study.

Neurogastroenterol Motil 2021;:e14187. doi:10.1111/nmo.14187

154 Strumiliene E, Zeleckiene I, Bliudzius R, *et al.* Follow-Up Analysis of Pulmonary Function, Exercise Capacity, Radiological Changes, and Quality of Life Two Months after Recovery from SARS-CoV-2 Pneumonia. *Medicina (Kaunas)* 2021;**57**. doi:http://dx.doi.org/10.3390/medicina57060568

155 Rass V, Ianosi B-A, Zamarian L, *et al.* Factors associated with impaired quality of life three months after being diagnosed with COVID-19. *Qual Life Res* Published Online First: 28 September 2021. doi:10.1007/s11136-021-02998-9

156 Sami R, Soltaninejad F, Amra B, *et al.* A one-year hospital-based prospective COVID- 19 open-cohort in the Eastern Mediterranean region: The Khorshid COVID Cohort (KCC) study. *PLoS One* 2020;**15**:e0241537. doi:http://dx.doi.org/10.1371/journal.pone.0241537

157 Sun L-L, Wang J, Hu P-F, *et al.* Symptomatic features and prognosis of 932 hospitalized COVID-19 patients in Wuhan. *J Dig Dis* Published Online First: 2021. doi:http://dx.doi.org/10.1111/1751-2980.12983

158 Anaya J-M, Rojas M, Salinas ML, *et al.* Post-COVID Syndrome. A Case Series and Comprehensive Review. *medRxiv* 2021;:2021.07.17.21260655. doi:10.1101/2021.07.17.21260655

159 Peghin M, Palese A, Venturini M, *et al.* Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. *Clin Microbiol Infect* 2021;**27**:1507–13. doi:10.1016/j.cmi.2021.05.033

160 Pilotto A, Cristillo V, Piccinelli SC, *et al.* Long-term neurological manifestations of COVID-19: prevalence and predictive factors. *Neurol Sci* 2021;:2020.12.27.20248903. doi:10.1101/2020.12.27.20248903

161 Fang X, Ming C, Cen Y, *et al.* Post-sequelae one year after hospital discharge among older COVID-19 patients: A multi-center prospective cohort study. *J Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.jinf.2021.12.005

162 Labarca G, Henriquez-Beltran M, Lastra J, *et al.* Analysis of clinical symptoms, radiological

changes and pulmonary function data 4 months after COVID-19. *Clin Respir J* 2021;**15**:992–1002. doi:https://dx.doi.org/10.1111/crj.13403

163 Townsend L, Dyer AH, Jones K, *et al.* Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020;**15**:e0240784. doi:http://dx.doi.org/10.1371/journal.pone.0240784

164 Tomasoni D, Bai F, Castoldi R, *et al.* Anxiety and depression symptoms after virological clearance of COVID-19: A cross-sectional study in Milan, Italy. *J Med Virol* 2021;**93**:1175–9. doi:10.1002/jmv.26459

165 Bottemanne H, Gouraud C, Hulot J-S, *et al.* Do Anxiety and Depression Predict Persistent Physical Symptoms After a Severe COVID-19 Episode? A Prospective Study. *Front psychiatry* 2021;**12**:757685. doi:https://dx.doi.org/10.3389/fpsyt.2021.757685

166 Albu S, Zozaya NR, Murillo N, *et al.* What's going on following acute COVID-19? Clinical characteristics of patients in an out-patient rehabilitation program. *NeuroRehabilitation* 2021;**48**:469–80. doi:http://dx.doi.org/10.3233/NRE-210025

167 Silva LS, Joao RB, Nogueira MH, *et al.* Functional and microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19. *medRxiv* 2021;:2021.03.20.21253414. doi:10.1101/2021.03.20.21253414

168 Elanwar R, Hussein M, Magdy R, *et al.* Physical and mental fatigue in subjects recovered from covid-19 infection: A case-control study. *Neuropsychiatr Dis Treat* 2021;**17**:2063–71. doi:http://dx.doi.org/10.2147/NDT.S317027

169 Danesh V, Arroliga AC, Bourgeois JA, *et al.* Post-acute sequelae of COVID-19 in adults referred to COVID recovery clinic services in an integrated health system in Texas. *Baylor Univ Med Cent Proc* 2021;**34**:645–8. doi:10.1080/08998280.2021.1972688

170 Mandal S, Barnett J, Brill SE, *et al.* Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2020;**0**:1–3. doi:http://dx.doi.org/10.1136/thoraxjnl-2020-215818

171 Moradian ST, Parandeh A, Khalili R, *et al.* Delayed Symptoms in Patients Recovered from

COVID-19. *Iran J Public Health* 2020;**49**:2120–7. doi:10.18502/ijph.v49i11.4729

172 Ahmed H, Patel K, Greenwood DC, *et al.* Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. *J Rehabil Med* 2020;**52**:0. doi:10.2340/16501977-2694

173 Liu K, Zhang W, Yang Y, *et al.* Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. *Complement Ther Clin Pract* 2020;**39**:101166. doi:10.1016/j.ctcp.2020.101166

174 Herridge MS, Cheung AM, Tansey CM, *et al.* One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;**348**:683–93. doi:10.1056/NEJMoa022450

175 Hatch R, Young D, Barber V, *et al.* Anxiety, Depression and Post Traumatic Stress Disorder after critical illness: a UK-wide prospective cohort study. *Crit Care* 2018;**22**:310. doi:10.1186/s13054-018-2223-6

176 Lam M, Wing Y, Yu MWM, *et al.* Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: Long-term follow-up. *Arch Intern Med* 2009;**169**:2142–7. doi:10.1001/archinternmed.2009.384

177 Wing YK, Leung CM. Mental health impact of severe acute respiratory syndrome: a prospective study. *Hong Kong Med J = Xianggang yi xue za zhi / Hong Kong Acad Med J = Xianggang yi xue za zhi / Hong Kong Acad Med* 2012;**18 Suppl 3**:24–7.https://pubmed.ncbi.nlm.nih.gov/22865219/ (accessed 29 Jun 2020).

178 Tessitore E, Handgraaf S, Poncet A, *et al.* Symptoms and quality of life at 1-year follow up of patients discharged after an acute COVID-19 episode. *Swiss Med Wkly* 2021;**151**:w30093. doi:https://dx.doi.org/10.4414/smw.2021.w30093

179 Morgul E, Jordan TR, Akyel S, *et al.* COVID-19 pandemic and psychological fatigue in Turkey. *Int J Soc Psychiatry* 2020;**67**:20764020941889. doi:http://dx.doi.org/10.1177/0020764020941889

180 Soares MN, Eggelbusch M, Naddaf E, *et al.* Skeletal muscle alterations in patients with acute

Covid-19 and post-acute sequelae of Covid-19. *J Cachexia Sarcopenia Muscle* 2022;**13**:11–22. doi:10.1002/jcsm.12896

181 Goertz YMJ, Van Herck M, J.M. D, *et al.* Persistent symptoms 3 months after a SARS-CoV-2 infection: The post-COVID-19 syndrome? *ERJ Open Res* 2020;**6**:1–10. doi:http://dx.doi.org/10.1183/23120541.00542-2020

182 Carfì A, Bernabei R, Landi F, *et al.* Persistent Symptoms in Patients After Acute COVID-19. *JAMA - J Am Med Assoc* 2020;**324**:603–5. doi:http://dx.doi.org/10.1001/jama.2020.12603

183 Dennis A, Wamil M, Alberts J, *et al.* Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021;**11**:e048391. doi:https://dx.doi.org/10.1136/bmjopen-2020-048391

184 Gautam N, Goyal S, Qureshi H, *et al.* Medium-term outcome of severe to critically ill patients with SARS-CoV-2 infection. *Clin Infect Dis* Published Online First: 2021. doi:http://dx.doi.org/10.1093/cid/ciab341

185 Darley DR, Dore GJ, Byrne AL, *et al.* Limited recovery from post-acute sequelae of SARS-CoV-2 at 8 months in a prospective cohort. *ERJ Open Res* 2021;**7**:00384–2021. doi:10.1183/23120541.00384-2021

186 Roth A, Chan PS, Jonas W. Addressing the Long COVID Crisis: Integrative Health and Long COVID. *Glob Adv Heal Med* 2021;**10**:21649561211056596. doi:https://dx.doi.org/10.1177/21649561211056597

187 Asadi-Pooya AA, Akbari A, Emami A, *et al.* Risk Factors Associated with Long COVID Syndrome: A Retrospective Study. *Iran J Med Sci* 2021;**46**:428–36. doi:https://dx.doi.org/10.30476/ijms.2021.92080.2326

188 Chopra N, Chowdhury M, Kumar A, *et al.* Clinical predictors of long COVID-19 and phenotypes of mild COVID-19 at a tertiary care centre in India. *Drug Discov Ther* 2021;**15**:156–61. doi:http://dx.doi.org/10.5582/DDT.2021.01014

189 Wong-Chew RM, Rodríguez Cabrera EX, Rodríguez Valdez CA, *et al.* Symptom cluster analysis of long COVID-19 in patients discharged from the Temporary COVID-19 Hospital in

Mexico City. *Ther Adv Infect Dis* 2022;**9**:204993612110692. doi:10.1177/20499361211069264

190 Novak P, Mukerji SS, Alabsi HS, *et al.* Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19. *Ann Neurol* Published Online First: 2021. doi:https://dx.doi.org/10.1002/ana.26286

191 Sollini M, Morbelli S, Ciccarelli M, *et al.* Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. *Eur J Nucl Med Mol Imaging* 2021;**48**:3187–97. doi:https://dx.doi.org/10.1007/s00259-021-05294-3

192 Vanichkachorn G, Newcomb R, Cowl CT, *et al.* Post-COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at Mayo Clinic and Characteristics of the Initial Patient Cohort. *Mayo Clin Proc* 2021;**96**:1782–91. doi:https://dx.doi.org/10.1016/j.mayocp.2021.04.024

193 Kedor C, Freitag H, Meyer-Arndt L, *et al.* Chronic COVID-19 Syndrome and Chronic Fatigue Syndrome (ME/CFS) following the first pandemic wave in Germany – a first analysis of a prospective observational study. *medRxiv* 2021;:2021.02.06.21249256. doi:10.1101/2021.02.06.21249256

194 Chan JCK. Recovery pathway of post-SARS patients. Thorax. 2005;**60**:361–2. doi:10.1136/thx.2004.035972

1. Chen Y, Liu C, Wang T, et al. Efficacy and safety of Bufei Huoxue capsules in the management of convalescent patients with COVID-19 infection: A multicentre, double-blind, and randomised controlled trial. *J Ethnopharmacol*. 2022;284:114830. doi:10.1016/j.jep.2021.114830
2. Critical Appraisal Skills Programme (2019). CASP (Randomised Controlled Trial, Cohort Study, Case Control Study) Checklists. Available at https://casp-uk.net/casp-tools-checklists/

3. Frontera, AJ, Yang D, Lewis A, *et al.* A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *Jl Neuro Sci 2021*;***426***:117486. https://doi.org/10.1016/j.jns.2021.117486

4. Ganesh R, Ghosh AK, Nyman MA, *et al.* PROMIS Scales for assessment of persistent Post-COVID symptoms: A cross sectional study. *J Prim Care Community Health* 2021;***12***:21501327211030413. https://doi.org/10.1177/21501327211030413

5. Graham EL, Clark JR, Orban ZS, *et al*. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers". *Ann Clin Transl Neurol* 2021;**8**:1073-1085. https://doi.org/10.1002/acn3.51350

6. Gautam N, Madathil S, Tahani N, *et al*. Medium-term outcomes in severely to critically ill patients with severe acute respiratory syndrome coronavirus 2 Infection. *Clin Infect Dis*. 2022;**74**:301-308. doi:10.1093/cid/ciab341

7. Gupta A, Garg I, Iqbal A, *et al.* Long-Term X-ray findings in patients with coronavirus disease-2019. *Cureus* 2021;***13***:e15304. https://doi.org/10.7759/cureus.15304

8. IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp

9. Kozak R, Armstrong SM, Salvant E, *et al.* Recognition of Long-COVID-19 patients in a Canadian tertiary hospital setting: A retrospective analysis of their clinical and laboratory characteristics. *Pathogens 2021;**10***:1246. https://doi.org/10.3390/pathogens10101246

10. Labarca G, Henríquez-Beltrán M, Lastra J, *et al.* (2021). Analysis of clinical symptoms, radiological changes and pulmonary function data 4 months after COVID-19. *Clin Respir J 2021;**15***:992–1002. https://doi.org/10.1111/crj.13403

11. Lemhöfer C, Sturm C, Loudovici-Krug D, *et al.* The impact of Post-COVID-Syndrome on functioning - results from a community survey in patients after mild and moderate SARS-CoV-2-infections in Germany. *J Occup Med Toxicol* 2021;***16***:45. https://doi.org/10.1186/s12995-021-00337-9

4

12. Leth S, Gunst JD, Mathiasen V, *et al*. Persistent Symptoms in Patients Recovering From COVID-19 in Denmark. *Open Forum Infect Dis*. 2021;**8**:ofab042. doi:10.1093/ofid/ofab042
13. Liang L, Yang B, Jiang N, *et al*. Three-month follow-up study of survivors of coronavirus disease 2019 after Discharge. *J Korean Med Sci*. 2020;**35**:e418. doi:10.3346/jkms.2020.35.e418
14. Liu T, Wu D, Yan W, *et al*.Twelve-month systemic consequences of coronavirus disease 2019 (COVID-19) in patients discharged from hospital: A prospective cohort study in Wuhan, China *Clinl Infect Dis* 2021;ciab703. https://doi.org/10.1093/cid/ciab703
15. Logue JK, Franko NM, McCulloch DJ, *et al*. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open*. 2021;**4**:e210830. doi:10.1001/jamanetworkopen.2021.0830
16. Miyazato Y, Morioka S,Tsuzuki S *et al*. Prolonged and late-onset symptoms of coronavirus disease 2019, *Open Forum Infect Dis* 2020;7:2020.ofaa507 https://doi.org/10.1093/ofid/ofaa507
17. Ortelli P, Ferrazzoli D, Sebastianelli L, *et al*. Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *J Neurol Sci*. 2021;420:117271. doi:10.1016/j.jns.2020.117271
18. RStudio Team (2020). RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/
19. Rosales-Castillo A, García de Los Ríos C, Mediavilla García JD. Persistent symptoms after acute COVID-19 infection: Importance of follow-up. Persistencia de manifestaciones clínicas tras la infección COVID-19: importancia del seguimiento. *Med Clin (Barc)*. 2021;**156**:35-36. doi:10.1016/j.medcli.2020.08.001
20. Sera F, Armstrong B, Blangiardo M, *et al*. An extended mixed-effects framework for meta-analysis. *Stat Med* 2019;***38***:5429–5444. https://doi.org/10.1002/sim.8362

21. Shoucri SM, Purpura L, DeLaurentis C*, et al*. Characterising the long-term clinical outcomes of 1190 hospitalised patients with COVID-19 in New York City: a retrospective case series. *BMJ Open* 2021;**11**: e049488.doi:10.1136/bmjopen-2021-049488

22. Søraas A, Kalleberg KT, Dahl JA, *et al*. Persisting symptoms three to eight months after non-hospitalized COVID-19, a prospective cohort study. *PLoS One*. 2021;**16**:e0256142. doi:10.1371/journal.pone.0256142

23. Sultana S, Islam MT, Salwa M, *et al*. Duration and Risk Factors of Post-COVID Symptoms Following Recovery Among the Medical Doctors in Bangladesh. *Cureus*. 2021;**13**:e15351. doi:10.7759/cureus.15351

24. Tiwari B, Ghimire M, Bhatta G, et al. Persistent Symptoms in Non-critical COVID-19 Patients at Two Months Follow-Up in a District Hospital: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc*. 2021;**59**:550-553. doi:10.31729/jnma.6440

25. Tosato M, Carfì A, Martis I, et al. Prevalence and Predictors of Persistence of COVID-19 Symptoms in Older Adults: A Single-Center Study. *J Am Med Dir Assoc*. 2021;**22**:1840-1844. doi:10.1016/j.jamda.2021.07.003

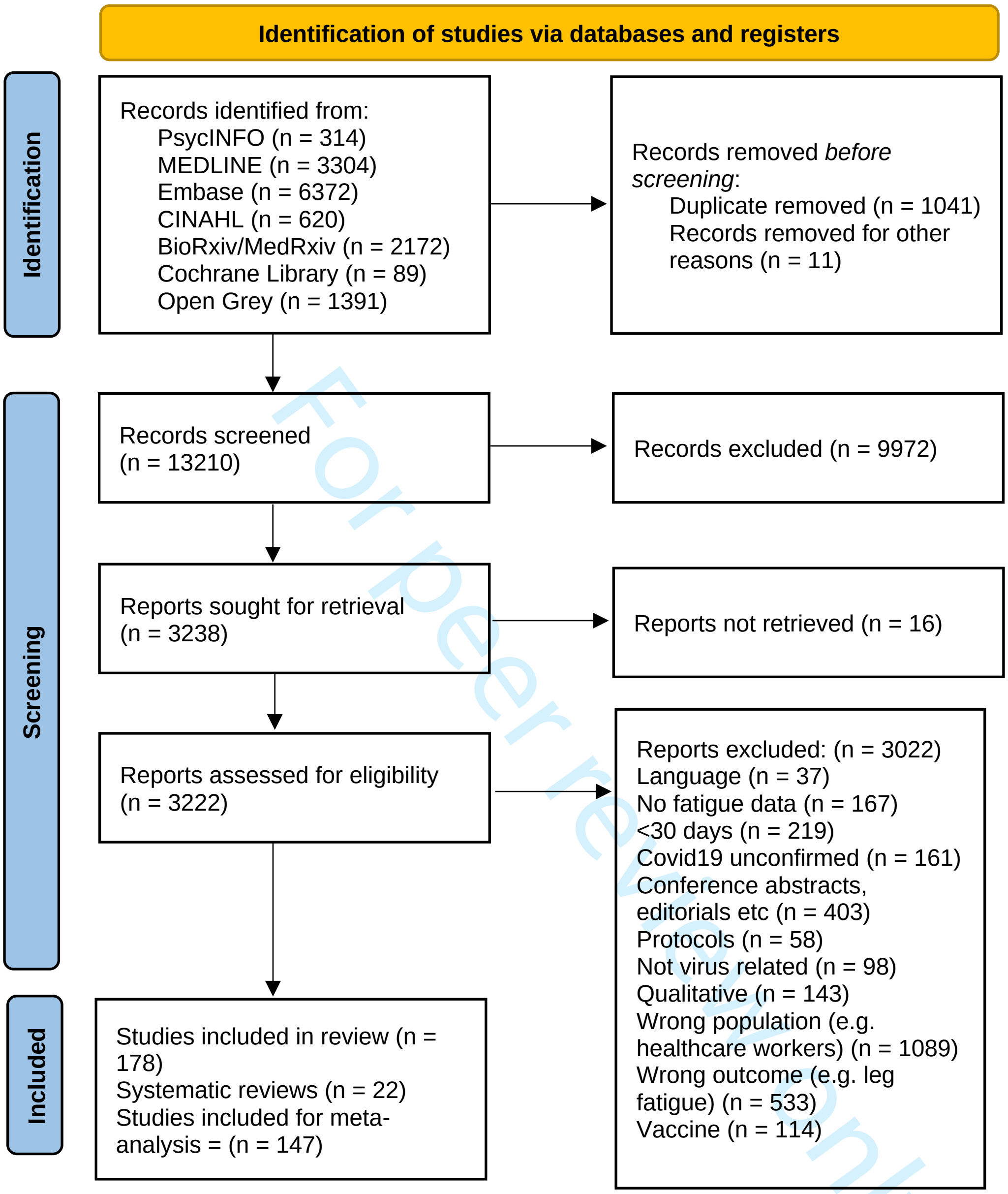
26. Venturelli S, Benatti SV, Casati M, *et al*. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. *Epidemiol Infect* 2021;***149***: e32. https://doi.org/10.1017/S0950268821000145

27. Weerahandi H, Hochman KA, Simon E, *et al*. Post-discharge health status and symptoms in patients with severe COVID-19. Preprint. *medRxiv*. 2020;2020.08.11.20172742. doi:10.1101/2020.08.11.20172742

28. Zhou Y, Zhang J, Zhang D, *et al*. Linking the gut microbiota to persistent symptoms in survivors of COVID-19 after discharge. *J Microbiol 2021; **59***:941–948. https://doi.org/10.1007/s12275-021-1206-5

29. Zulu JE, Banda D, Hines JZ, et al. Two-month follow-up of persons with SARS-CoV-2 infection-Zambia, September 2020: a cohort study. *Pan Afr Med J*. 2022;**41**:26. doi:10.11604/pamj.2022.41.26.30721

Figure 1. PRISMA 2020 flow diagram



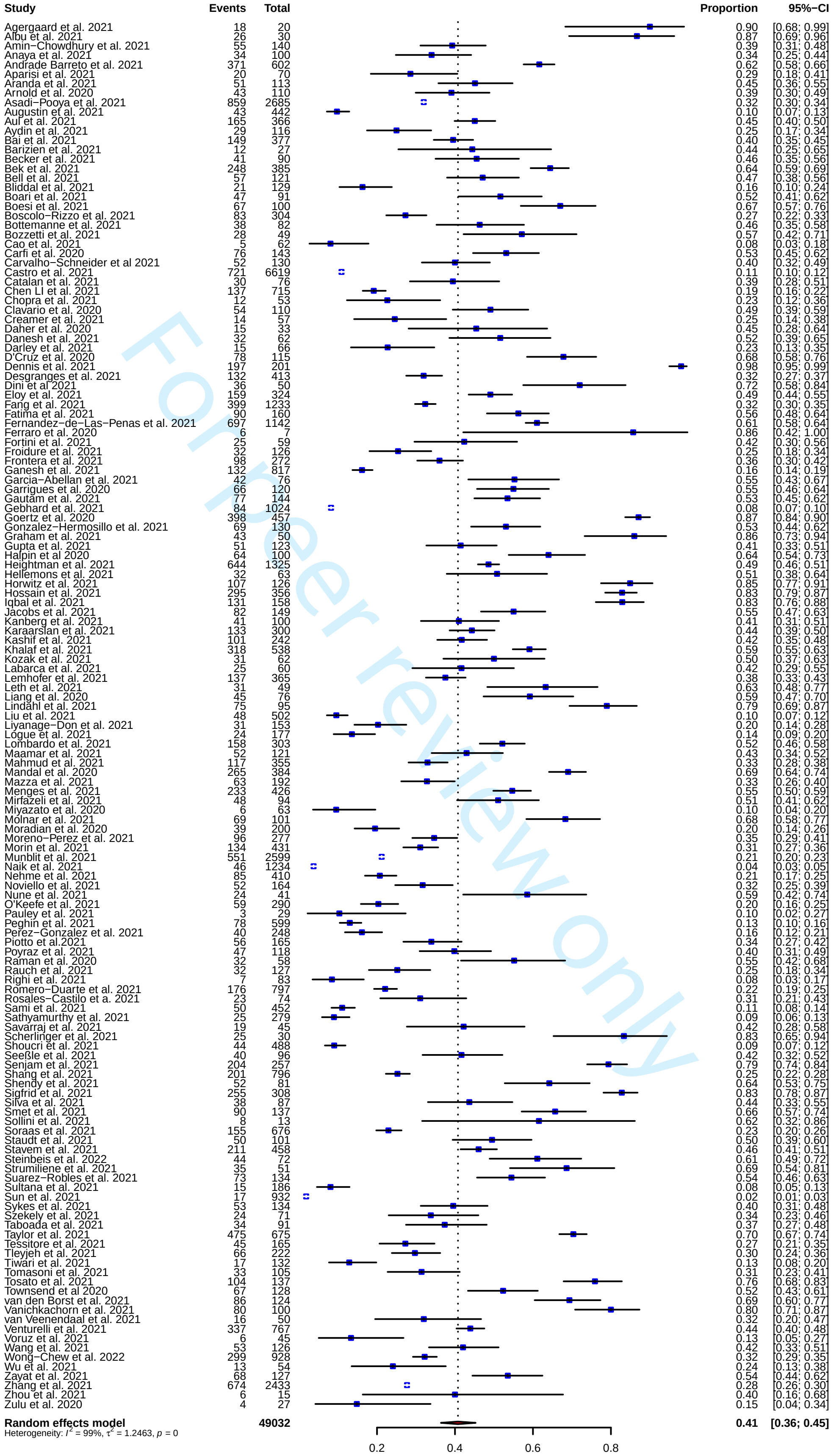
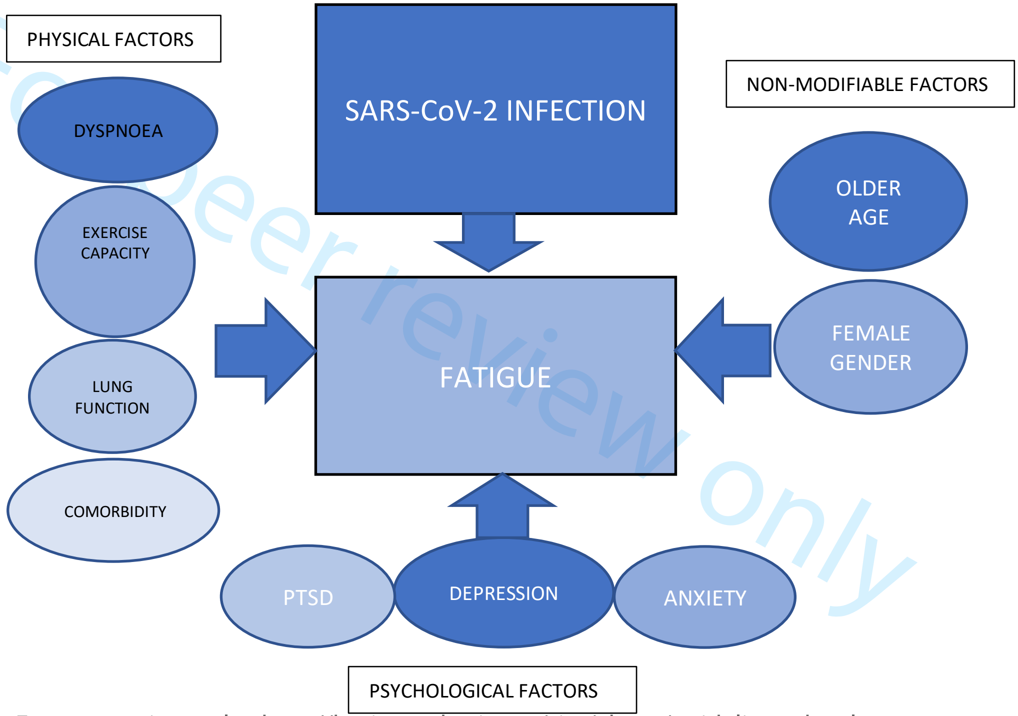

Study Events Total Proportion 95%−CI
Agergaard et al. 2021 18 20 0.90 [0.68; 0.99]
Albu et al. 2021 26 30 0.87 [0.69; 0.96]
Amin−Chowdhury et al. 2021 55 140 0.39 [0.31; 0.48]
Anaya et al. 2021 34 100 0.34 [0.25; 0.44]
Andrade Barreto et al. 2021 371 602 0.62 [0.58; 0.66]
Aparisi et al. 2021 20 70 0.29 [0.18; 0.41]
Aranda et al. 2021 51 113 0.45 [0.36; 0.55]
Arnold et al. 2020 43 110 0.39 [0.30; 0.49]
Asadi−Pooya et al. 2021 859 2685 0.32 [0.30; 0.34]
Augustin et al. 2021 43 442 0.10 [0.07; 0.13]
Aul et al. 2021 165 366 0.45 [0.40; 0.50]
Aydin et al. 2021 29 116 0.25 [0.17; 0.34]
Bai et al. 2021 149 377 0.40 [0.35; 0.45]
Barizien et al. 2021 12 27 0.44 [0.25; 0.65]
Becker et al. 2021 41 90 0.46 [0.35; 0.56]
Bek et al. 2021 248 385 0.64 [0.59; 0.69]
Bell et al. 2021 57 121 0.47 [0.38; 0.56]
Bliddal et al. 2021 21 129 0.16 [0.10; 0.24]
Boari et al. 2021 47 91 0.52 [0.41; 0.62]
Boesi et al. 2021 67 100 0.67 [0.57; 0.76]
Boscolo−Rizzo et al. 2021 83 304 0.27 [0.22; 0.33]
Bottemanne et al. 2021 38 82 0.46 [0.35; 0.58]
Bozzetti et al. 2021 28 49 0.57 [0.42; 0.71]
Cao et al. 2021 5 62 0.08 [0.03; 0.18]
Carfi et al. 2020 76 143 0.53 [0.45; 0.62]
Carvalho−Schneider et al 2021 52 130 0.40 [0.32; 0.49]
Castro et al. 2021 721 6619 0.11 [0.10; 0.12]
Catalan et al. 2021 30 76 0.39 [0.28; 0.51]
Chen LI et al. 2021 137 715 0.19 [0.16; 0.22]
Chopra et al. 2021 12 53 0.23 [0.12; 0.36]
Clavario et al. 2020 54 110 0.49 [0.39; 0.59]
Creamer et al. 2021 14 57 0.25 [0.14; 0.38]
Daher et al. 2020 15 33 0.45 [0.28; 0.64]
Danesh et al. 2021 32 62 0.52 [0.39; 0.65]
Darley et al. 2021 15 66 0.23 [0.13; 0.35]
D'Cruz et al. 2020 78 115 0.68 [0.58; 0.76]
Dennis et al. 2021 197 201 0.98 [0.95; 0.99]
Desgranges et al. 2021 132 413 0.32 [0.27; 0.37]
Dini et al 2021 36 50 0.72 [0.58; 0.84]
Eloy et al. 2021 159 324 0.49 [0.44; 0.55]
Fang et al. 2021 399 1233 0.32 [0.30; 0.35]
Fatima et al. 2021 90 160 0.56 [0.48; 0.64]
Fernandez−de−Las−Penas et al. 2021 697 1142 0.61 [0.58; 0.64]
Ferraro et al. 2020 6 7 0.86 [0.42; 1.00]
Fortini et al. 2021 25 59 0.42 [0.30; 0.56]
Froidure et al. 2021 32 126 0.25 [0.18; 0.34]
Frontera et al. 2021 98 272 0.36 [0.30; 0.42]
Ganesh et al. 2021 132 817 0.16 [0.14; 0.19]
Garcia−Abellan et al. 2021 42 76 0.55 [0.43; 0.67]
Garrigues et al. 2020 66 120 0.55 [0.46; 0.64]
Gautam et al. 2021 77 144 0.53 [0.45; 0.62]
Gebhard et al. 2021 84 1024 0.08 [0.07; 0.10]
Goertz et al. 2020 398 457 0.87 [0.84; 0.90]
Gonzalez−Hermosillo et al. 2021 69 130 0.53 [0.44; 0.62]
Graham et al. 2021 43 50 0.86 [0.73; 0.94]
Gupta et al. 2021 51 123 0.41 [0.33; 0.51]
Halpin et al 2020 64 100 0.64 [0.54; 0.73]
Heightman et al. 2021 644 1325 0.49 [0.46; 0.51]
Hellemons et al. 2021 32 63 0.51 [0.38; 0.64]
Horwitz et al. 2021 107 126 0.85 [0.77; 0.91]
Hossain et al. 2021 295 356 0.83 [0.79; 0.87]
Iqbal et al. 2021 131 158 0.83 [0.76; 0.88]
Jacobs et al. 2021 82 149 0.55 [0.47; 0.63]
Kanberg et al. 2021 41 100 0.41 [0.31; 0.51]
Karaarslan et al. 2021 133 300 0.44 [0.39; 0.50]
Kashif et al. 2021 101 242 0.42 [0.35; 0.48]
Khalaf et al. 2021 318 538 0.59 [0.55; 0.63]
Kozak et al. 2021 31 62 0.50 [0.37; 0.63]
Labarca et al. 2021 25 60 0.42 [0.29; 0.55]
Lemhofer et al. 2021 137 365 0.38 [0.33; 0.43]
Leth et al. 2021 31 49 0.63 [0.48; 0.77]
Liang et al. 2020 45 76 0.59 [0.47; 0.70]
Lindahl et al. 2021 75 95 0.79 [0.69; 0.87]
Liu et al. 2021 48 502 0.10 [0.07; 0.12]
Liyanage−Don et al. 2021 31 153 0.20 [0.14; 0.28]
Logue et al. 2021 24 177 0.14 [0.09; 0.20]
Lombardo et al. 2021 158 303 0.52 [0.46; 0.58]
Maamar et al. 2021 52 121 0.43 [0.34; 0.52]
Mahmud et al. 2021 117 355 0.33 [0.28; 0.38]
Mandal et al. 2020 265 384 0.69 [0.64; 0.74]
Mazza et al. 2021 63 192 0.33 [0.26; 0.40]
Menges et al. 2021 233 426 0.55 [0.50; 0.59]
Mirfazeli et al. 2021 48 94 0.51 [0.41; 0.62]
Miyazato et al. 2020 6 63 0.10 [0.04; 0.20]
Molnar et al. 2021 69 101 0.68 [0.58; 0.77]
Moradian et al. 2020 39 200 0.20 [0.14; 0.26]
Moreno−Perez et al. 2021 96 277 0.35 [0.29; 0.41]
Morin et al. 2021 134 431 0.31 [0.27; 0.36]
Munblit et al. 2021 551 2599 0.21 [0.20; 0.23]
Naik et al. 2021 46 1234 0.04 [0.03; 0.05]
Nehme et al. 2021 85 410 0.21 [0.17; 0.25]
Noviello et al. 2021 52 164 0.32 [0.25; 0.39]
Nune et al. 2021 24 41 0.59 [0.42; 0.74]
O'Keefe et al. 2021 59 290 0.20 [0.16; 0.25]
Pauley et al. 2021 3 29 0.10 [0.02; 0.27]
Peghin et al. 2021 78 599 0.13 [0.10; 0.16]
Perez−Gonzalez et al. 2021 40 248 0.16 [0.12; 0.21]
Piotto et al.2021 56 165 0.34 [0.27; 0.42]
Poyraz et al. 2021 47 118 0.40 [0.31; 0.49]
Raman et al. 2020 32 58 0.55 [0.42; 0.68]
Rauch et al. 2021 32 127 0.25 [0.18; 0.34]
Righi et al. 2021 7 83 0.08 [0.03; 0.17]
Romero−Duarte et al. 2021 176 797 0.22 [0.19; 0.25]
Rosales−Castillo et a. 2021 23 74 0.31 [0.21; 0.43]
Sami et al. 2021 50 452 0.11 [0.08; 0.14]
Sathyamurthy et al. 2021 25 279 0.09 [0.06; 0.13]
Savarraj et al. 2021 19 45 0.42 [0.28; 0.58]
Scherlinger et al. 2021 25 30 0.83 [0.65; 0.94]
Shoucri et al. 2021 44 488 0.09 [0.07; 0.12]
Seeßle et al. 2021 40 96 0.42 [0.32; 0.52]
Senjam et al. 2021 204 257 0.79 [0.74; 0.84]
Shang et al. 2021 201 796 0.25 [0.22; 0.28]
Shendy et al. 2021 52 81 0.64 [0.53; 0.75]
Sigfrid et al. 2021 255 308 0.83 [0.78; 0.87]
Silva et al. 2021 38 87 0.44 [0.33; 0.55]
Smet et al. 2021 90 137 0.66 [0.57; 0.74]
Sollini et al. 2021 8 13 0.62 [0.32; 0.86]
Soraas et al. 2021 155 676 0.23 [0.20; 0.26]
Staudt et al. 2021 50 101 0.50 [0.39; 0.60]
Stavem et al. 2021 211 458 0.46 [0.41; 0.51]
Steinbeis et al. 2022 44 72 0.61 [0.49; 0.72]
Strumiliene et al. 2021 35 51 0.69 [0.54; 0.81]
Suarez−Robles et al. 2021 73 134 0.54 [0.46; 0.63]
Sultana et al. 2021 15 186 0.08 [0.05; 0.13]
Sun et al. 2021 17 932 0.02 [0.01; 0.03]
Sykes et al. 2021 53 134 0.40 [0.31; 0.48]
Szekely et al. 2021 24 71 0.34 [0.23; 0.46]
Taboada et al. 2021 34 91 0.37 [0.27; 0.48]
Taylor et al. 2021 475 675 0.70 [0.67; 0.74]
Tessitore et al. 2021 45 165 0.27 [0.21; 0.35]
Tleyjeh et al. 2021 66 222 0.30 [0.24; 0.36]
Tiwari et al. 2021 17 132 0.13 [0.08; 0.20]
Tomasoni et al. 2021 33 105 0.31 [0.23; 0.41]
Tosato et al. 2021 104 137 0.76 [0.68; 0.83]
Townsend et al 2020 67 128 0.52 [0.43; 0.61]
van den Borst et al. 2021 86 124 0.69 [0.60; 0.77]
Vanichkachorn et al. 2021 80 100 0.80 [0.71; 0.87]
van Veenendaal et al. 2021 16 50 0.32 [0.20; 0.47]
Venturelli et al. 2021 337 767 0.44 [0.40; 0.48]
Voruz et al. 2021 6 45 0.13 [0.05; 0.27]
Wang et al. 2021 53 126 0.42 [0.33; 0.51]
Wong−Chew et al. 2022 299 928 0.32 [0.29; 0.35]
Wu et al. 2021 13 54 0.24 [0.13; 0.38]
Zayat et al. 2021 68 127 0.54 [0.44; 0.62]
Zhang et al. 2021 674 2433 0.28 [0.26; 0.30]
Zhou et al. 2021 6 15 0.40 [0.16; 0.68]
Zulu et al. 2020 4 27 0.15 [0.04; 0.34]
Random effects model 49032 0.41 [0.36; 0.45]
Heterogeneity: I^2 = 99%, τ^2 = 1.2463, p = 0
0.2
0.4
0.6
0.8

Figure 3. Diagram of fatigue associations



Supplementary Table 1. Summary of included studies with fatigue and vitality outcomes

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Agergaard et al. (2021) Denmark	Outpatients	Case-control	20	77-255 days	ADQ	NR	18 (90)	
Albu et al. (2021) Spain	Outpatients	Cross-sectional	30	≥ 3 months	MFIS	Range = 0-84 Higher score = severe impact	26 (86)	
Amin-Chowdhury et al. (2021) UK	Survey	Prospective cohort	1671	7 months	ADQ	NR	**+Ve cases** 55 (39.3) **-Ve controls** 203 (17.5)	<.001
Anaya et al. (2021) Colombia	Survey	Case series	100	219 days	ADQ	NR	34 (34)	
Andrade Barreto et al. (2021) Brazil	Outpatients	Cross-sectional	602	> 1 month	ADQ	NR	371 (61.6)	
Aparisi et al. (2021) Italy	Outpatients	Prospective cohort	70	3 months	NR	NR	20 (28.6)	
Aranda et al. (2021) Spain	Outpatients	Prospective cohort	113	240 days	ADQ	Range 0 - 10	51 (45)	
Arnold et al. (2020) UK	Outpatients	Prospective cohort	110	8-12 weeks	ADQ	NR	32/81 (39)	
Asadi-Pooya et al. 2021 Iran	Telephone	Retrospective cohort	4681	3-6 months 6-12 months	ADQ	NR	**3 months** 859/2685 (32) **6 months** 499/1996 (25)	.001
Augustin et al. (2021) Germany	Outpatients	Prospective cohort	958	4 months 7 months	ADQ	NR	**4 months** 43/442 (9.7) **7 months** 50/353 (14.2)	
Aul et al. (2021) UK	Telephone	Cross-sectional	387	6 weeks	ADQ	NR	165/366 (45.1)	
Aydin et al. (2021) Turkey	Outpatients	Cohort	116	44 days	ADQ	NR	29 (25)	
Bai et al. 2021 Italy	Outpatients	Prospective cohort	377	102 days	Clinical interview	NR	149 (39.5)	
Barizien et al. (2021) France	Outpatients	Prospective cohort	39	7 months	Clinician assessment	NR	-	
Becker et al. 2021 Switzerland	Outpatients	Prospective cohort	90	12 months	ADQ VAS for severity	NR Range 0-10	41/90 (46%) M 5.54 (SD 2.34)	
Bek et al. 2021 Netherlands	Outpatients	Prospective cohort	492	3, 6, 12 months	FAS	≥ 36 = caseness	**3 months** 248/385 (64.5) **6 months** 277/483 (63.1) **12 months** 156/271 (60.2)	.932

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Bell et al. (2021) USA	Survey	Prospective cohort	303	> 30 days	ADQ	NR	**>30 days** 78/208 (37.5) **30-59 days** 21/87 (24.1) **> 60 days** 57/121 (47.1)	
Bliddal et al. (2021) Denmark	Survey	Cohort	445	> 4 weeks	ADQ	NR	**4 weeks** 32/198 (16) **12 weeks** 21/129 (16)	
Boari et al. (2021) Italy	Outpatients	Prospective cohort	91	4 months	ADQ	NR	47 (52)	
Boesl et al. (2021) Italy	Outpatients	Cohort	100	≥ 12 weeks	FSS	4-7 impairment due to fatigue ≥ 36 = caseness	**N (%)** 67 (67)	
Boscolo-Rizzo et20 al. (2021) Italy	Outpatients	Cohort	304	12 months	ADQ	NR	83 (27.3)	
Bottemanne et al. 2021 France	Outpatients Telephone	Prospective cohort	84	1, 3 months	Clinical interview	NR	**1 month** 50/84 (59.5) **3 months** 38/82 (46.3)	
Bozzetti et al. (2021) Italy	Outpatients	Prospective cohort	49	6 months	Modified BORG Scale	6 = No exertion 20 = Maximal exertion	28 (57.1)	
Cao et al. (2021) China	Survey	Cohort	81	1-3 months	ADQ	NR	**1 month** 7 (11) **3 months** 5 (8)	
Carfi et al. (2020) Italy	Outpatients	Cohort	143	60 days	ADQ	NR	76 (53.1)	
Carvalho-Schneider et al. (2021) France	Survey	Prospective cohort	150	30-60 days	WHO Performance Status Classification	Grade 3 Grade 4	**Day 30** 74 (49.3) **Day 60** 52 (40)	
Castro et al. (2021) USA	EHR	Retrospective case-control	6619	> 30 days	EHR	NR	**31-90 days** 887 (13.4) **91-150 days** 721 (10.9)	
Catalan et al. (2021) Spain	Telephone	Cohort	76	12 months	ADQ SF-36 Vitality	NR	**No steroids** 19/44 (43.2) **Steroids** 11/32 (34.4)	
Chen, Li et al. (2021) China	Telephone	Longitudinal cohort	715	M 225 days	ADQ	NR	137 (19.2%)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Chopra et al. (2021) India	Survey	Cohort	53	30 days	ADQ	NR	12 (22.6)	
Chudzik et al. (2021) Poland	Outpatients	RCT	50	4 weeks	FAS	Score ≥4 = severe	-	
Clavario et al. (2020) Italy	Outpatients	Prospective cohort	110	3 months	ADQ	NR	54 (49.1)	
Creamer et al. (2021) UK	Outpatients Telephone	Cohort	57	6, 9 weeks	NR	NR	14 (25)	
Daher et al. (2020) Germany	Outpatients	Prospective cohort	33	6 weeks	BORG	Range 6 - 20	15 (45)	
Danesh et al. (2021) USA	Telephone	Cross-sectional	200	2-10 months	ADQ	NR	32/62 (52)	
Darley et al. (2021) Australia	Outpatients	Longitudinal cohort	66	8 months	SPHERE-34 VAS-F	NR Range 0 – 10 ≥ 7 = severe	15 (23) 2.0 (0.38-5.0)	
Daugherty et al. (2021) USA	EHR	Retrospective cohort	27074	1-6 months	ICD10		-	
D'Cruz et al. (2020) UK	Outpatients	Prospective cohort	119	61 days	NRS	NR	78/115 (67.8)	
Dennis et al. (2021 UK	Outpatients	Prospective cohort	201	Median 141 days	NR		197 (98)	
Desgranges et al. (2021) Switzerland	Telephone	Cohort	413	3-10 months	ADQ	NR	**Cases** 132 (32) **Controls** 15 (17)	.006
Dini et al. (2021) Italy	Outpatients	Cross-sectional	50	5 months	ADQ	NR	3637 (71)	
Eloy et al. (2021) France	Survey	Prospective cohort	324	3-6 months	ADQ	NR	**3 months** 159 (49) **6 months** 152 (47)	.05
Fang et al. 2021 China	Telephone	Prospective cohort	1233	12 months	Physician interview	NR	400 (32.4)	
Fatima et al. (2021) India	Survey	Cohort	160	40 days	ADQ	NR	90 (56.2)	
Fernandez-de-Las-Penas et al. (2021) Spain	Survey	Cohort	1142	7 months	FIC ADQ	Mild = 25% Moderate = 50% Severe = 75%	695 (61)	
Ferraro et al. (2020) Italy	Outpatients	Case-series	7	Post-discharge	BORG Scale	Range 6 - 20	6 (85.7)	
Fortini et al. (2021) Italy	Outpatients	Prospective cohort	59	4 months	ADQ	NR	25 (42.4)	
Froidure et al. (2021) Italy	Outpatients	Cohort	126	3 months	ADQ	NR	32 (25)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Frontera et al. (2021) USA	Survey	Prospective cohort	272	6 months	ADQ	NR	98 (36)	
Ganesh et al. (2021) USA	Survey	Cross-sectional	817	6 months	PROMIS-Fatigue	NR	132 (16.2)	
Garcia-Abellan et al. (2021) Spain	Outpatients	Prospective cohort	116	1-6 months	ADQ	NR	**6 months** 12 (10.3)	
Garrigues et al. (2020) France	Outpatients	Cross-sectional	120	110.9 days	ADQ	NR	66 (55)	
Gautam et al. (2021) UK	Outpatients	Case-series	200	4-7 months	ADQ	NR	77/144 (53.5)	
Gebhard et al. (2021) Switzerland	Survey	Cohort	1024	6.5 months	ADQ	NR	84 (8.2)	
Goertz et al. (2020) Belgium Netherlands	Survey	Cohort	457	3 months	ADQ	NR	398 (87)	
Gonzalez-Hermosillo et al. (2021) Mexico	Survey	Prospective cohort	130	3 months 6 months	ADQ	NR	**3 months** 69 (53) **6 months** 61 (46.9)	.019
Graham et al. (2021) USA	Survey	Cohort	50	7 months	PROMIS	≥ 50 = average	43 (85)	
Gupta et al. (2021) Pakistan	Outpatients	Prospective cohort	371	30 days	ADQ	NR	51/123 (41.4)	
Halpin et al. (2020) UK	Telephone	Cross-sectional	100	4-8 weeks	ADQ	Mild = 0-3 Moderate = 4-6 Severe = 7-10	64(64)	
Heightman et al. (2021) UK	Outpatients	Cohort	1325	≥ 6 weeks	FAS	< 22 = no fatigue ≥ 22 = fatigue	644 (48.6)	
Hellemons et al. (2021) Netherlands	Outpatients Survey	Prospective cohort	92	3-6 months	FAS	≥ 22 = fatigue	**6 months** 32/63 (50.8)	
Horwitz et al. (2021) USA	Survey	Prospective cohort	126	6 months	PROMIS-10	≥ 50 = average > 0 = fatigued	107 (85)	
Hossain et al. 2021 Bangladesh	Outpatients	Prospective cohort	2198	12 weeks	ADQ	NR	295/356 (82.9)	
Iqbal et al. (2021) Pakistan	Survey	Cross-sectional	158	38 days	ADQ	NR	131 (82.9)	
Jacobs et al. (2020) USA	Survey	Cohort	149	35 days	PROMIS	NR	82 (55)	
Kanberg et al. (2021) Sweden	Outpatients	Prospective cohort	100	6 months	KEDS	19 points	40 (41)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Karaarslan et al. (2021) Turkey	Survey	Cohort	300	1 month	ADQ	NR	133 (44.3)	
Kashif et al. 2021 Pakistan	Telephone	Cohort	242	3 months	ADQ	NR	101 (41.7)	
Khalaf et al. (2021) Egypt	Survey	Cross-sectional	538	83 days	ADQ	NR	318 (59.1)	
Kozak et al. (2021) Canada	EHR	Retrospective cohort	223	3 months	ADQ	NR	31/62 (50)	
Labarca et al. (2021) Chile	Outpatients	Cross-sectional	60	4 months	CFQ	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	25 (41.7)	
Lemhofer et al. 2021 Germany	Survey	Cross-sectional	365	3 months	ADQ SF-36 Vitlity	NR Range 0 – 100 100 = max vitality	137 (37.5) M 54.6	
Leth et al. (2021) Denmark	Outpatients Telephone	Prospective cohort	49	6 weeks 12 weeks	ADQ	NR	**6 weeks** 32 (65) **12 weeks** 31 (63)	
Liang et al. (2020) China	Outpatients	Prospective cohort	76	3 months	ADQ	NR	45 (59)	
Lindahl et al. (2021) Finland	Survey	Cohort	101	6 months	ADQ SF-36 Vitality	Range 0 – 100 100 = max vitality	75 (79) **M (SD)** 54.2 (23.6)	
Liu et al. (2021) China	Outpatients	Prospective cohort	594	3, 6, 12 months	ADQ	NR	-	
Liyanage-Don et al. (2021) USA	Survey	Cross-sectional	153	3 months	ADQ	NR	31 (20.3)	
Logue et al. (2021) USA	Survey	Prospective cohort	177	3 months 9 months	ADQ	NR	24 (13.6)	
Lombardo et al. (2021) Italy	Telephone	Prospective cohort	303	12 months	ADQ	NR	158 (52)	
Maamar et al. (2021) Spain	Outpatients	Cross-sectional	121	3 months	Interview	NR	52 (42.8)	
Mahmud et al. (2021)	Telephone	Prospective cohort	355	30 days	ADQ	NR	117 (33)	
Mandal et al. (2020) UK	Outpatients Telephone	Cross-sectional	384	54 days	ADQ	NR	265 (69)	
Mazza et al. 2021 Italy	Outpatients Online	Prospective cohort	402	1, 6, 12 months	FSS	Range 0 – 63 ≥ 36 = caseness	**12 months** 63/192 (33)	
Menges et al. (2021) Switzerland	Survey	Prospective cohort	431	6-8 months	FAS	≥ 22 = fatigue	233/426 (54.7)	
Mirfazeli et al. (2021)	Survey	Prospective cohort	94	9 months	CDC Criteria for	≥ 25 = fatigue	48 (51.0)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Iran	Interview				Fatigue Scale			
Miyazato et al.(2020) Japan	Telephone	Cross-sectional	63	1-4 months	ADQ	NR	6 (9.5)	
Molnar et al. (2021) Hungary	Outpatients	Prospective cohort	101	> 4 weeks	CFQ-11	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	69 (68.3)	
Moradian et al. (2020) Iran	Telephone	Cross-sectional	300	6 weeks	ADQ	NR	39 (19.5)	
Moreno-Perez et al. 2021 Spain	Outpatients	Prospective cohort	277	8 – 12 weeks	ADQ	NR	96 (34.8)	
Morin et al. (2021) France	Telephone	Prospective cohort	478	3-4 months	MFI	Range 4 – 20 ≥ 15 severe	134/431 (31)	
Munblit et al. (2021) Russia	Telephone	Longitudinal cohort	2599	218 days	ADQ	NR	551 (21.2)	
Naik et al. (2021) India	Outpatients	Prospective cohort	1234	3-6 months	ADQ	NR	45 (3.7)	
Nehme et al. (2021) Switzerland	Survey	Cohort	410	7-9 months	ADQ ECOG	NR 0 no limitations – 4 disabled	85 (20)	
Noviello et al. (2021) Italy	Survey	Case-control	164 cases 184 controls	4.8 months	SAGIS	NR	**Cases v. Controls** 52 (31.7) v. 25 (13.7) = <.001	
Nune et al. (2021) UK	Telephone	Prospective cohort	271	3, 6, 9 months	ADQ VAS	NR Range 0 – 10 ≥ 7 = severe	**9 months** 24/41 (58) M 5.8	
O'Keefe et al. (2021) USA	Survey	Cross-sectional	290	1-6 months	ADQ	NR	59 (20.3)	
Pauley et al. (2021) UK	Telephone/ Outpatients	Prospective cohort	332	3 months 12 months	VAS	Range 0 – 10 ≥ 7 = severe	**3 months (Cases v. Controls)** 7 (8.9) v. 51 (27.1) **6 months** 3 (10.3) v. 54 (32.5)	.809 .001
Peghin et al. (2021) Italy	Telephone	Prospective cohort	599	6 months	PRO	NA	78 (13.1)	
Pérez-González et al. (2021) Spain	Telephone	Prospective cohort	248	6 months	ADQ	NR	40 (16.1)	
Pilotto et al. (2021) Italy	Outpatients	Cohort	165	6 months	ADQ	NR	56 (33.9)	
Poyraz et al. (2021) Turkey	Survey	Cohort	118	50 days	ADQ	Range 0 - 8	47 (40)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Raman et al. (2020) UK	Outpatients	Cohort	58	2-3 months	FSS	Range 0 – 63 ≥ 36 = caseness	33 (55)	
Rass et al. (2021) Austria	Outpatients	Prospective cohort	90	3 months	SF-36 Vitality	< 40 = low energy/vitality	-	
Rauch et al. (2021) Germany	Survey	Prospective cohort	127	3, 6, 12 months	ADQ	NR	**6 months** 32 (25)	
Righi et al. (2021) Italy	Outpatients Telephone	Prospective cohort	448	6 - 12 weeks	ADQ	NR	**T1** = 45/175 (26) **T2** = 7/83 (9)	
Romero-Duarte et al. (2021) Spain	EHR	Retrospective cohort	797	6 months	EHR	NR	176 (22.1)	
Rosales- Castillo et al. (2021) Spain	Outpatients	Retrospective cohort	118	50 days	Question	NR	22/74 (30.5)	
Sami et al. (2020) Iran	Telephone	Cohort	452	4 weeks	ADQ	NR	50 (11)	
Sathyamurthy et al. (2021) India	Telephone	Prospective cohort	279	90 days	ADQ	NR	25 (8.9)	
Savarraj et al. (2021) USA	Telephone	Prospective cohort	48	3 months	FSS	Range 0 – 63 ≥ 36 = caseness	20 (42)	
Scherlinger et al. (2021) France	Outpatients	Prospective cohort	30	152 days	VAS	Range 0 – 10 ≥ 7 = severe	25 (82)	
Shoucri et al. 2021 USA	EHR	Retrospective cohort	929	3, 6 months	EHR	NA	**3 months** 44/488 (9.0) **6 months** 38/364 (10.4)	
Seeßle et al. (2021) Germany	Outpatients	Prospective cohort	96	5, 12 months	ADQ	NR	**5 months** 40 (41.7) **12 months** 51 (53.1)	.043
Senjam et al. (2021) India	Online	Cross-sectional	773	1 month	ADQ	NR	204/257 (79·3)	
Shang et al. (2021) China	Telephone	Cohort	796	6 months	ADQ	NR	201 (25.3)	
Shendy et al. (2021) Egypt	Telephone	Cohort	81	3-5 months	MFIS	Range 0 – 84 ≥ 38 caseness	52 (64.2)	
Sigfrid et al. (2021) UK	Outpatients Survey	Prospective cohort	308	222 days	VAS	Range 0 – 10 ≥ 7 = severe	255 (82.8)	
Silva et al. (2021) Brazil	Outpatients	Cross-sectional	87	54 days	ADQ CFQ-11	NR Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	38 (43.7)	
Smet et al. (2021) Belgium	Outpatients	Cohort	220	10 weeks	ADQ	NR	90/137 (66)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Sollini et al. (2021) Italy	Outpatients	Case control	39	98 days	NR	NR	Cases 8/18 (62)	
Soraas et al. (2021) Norway	Survey	Cohort	794	3-8 months	ADQ	NR	157/597 (23)	
Staudt et al. 2021 Germany	Outpatients	Prospective cohort	101	10 months	ADQ	NR	50 (49.5)	
Stavem et al.(2021) Norway	Survey	Cohort	458	1.5-6 months	CFQ-11 RAND-36	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	211 (46)	
Steinbeis et al. 2022 Germany	Outpatients	Prospective cohort	72	3, 6, 12 months	ADQ	NR	44 (60.8)	
Strumiliene et al. (2021) Lithuania	Outpatients	Cohort	51	2 months	ADQ	NR	35 (68.6)	
Suarez-Robles et a. 2021 Spain	Telephone	Cross-sectional	134	90 days	ADQ	NR	73 (54.5)	
Sultana et al. (2021) Bangladesh	Telephone	Cross-sectional	186	30-60 days	ADQ	NR	**≥ 60 days** 15 (8.1)	
Sun et al (2021) China	Telephone	Retrospective cohort	932	3 months	ADQ	NR	17 (1.8)	
Sykes et al. (2021) UK	Outpatients	Retrospective cohort	134	113 days	ADQ	NR	53 (39.6)	
Szekely et al. (2021) Israel	Outpatients	Prospective cohort	71	90 days	Modified BORG Scale	6 - 20 17 = very hard exertion	COVID 24 (34) Control 9/35 (26)	
Taboada et al. (2021) Spain	NR	Prospective cohort	91	6 months	ADQ	NR	34 (37.4)	
Taylor et al. (2021) UK	Telephone Survey	Cohort	675	> 12 weeks	Amplitude Questionnaire	NR	-	
Tessitore et al. (2021) Switzerland	Telephone	Prospective cohort	184	1, 12 months	PROMIS	NR	**1 month** 113 (61) **12 months** 45/165 (27)	
Tleyjeh et al. (2021) Saudi Arabia	Telephone	Prospective cohort	222	122 days	ADQ	NR	66 (29.7)	
Tiwari et al. (2021) Nepal	Outpatients	Cross-sectional	132	2 months	ADQ	NR	17 (13)	
Tomasoni et al. (2021) Italy	Outpatients	Cross-sectional	105	1-3 months	ADQ	NR	33 (31.4)	
Tosato et al. (2021) Italy	Outpatients	Cohort	165	76 days	ADQ	NR	104/137 (75.9)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Townsend et al. (2020) Ireland	Outpatients	Prospective cohort	128	10 weeks	CFQ-11	Range 0 – 33 > 29 = caseness 0 – 11 > 4 = caseness	67 (52.3)	
van den Borst et al. (2021) Netherlands	Outpatients	Prospective cohort	124	3 months	NCSI	Range [illegible] - [illegible]4	86 (69)	
Vanichkachom et al. (2021) USA	Outpatients	Cohort	100	3 months	NR	NR	80 (80)	
van Veenendaal et al. (2021) Netherlands	Survey	Prospective cohort	50	3, 6 months	ADQ	NR	17 (33)	
Venturelli et al. (2021) Italy	Telephone	Cohort	767	49 days 81 days	BFI	Range 1 - 10 8-10 = severe	334 (44.1)	
Voruz et al. (2021) Switzerland	Outpatients Survey	Cohort	75	6-9 months	FIS SF-36 Vitality	Range [illegible] - 84	6 (8)	
Wang et al. (2021) USA	Outpatients	Cohort	126	5 months	NR	-	53 (42)	
Wong-Chew et al. 2022 Mexico	Telephone	Prospective cohort	1303	1, 3 months	ADQ	NR	**30 days** 449/1303 (34.5) **90 days** 299/928 (32.2)	.001
Wu et al. (2021) China	Outpatients	Cohort	54	6 months	ADQ	NR	13 (24.1)	
Yomogida et al. (2021) USA	Telephone	Prospective cohort	366	1, 2, 6 months	ADQ	NR	**1 month** 88 (24.0) **2 months** 62 (16.9) **6 months** 50 (13.7)	
Zayet et al. (2021) France	Telephone	Retrospective cohort	354	289 days	ADQ	NR	68 (53.5)	
Zhang et al. (2021) China	Telephone	Cohort	2433	1 year	ADQ	NR	673 (27.7)	
Zhou et al. (2021) China	Outpatients	Case-control	15 patients 14 controls	3 months	NR	-	6 (40)	
Zulu et al. (2020) Zambia	Telephone	Cohort	302	54 days	ADQ	NR	4/27 (14.8)	
CONTINUOUS FATIGUE OUTCOMES								
Bardakci et al. (2021) Turkey	Outpatients	Cohort	65	6-7 months	SF-36 Vitality	Range 0 – 100 100 = max vitality	**M (SD)** 70.8 (NR)	
Chen, Liu et al. (2021) China	Outpatients	RCT	129	94 days	FAI	> 4 = severe fatigue	**BFHX group (n. 64)** 85.5 ± 27.6 **Placebo group (n. 65)** 100.4 ± 25.7	.0019

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Dalbosco-Salas et al. (2021) Chile	Outpatients	Prospective cohort	115	30 days	SF-36 Vitality VAS Fatigue	Range 0 – 10 ≥ 7 = severe	- **VAS Fatigue** Pre-rehab = 3 (0-5) Post-rehab = 1 (0-3)	
dal et al. (2021) UK	Outpatients	Cohort	30		FACIT	Range 0 - 52 < 30 = severe	**Pre rehabilitation** 29 (14) **Post rehabilitation** 34 (13)	
Donaghy et al. (2021) N. Ireland	Outpatients/ Telephone	Prospective cohort	113	3 months	FIS	Range 0-160	**M** =65	
Elanwar et al. (2021) Egypt	Outpatients	Case-control	46 fatigue 46 no fatigue	6 months	CFQ	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	**Fatigued** 6 (3-9)	
Elkan et al. (2021) Israel	Survey	Case-control	66 Cases 42 Controls	9 months	SF-36 Vitality		**Cases v Controls** 57.5 (30–76.2) v. 50 (23.7-80)	NS
Evans et al. (2021) UK	Outpatients	Prospective cohort	1077	5 months	FACIT	Range 0 - 52 < 30 = severe	16·8 (13·2)	
Gamberini et al. (2021) Italy	Telephone	Prospective cohort	205	3, 12 months	15D	5 = worst 1 = best	**12 months** M 0.816 (0.196)	
Guo et al. (2020) China	Outpatients	Prospective cohort	259	1 month	SF-36		-	
Henneghan et al. (2021) USA	Survey	Cross-sectional	52	4 months	PROMIS	NR	51.14 (7.61)	
Kayaaslan et al. (2021) Turkey	Outpatients Survey	Prospective cohort	1007	3 months	ADQ	4 (3–5) (Range 0-10)	24 (24.3)	
Kedor et al. (2021) Germany	Outpatients	Prospective cohort	42	6 months	CFQ	0 – 11 ≥ 4 = caseness	**Chronic Covid Syndrome** 7 (2-10) **CFS** 8 (5-10)	
Latronico et al. (2021) Italy	Survey	Prospective cohort	114	3-12 months	SF-36	Range 0 – 100 100 = max vitality	**M (IQR)** **3 months** 53 (46–59) **6 months** 77 (44–59) **12 months** 54 (47–59)	.600

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Liu et al. (2020) China	Outpatients	RCT	72	6 weeks	SF-36		**Post-pulmonary rehabilitation** 75.6 (7.1) **Controls** 61.2 (6.3)	
Mancini et al. (2021) USA	Outpatients	Prospective cohort	41	3 months	BORG	Range 6 - 20	**M (SD)** 15 (NR)	
Mantovani et al. (2021) Italy	Outpatients	Cohort	37	6 months	Clinical interview BORG	NR Range 6 - 20	**M (SD)** 42.5 (20.0-36.0) 0.16 (0.45-0.0	
Novak et al. (2021) USA	Outpatients	Retrospective cohort	24	> 4 weeks	BRAF-NRS, V2 Revised	Range 0-70 > 3 (0-10)	**PASC** 9/9 (100) **Controls** 0/5 (0) **POTS** 10/10 (100)	.001
Ortelli et al (2021) Italy	Outpatients	Case-control	12 cases 12 controls	11 weeks	FRS FSS	≥ 6 = caseness Range 0 – 10 ≥ 36 = caseness Range 9 – 63	**M (SD)** **Cases** 8.1 (1.7) 31.6 (10.8) **Controls** 0.7 (0.5) 9.5 (0.5)	<.001
Qin et al. (2021) USA	Telephone	Cross-sectional	55	1 month	PROMIS-7a	Standard T-score = 50 (SD 10)	**Before hospitalisation** 44.2 (7.4) **After hospitalisation** 54.5 (9.8)	
Schandl et al. (2021) Sweden	Outpatients	Prospective cohort	113	5 months	SF-36	Range 0 – 100 100 = max vitality	**M (95% CI)** **High-flow nasal O²/ Non-Invasive ventilation** 44 (32- 56) **Invasive mechanical ventilation** 50 (44- 57)	
Valent et al. (2020) France	Outpatients	Retrospective cohort	19	3 months	SF-36	Range 0 – 100 100 = max vitality	60 (IQR - 50-65)	
van der Sar -van der Brugge (2021) Netherlands	Outpatients	Prospective cohort	101	6 weeks	SF-36	"	NR	
Weerahandi et al. (2020) USA	Telephone	Prospective cohort	152	37 days	PROMIS	NR	**Before Covid** 4 (IQR 4-5) **After Covid** 3 (3-4)	
Yildirim et al. (2021) Turkey	Outpatients	Prospective cohort	70	6 months	SF-36	Range 0 – 100 100 = max vitality	NR	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Zhao et al. (2021) China	Outpatients	Prospective cohort	94	1 year	SF-36		75 (63.75, 90)	

NA = Not analysed; NR = Not reported; NS = not significant; r = Pearson's correlation; OR = Odds Ratio; CFS = chronic fatigue syndrome; 6MWT = 6-minute walking test; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for CO^2; KCO = carbon monoxide transfer coefficient; TLco = gas transfer capacity; ECLA = extracorporeal lung assist; ARDS = acute respiratory distress syndrome; FMA = fibromyalgia; BFHX = Bufei Huoxue supplement, PTSD = post-traumatic stress disorder; CXR = chest X-ray; WBC – white blood cell; CRP = c-reactive protein; ADQ = author designed ADQ; BFI = Brief Fatigue Inventory; BORG = Borg rating of perceived exertion scale; BRAF-NRS, V2 Revised = Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale-Revised; CFQ = Chalder Fatigue Scale; ECOG = Eastern Cooperative Oncology Group performance scale; EHR = electronic health records; FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue; FAI = Fatigue Assessment Inventory; FIC = Functional Impairment Checklist; FSS = Fatigue Severity Scale; FAS = Fatigue Assessment Scale; FIS = Fatigue Impact Scale; FRS = Fatigue Rating Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; KEDS = Karolinska Exhaustion Disorder Scale; NCSI = Nijmegen Clinical Screening Instrument; NRS = Numeric Rating Score; PCL-5 = Post-Traumatic Stress Disorder Checklist; PRO = Patient reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS-7a = short-form Fatigue; SAGIS = Structured Assessment of Gastrointestinal Symptoms Scale; SF-36 = 36-Item Short-Form Survey; SPHERE-34 = Somatic & Psychological Health Report; VAS-F = Visual Analogue Scale- Fatigue.

Supplementary File 1 PRISMA-P Protocol

TITLE:	PRISMA-P Protocol for a Systematic Review: Fatigue outcomes following COVID-19: A systematic review and meta-analysis
REGISTRATION:	PROSPERO 2020 CRD42020201247

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	Professor Trudie Chalder	Senior Reviewer

AMENDMENTS: Protocol amendments will be tracked, dated and numbered. The responsibility for tracking and registering changes to the protocol will be held by the 1st Reviewer with prior agreement and approval from the Senior Reviewer. Final authorisation for any changes to the protocol will be from the Senior Reviewer.

A summary of changes table (Table 1, Appendix A.) will be utilised to track changes and record authorisations. An explanation and rationale for the amendments will be recorded in Table 2 (Appendix A.)

FUNDING: No specific funding has been obtained for this review.
This protocol was developed and designed in collaboration between all stated authors.

RATIONALE: Fatigue is a commonplace presenting symptom for a number of infectious diseases, including coronaviruses. Studies reporting fatigue in the current COVID-19 epidemic suggest a fatigue prevalence of between 18% in children to 100% in emergency department patients (O'Reilly et al., 2020) during the acute phase. Fatigue has been implicated in increasing the risk for ICU care in some patients presenting with COVID-19, with a risk ratio of between 1.24 and 1.52 (Zhao et al., 2020) Further, it is an emerging symptom associated with chronic stress among healthy populations during forced lockdown conditions, who reported increased somatic symptomology such as sleepiness, insomnia, headaches, digestive disturbances and fatigue compared to before lockdown conditions (Majumdar, Biswas, & Sahu, 2020).

Apart from acute clinical symptoms, fatigue may continue post-recovery or have a sudden onset following an acute viral infection. The current pandemic has revealed a considerable burden of lasting symptoms with approximately 1 in 4 people experiencing fatigue by one estimate (Badenoch et al., 2021) Studies also indicate fatigue as one of the primary persistent symptoms. Systematic reviews indicate a pooled-prevalence of post-COVID-19 fatigue to vary between 45% (Hoshijima et al., 2021), 52% (Cares-Marambio et al., 2021) and 64%.(Malik et al., 2021). For a considerable number of COVID-19 patients, fatigue symptoms extend beyond 3 months and represent the largest burden of post-infection symptomology (Becker et al., 2021; Khalaf et al., 2020). This accords with evidence for post-viral fatigue in previous coronavirus outbreaks. One study investigating recovered SARS patients, found that 64% suffered continuing fatigue 3 months post-discharge and 60% experienced continuing fatigue at 12 months (Tansey et al., 2007). Another Hong Kong study reported 40.3% of recovered patients had chronic fatigue 4 years after contracting SARS and around 27% met the criteria for chronic fatigue syndrome.

Factors associated with post-illness fatigue include disease severity at the acute stage, which is more likely to require critical care or hospitalisation (Rauch et al., 2021; Van Den Borst et al., 2021; van der Sar - van der Brugge et al., 2021; Zhang et al., 2021) Physical factors have also been implicated in some studies. Reduced exercise capacity, for instance, is common in recovered patients even at 6 months post-infection and has been related to lower vitality. This is despite no concurrent impairments in pulmonary functions (Bardakci et al., 2021). Although pulmonary functions are weakly related to fatigue, dyspnoea remains a problem for recovered patients, with studies indicating a positive correlation with fatigue.
Other determinants include female gender, (Amin-Chowdhury et al., 2021; Bai et al., 2021; Hellemons et al., 2021; Lombardo et al., 2021) and older age, particularly over 50 years old (Daugherty et al., 2021; Qin et al., 2021; Yomogida et al., 2021) have been related to worse fatigue following a COVID-19 infection. Psychological factors include anxiety, post-traumatic stress and depressive symptoms, which are frequent in survivors of respiratory viral infections, (D'Cruz et al., 2021; Daher et al., 2020; Liyanage-Don et al., 2021) have a consistent relationship with higher fatigue. Depression and PTSD, for instance, were related to fatigue severity in 402 post-Covid patients (Mazza et al., 2021).

Current systematic reviews and meta-analyses support fatigue as a primary symptom during COVID-19 recovery, which may persist for serval months post-infection. Given the potential to affect recovery, this review will add to the current body of knowledge in both prevalence and associations to potentially aid in developing interventions for fatigue outcomes following the current coronavirus pandemic. The overall aim is to investigate the prevalence of long-term fatigue outcomes in survivors of COVID-19.

This systematic review will comply with the PRISMA-P guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (Shamseer et al., 2015).

OBJECTIVES: The objective of this review are: (a) to examine the prevalence of continuing/persistent fatigue among recovered patients, (b) to explore potential explanatory variables associated with fatigue outcomes where data is available (e.g. psychological, physical and sociodemographic). The study objectives will utilise a PICO framework (Appendix B.)

METHODS:

Eligibility Criteria

- Original articles available in English;
- Studies with primary data;
- Studies reporting fatigue using a valid fatigue measure (e.g. Chalder Fatigue Questionnaire), the 'vitality' subscale of the SF-36 or SF-12 instruments or studies using a clinical interview, checklist or questionnaire with a fatigue item(s);
- Studies investigating fatigue occurring $\geq$ 30 days after the acute phase/hospitalisation or post-infection as defined in each article. Fatigue defined as 'post-discharge', 'post-hospitalisation', 'post-acute', 'post-illness' or 'post-onset' must have been measured at a median/mean time of $\geq$ 30 days.
- Patient populations with a diagnosis of SARS-CoV-2 (COVID-19) confirmed by RT-PCR, IgM/IgG serology or clinical assessment (e.g. CT scan, chest X-ray);
- Adults $\geq$ 18 years old;
- Letters containing primary data;
- Any study design including cohort, case-control, cross-sectional, randomised control trials, meta-analysis.

Exclusion criteria

- Pandemic fatigue (defined as 'worn out' by pandemic warnings, or by government safety instructions, or with media coverage, or with compliance requirements');
- 'Muscle fatigue', 'leg fatigue' and fatigue data combined with 'malaise' or 'muscle weakness';
- Fatigue associated with physical disorders (e.g. thyroiditis, Parkinson's disease, cancer);
- Pregnant participants; children and adolescents < 18 years old;
- Fatigue measured or reported as a clinical symptom during the 'acute phase' (defined as the period of hospitalisation or fatigue occurring < 30 days post-infection);
- Participants without a confirmed diagnosis of COVID-19 (i.e. participants who self-report a diagnosis), or studies including 'probable' cases;
- Fatigue among healthcare workers, which arising in the context of their work (e.g. burnout, compassion fatigue);
- Newspaper articles, conference papers/abstracts, editorials, opinions, background articles;
- Clinical or treatment procedures or protocols,
- Case reports and qualitative studies;
- COVID-19 vaccination studies, animals;
- Absence of outcome data (i.e. not quantified or reported in text).

Information sources:

PsycINFO, MEDLINE, EMBASE, CINAHL, OpenGrey, Cochrane Database of Systematic Reviews.

Search Strategy:

The search strategy will be piloted and amended where appropriate to select the most appropriate studies. An example of the search strategy is available in Appendix C. The search strategy language will be amended according to each database requirements.

Study Records:

The following data will be extracted and recorded in a spreadsheet: author(s), title, population and participant numbers, follow-up period, control/comparator, location, study inclusion/exclusion criteria, study design, study objectives, outcomes of interest, associations with fatigue, scales/instruments employed, results, effect size and power calculation (Y/N) In addition, the quality of each study (see Risk of Bias) will be indicated. A separate database will be compiled detailing the studies that will be fully-screened but excluded, together with the rationalisation for the exclusion.

Selection Process:
The 1st reviewer will conduct the initial search in the selected databases for relevant studies. The senior reviewer will review a proportion of the identified studies based on the inclusion and exclusion criteria. The senior reviewer will independently audit the selected studies and review the data extraction spreadsheet. Agreement for the final included studies for any meta-analysis and narrative review will be in collaboration. Disagreements will be settled through consensus and agreement. A PRISMA flow chart will be used to record the number of records collected, number of fully-screened records, number of records excluded, studies identified through reference lists and total number of records for inclusion in any meta-analysis.

Data items/collection:
The variables for the data to be recorded will include the following and will be entered into a data extraction spreadsheet:

- citation details
- target population & location (survivors, region/country),
- study eligibility criteria,
- population characteristics (sample size, socio-demographics)
- outcomes under study (fatigue, vitality),
- how the outcomes were measured (Chalder Fatigue Scale (Chalder et al., 1993), vitality scale of the SF-36/SF-12, including the definition of clinical outcomes for a scale, cut-off points, upper/lower scores, explanation of whether a high or low score is favourable,
- study variables (e.g. PTSD, depressive symptoms, exercise capacity),
- metrics (e.g. changes in fatigue),
- timing of outcome measurements (e.g. assessments at 6-week intervals),
- mean and standard deviations for each group,
- comparator group,
- effect size,
- time (baseline data and follow-up times e.g. 1 month, 3 months),
- study design and setting (e.g. hospital, outpatients, population),
- study methods (single, multicentre, parallel, cluster)

For randomised control trials:
- Intervention or comparator descriptions (e.g. drug type, control group, placebo group),
- Doses, times and frequencies, length of intervention,
- How an intervention was assessed, length of exposure, cumulative exposure,
- Integrity of the intervention (the degree to which the procedures were implemented as stated/planned),

- Post-intervention metrics (e.g. changes in fatigue, pre-post-test),
- Randomisation procedures,
- Adverse effects,

Results

- Number of participants in each stated group (including number of patients lost, withdrawn, lost to follow-up or excluded with reasons),
- Summary data for each group, each outcome and each time point (means and standard deviations for continuous data, OR for dichotomous data),
- Between-group estimates measuring effect of the intervention on the outcome (e.g. OR, RR, mean differences) and their confidence intervals
- Confounders measured.

In the event of incomplete data regarding the exposures or outcomes, effect sizes or other important data, reviewers will request this information from the authors. Where there is no response, the missing data will be calculated according to (Higgins, 2003) or the paper will be excluded.

Risk of bias:
Risk of bias (RoB) assessment will be conducted for each included study using the relevant Critical Appraisal Skills Programme tools (CASP). The RoB will be conducted independently by two researchers. The assessments (e.g. good, moderate, poor) will be reported. A selection of reviews will be independently cross-checked by both researchers to establish reliability of the assessments. Methods to summarise the RoB assessments for all the studies and a description of these assessments will be incorporated into the data synthesis (i.e. sensitivity analyses) and their potential influence on the findings will be discussed.

Data synthesis
This systematic review will employ a quantitative approach and provide a summary pooled estimate of the risk for fatigue, combining the results of all the studies where appropriate. Where 3 or more studies can be combined based on the same outcome measure, a meta-analysis will be performed. Where there are less than 3 studies identified for the same outcome, the effect sizes will be described in text. For the meta-analysis, we will compute odds ratios (OR) for binary outcomes to estimate the risk of fatigue relative to the exposure virus and target population (survivors), with 95% confidence intervals as an overall synthesised measure of effect size. For continuous outcomes, standardised mean differences for the combined effect size will be computed. Data from all studies will included in the analysis. Additional statistical tests may be conducted dependent upon data availability (e.g. fatigue outcome relative to gender, socioeconomic status, pre-existing psychiatric conditions etc).

It is expected that there will be considerable heterogeneity in study types and outcome measures, therefore it is expected that a random effects model will be performed for the meta-analysis to provide an estimate of the mean effect size for the included studies. The random effects model is expected to allow for wider heterogeneity and take account of the estimated between-study weight differences. To assess between-study-heterogeneity a Cochran's Q will be performed and the effect of heterogeneity will be quantified using the I^2 statistical-test. A value of 50% or greater for the I^2 will be considered as indicative of greater variability. A value of greater than 75% will be considered as considerable variability. Statistical measures of effect will be extracted from the included studies for calculating pooled effect sizes of the association between an included influenza virus and fatigue outcomes. Effect sizes, 95% confidence intervals and statistical significance will be presented by quantitative and graphical representations (i.e. forest plots). Statistical significance will be set at $p < 0.05$ (2-tailed) for all analyses. Sensitivity analysis will be conducted utilising the RoB assessments across all the studies. For example, excluding low grade studies, studies with declared conflicts of interest. A funnel plot will be performed to assess publication bias.

Meta-bias(es)

In order to assess publication bias, funnel plots (observed for 10+ studies included in the meta-analysis) with an Egger test (Egger, Smith, Schneider, & Minder, 1997) to test asymmetry at alpha level 0.1 will be conducted.

Confidence in cumulative evidence

GRADE (Grading of Recommendations, Assessment, Development and Evaluation working group methodology) will be used to assess the quality of evidence for all outcomes. The quality of evidence will be assessed for risk of bias, consistency, directness, precision and publication bias. Quality will be judged as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect)

Reporting standards

The reporting of this systematic review will be in compliance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2010).

References

Amin-Chowdhury, Z., Harris, R. J., Aiano, F., Zavala, M., Bertran, M., Borrow, R., … Ladhani, S. N. (2021). Characterising post-COVID syndrome more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. *MedRxiv*, 2021.03.18.21253633. https://doi.org/10.1101/2021.03.18.21253633

Badenoch, J. B., Rengasamy, E. R., Watson, C. J., Jansen, K., Chakraborty, S., Sundaram, R. D., … Collaboration, for the S.-C.-N. (2021). Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *MedRxiv*, 2021.04.30.21256413. https://doi.org/10.1101/2021.04.30.21256413

Bai, F., Tomasoni, D., Falcinella, C., Barbanotti, D., Castoldi, R., Mule, G., … Monforte, A. d'Arminio. (2021). Female gender is associated with long COVID syndrome: a prospective cohort study. *Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases*. https://doi.org/https://dx.doi.org/10.1016/j.cmi.2021.11.002

Bardakci, M. I., Ozkarafakili, M. A., Ozturk, E. N., Ozturk, H., Yanc, U., & Yildiz Sevgi, D. (2021). Evaluation of long-term radiological findings, pulmonary functions, and health-related quality of life in survivors of severe COVID-19. *Journal of Medical Virology*, *93*(9), 5574–5581. https://doi.org/http://dx.doi.org/10.1002/jmv.27101

Becker, C., Beck, K., Zumbrunn, S., Memma, V., Herzog, N., Bissmann, B., … Hunziker, S. (2021). Long COVID 1 year after hospitalisation for COVID-19: a prospective bicentric cohort study. *Swiss Medical Weekly*, *151*, w30091. https://doi.org/https://dx.doi.org/10.4414/smw.2021.w30091

Cares-Marambio, K., Montenegro-Jiménez, Y., Torres-Castro, R., Vera-Uribe, R., Torralba, Y., Alsina-Restoy, X., … Vilaró, J. (2021). Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chronic Respiratory Disease*, *18*, 147997312110022. https://doi.org/10.1177/14799731211002240

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. *Journal of Psychosomatic Research*, *37*(2), 147–153. https://doi.org/10.1016/0022-3999(93)90081-P

D'Cruz, R. F., Patel, A., Perrin, F., Waller, M., Periselneris, J., Byrne, A., … Galloway, J. (2021). Clinical, radiological, functional and psychological characteristics of severe covid-19 pneumonia survivors: A prospective observational cohort study. *Thorax*, *76*(SUPPL 1), A34–A35. https://doi.org/http://dx.doi.org/10.1136/thorax-2020-BTSabstracts.60

Daher, A., Balfanz, P., Cornelissen, C., Muller, M., Bergs, I., Marx, N., … Dreher, M. (2020). Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respiratory Medicine*, *174*, 106197. https://doi.org/http://dx.doi.org/10.1016/j.rmed.2020.106197

Daugherty, S. E., Guo, Y., Heath, K., Dasmarinas, M. C., Jubilo, K. G., Samranvedhya, J., … Cohen, K. (2021). Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ (Clinical Research Ed.)*, *373*, n1098. https://doi.org/https://dx.doi.org/10.1136/bmj.n1098

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Hellemons, M. E., Huijts, S., Bek, L., Berentschot, J., Nakshbandi, G., Schurink, C. A. M., … Aerts, J. G. J. V. (2021). Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for SARS-CoV-2; A Longitudinal Study of Respiratory, Physical and Psychological Outcomes. *Annals of the American Thoracic Society*. https://doi.org/https://dx.doi.org/10.1513/AnnalsATS.202103-340OC

Higgins, J. P. T. (2003). Measuring inconsistency in meta-analyses. *BMJ*, *327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Hoshijima, H., Mihara, T., Seki, H., Hyuga, S., Kuratani, N., & Shiga, T. (2021). Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. *MedRxiv*, 2021.04.08.21255109. https://doi.org/10.1101/2021.04.08.21255109

Khalaf, M., Bazeed, S. E., Abdel-Gawad, M., Abdelmalek, M., Abu-Elfatth, A., Abdelhamed, W., … Alboraie, M. (2020). Prevalence and Predictors of Persistent Symptoms after Clearance of SARS-CoV-2 Infection: A Report from Egypt. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.3727954

Liyanage-Don, N. A., Cornelius, T., Sanchez, J. E., Trainor, A., Moise, N., Wainberg, M., & Kronish, I. M. (2021). Psychological Distress, Persistent Physical Symptoms, and Perceived Recovery After COVID-19 Illness. *Journal of General Internal Medicine*, *36*(8), 2525–2527. https://doi.org/10.1007/s11606-021-06855-w

Lombardo, M. D. M., Foppiani, A., Peretti, G. M., Mangiavini, L., Battezzati, A., Bertoli, S., … Zuccotti, G. V. (2021). Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. *Open Forum Infectious Diseases*, *8*(8), ofab384. https://doi.org/https://dx.doi.org/10.1093/ofid/ofab384

Majumdar, P., Biswas, A., & Sahu, S. (2020). COVID-19 pandemic and lockdown: cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. *Chronobiology International*, *37*(8), 1191–1200. https://doi.org/10.1080/07420528.2020.1786107

Malik, P., Patel, K., Pinto, C., Jaiswal, R., Tirupathi, R., Pillai, S., & Patel, U. (2021). Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *Journal of Medical Virology*. https://doi.org/https://dx.doi.org/10.1002/jmv.27309

Mazza, M. G., Palladini, M., De Lorenzo, R., Bravi, B., Poletti, S., Furlan, R., … Benedetti, F. (2021). One-year mental health outcomes in a cohort of COVID-19 survivors. *Journal of Psychiatric Research*, *145*, 118–124. https://doi.org/https://dx.doi.org/10.1016/j.jpsychires.2021.11.031

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., & Devereaux, P. J. (2010). *CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials* (Vol. 340, p. c869). Vol. 340, p. c869. Retrieved from https://doi.org/10.1136/bmj.c869

O'Reilly, G. M., Mitchell, R. D., Wu, J., Rajiv, P., Bannon-Murphy, H., Amos, T., … Cameron, P. A. (2020). Epidemiology and clinical features of emergency department patients with suspected COVID-19: Results from the first month of the COVID-19 Emergency Department Quality Improvement Project (COVED-2). *Emergency Medicine Australasia*, 1742-6723.13573. https://doi.org/10.1111/1742-6723.13573

Qin, E. S., Gold, L. S., Hough, C. L., Katz, P. P., Bunnell, A. E., Wysham, K. D., & Andrews, J. (2021). Patient-Reported Functional Outcomes Thirty Days after Hospitalization for COVID-19. *PM & R : The Journal of Injury, Function, and Rehabilitation*. https://doi.org/https://dx.doi.org/10.1002/pmrj.12716

Rauch, B., Kern-Matschilles, S., Haschka, S. J., Sacco, V., Potzel, A. L., Banning, F., … Lechner, A. (2021). COVID-19-related symptoms 6 months after the infection - Update on a prospective cohort study in Germany. *MedRxiv*, 2021.02.12.21251619. https://doi.org/10.1101/2021.02.12.21251619

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., … Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*, *349*(jan02 1), g7647–g7647. https://doi.org/10.1136/bmj.g7647

Tansey, C. M., Louie, M., Loeb, M., Gold, W. L., Muller, M. P., de Jager, J., … Herridge, M. S. (2007). One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. *Archives of Internal Medicine*, *167*(12), 1312–1320. https://doi.org/http://dx.doi.org/10.1001/archinte.167.12.1312

Van Den Borst, B., Van Hees, H. W. H., Van Helvoort, H., Reijers, M. H., Van Den Heuvel, M., Peters, J. B., … Van Der Hoeven Bram; ORCID: http://orcid.org/0000-0002-4597-2722, H. A. O.-V. D. B. (2021). Comprehensive Health Assessment 3 Months after Recovery from Acute Coronavirus Disease 2019 (COVID-19). *Clinical Infectious Diseases*, *73*(5), E1089–E1098. https://doi.org/http://dx.doi.org/10.1093/cid/ciaa1750

van der Sar - van der Brugge, S., Talman, S., de Mol, M., De Backer, I. C., Boonman - de Winter, L. J. M., Hoefman, E., & van Etten, R. W. (2021). Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respiratory Medicine*, *176*, 106272. https://doi.org/http://dx.doi.org/10.1016/j.rmed.2020.106272

Yomogida, K., Zhu, S., Rubino, F., Figueroa, W., Balanji, N., & Holman, E. (2021). Post-Acute Sequelae of SARS-CoV-2 Infection Among Adults Aged ≥18 Years — Long Beach, California, April 1–December 10, 2020. *MMWR. Morbidity and Mortality Weekly Report*, *70*(37), 1274–1277. https://doi.org/10.15585/mmwr.mm7037a2

Zhang, X., Wang, F., Shen, Y., Hu, B., Wang, M., He, Y., … Cheng, L. (2021). Symptoms and Health Outcomes among Survivors of COVID-19 Infection 1 Year after Discharge from Hospitals in Wuhan, China. *JAMA Network Open*, *4*(9), e2127403. https://doi.org/http://dx.doi.org/10.1001/jamanetworkopen.2021.27403

Zhao, J., Gao, Y., Huang, W., Li, X., Gao, Y., Huang, W., … Li, X. (2020). Risk factors for the exacerbation of patients with 2019 novel coronavirus: A meta-analysis. *International Journal of Medical Sciences*, *17*(12), 1744–1750. https://doi.org/http://dx.doi.org/10.7150/ijms.47052

Appendix A

Table 1. SUMMARY OF CHANGES TABLE

Document	*Protocol Version Number*	*Date*	*Authorisation*
Amendment No. 1			
Amendment No. 2			
Amendment No. 3			
Current Protocol			
Original	1.01		

Table 2. AMENDMENT RATIONALE

Section Number/Heading	***Description of Amendment***	***Rationale Summary***
Section Number/Heading	***Description of Amendment***	***Rationale Summary***

Appendix B
PICOS

Patient/Population	Exposure	Comparison	Outcome
Adults	**COVID19 diagnosis**	**Where applicable**	**Fatigue**
Patients Survivors Outpatients Inpatients	SARS-CoV-2 COVID-19 n-CoV-2 2019-nCoV2 Coronavirus Socio-demographics COVID-19 severity ICU admission Ventilation status Anxiety symptoms Depressive symptoms PTSD symptoms Stress/distress Sleep Quality of life	Healthy controls Non-treatment Treatment as usual	Fatigue Vitality Low energy Chronic fatigue Tiredness Exhaustion Asthenia General fatigue Lethargy

	Physical functioning BMI Clinical factors (lung function, serology, CT scans) Comorbidities		

Appendix C
Example Search Strategy

	Database	Search
	PSYCINFO	
1		("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").mp
2		exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp.
3		(COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp.
4		(covid19 or covid-19 or covid*).mp.
5		1 OR 2 OR 3 OR 4
6		chronic fatigue*. mp
7		(fatigue or tired*).mp [mesh word]. or exhaust*.tw.
8		((((quality adj2 life) or QoL or health related quality) adj2 life) or HRQoL).tw.
9		6 OR 7 OR 8
10		(5 and 9) not cancer not child* not adolescent* not vaccin* not burnout not HIV Limit 10 to up="20190101-2021"

Supplementary File 2. Full search protocols

APA PSYCINFO

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").mp.659
2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 9867
3 "chronic fatigue*".mp. 3079
4 (fatigue or tired*).mp [mesh word]. or exhaust*.tw. 47997
5 ((((quality adj2 life) or QoL or health related quality) adj2 life) or HRQoL).tw. 80465
6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 14627
7 (covid19 or covid-19 or covid*).mp. 14685
8 1 or 2 or 6 or 7 15226
9 3 or 4 or 5 124345
10 (8 and 9) not cancer not child* not adolescent* not vaccin* not burnout not HIV 386
11 limit 10 to up="20190101-20211231" 314

MEDLINE(R) ALL

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").ab. 28273
2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 133179
3 "chronic fatigue*".mp. 7798
4 (fatigue or tired*).mp. 128687
5 ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).ab. 53118
6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 237888
7 (covid19 or covid-19 or covid*).mp. 230830
8 1 or 2 or 6 or 7 252264
9 3 or 4 or ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).mp. 182154
10 (8 and 9) not cancer not vaccin* not child* not adolescent* not burnout not HIV.mp. 4117
11 limit 10 to yr="2019-2021" 3304

EMBASE CLASSIC+EMBASE

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").ab.28257

2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 83683

3 "chronic fatigue*".mp. 13417

4 (fatigue or tired*).mp. 317550

5 ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).ab. 78429

6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 242298

7 (covid19 or covid-19 or covid*).mp. 233333

8 1 or 2 or 6 or 7 269814

9 3 or 4 or ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).mp. 394392

10 (8 and 9) not cancer not vaccin* not child* not adolescent* not burnout not HIV.mp. 7449

11 limit 10 to yr="2019-2021" 6372

CINAHL

1 MH coronavirus infections or corona virus or corona* 10,982

2 AB severe acute respiratory syndrome coronavirus 3,719

3 MH severe acute respiratory syndrome 556

4 MH covid-19 or Covid19 or SARS-CoV* or SARS-CoV-2 or SARSCoV2 or SARSCOV-2 or covid19 or covid* 50,545

5 AB ncov-2019 or nCoV-2 or 2019-nCoV* or nCoV2 8,774

6 AB nCov-2019 or nCoV-2 or 2019-nCov* or ncov2 8,570

7 MH fatigue or AB (fatigue or exhaustion or tiredness) or AB (health related quality of life or hrqol) 17,446

8 1 or 2 or 3 or 4 or 5 or 6 not HIV not child* not adolescent* not vaccin* not burnout 64,543

9 7 and 8 Limiters – published date: 20190101-20211231, English language 620

MEDRXIV & BIORXIV

For term "COVID-19 or SARS-CoV-2 or coronavirus AND fatigue or tired" and posted between "01 Jan, 2019 and 21 Dec, 2021"

Returned 2,172 results

COCHRANE LIBRARY

Title abstract keyword COVID-19 or covid19 or or covid-19 or covid* or "corona virus" or "coronavirus infection" or "SARS CoV-2" or "SARS-CoV-2" or "SARS-CoV*" or "SARSCOV2" or "SARSCOV-2" or "nCoV-2" or "2019-nCoV*" or nCoV2" or *keyword* "severe acute respiratory syndrome coronavirus" AND fatigue or "chronic fatigue" or tired* or exhaust* or "health related quality adj1 life" or HRQoL

Selected Facets: 2019-2021 (Publication date)

Returned 89 Cochrane Reviews

OPEN GREY

"COVID-19"

Returned 1,391 results

Supplementary file 3. Summary of systematic reviews

Author	Title	Study Design	Included Articles N.	Follow-up Time	Fatigue Prevalence & Associations	*p*
Aiyegbusi et al. (2021)	Symptoms, complications and management of long COVID: a review	Systematic review & Meta-analysis	24	1 month	47% (CI 31–63) 16 studies	
Badenoch et al. (2021)	Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis	Systematic review & Meta-analysis	51	Mean 77 days (Range 14-182)	24·4% (CI 17·5-32.9)	
Cabera Martimbianco et al. (2021)	Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review	Narrative systematic review	25	Post-infection or discharge	-	
Cares-Marambio et al. (2021)	Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review	Systematic review & Meta-analysis	9	Post-discharge	52% (CI 0.38–0.66)	
Cha & Baek et al. (2021)	Symptoms and management of long COVID: A scoping review	Scoping review	34	> 4 weeks	-	
Chen et al. (2021)	Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review	Systematic review & Meta-analysis	40	> 28 days	**Total (22 studies)** 23 (CI 0.13-0.38) **Hospitalised (8 studies)** 26 (CI 0.17-0.38)	
Domingo et al. (2021)	Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review	Living systematic review & Meta-analysis	36	4-12 weeks ≥ 12 weeks	**4-12 weeks** 51%, (CI: 39-64) **≥ 12 weeks** 47%, (CI: 27-68)	
Falk et al. (2021)	Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review	Narrative systematic review	339	1-4 months post discharge	-	
Fernandez-de-Las-Penas et al. (2021)	Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis	Systematic review & Meta-analysis	33	30, 60, 90 days post-virus	**30 days** 11.7% (CI 3.1-35.3) **60 days** 56.2% (CI 28.3-80.7) **≥ 90 days** 35.3% (CI 25.3-46.8)	
Garg et al. (2021)	The Conundrum of 'Long-COVID-19': A Narrative Review	Systematic Review	212	-	-	
Gavriatopoulou et al. (2021)	Epidemiology and organ specific sequelae of post-acute COVID 19: A narrative review	Narrative Systematic review	12	> 4 weeks	-	

Author	Title	Study Design	Included Articles N.	Follow-up time	Fatigue Prevalence & Associations	*p*
Hoshijima et al. (2021)	Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis	Systematic review & Meta-analysis (RAPID)	35	1 month	45% (32-59%)	
Jennings et al. (2021)	A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: Ongoing symptomatic phase vs. post-COVID-19 syndrome	Systematic review & Meta-analysis	39	> 4 weeks	**Symptoms (16 studies)** 44% (CI 10-71) **Ongoing Symptoms (19 studies** 43% (CI 5-83)	
Long et al. (2021)	Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis	Systematic review & Meta-analysis	16	> 1 month Post-discharge	47%	
Malik et al. (2021)	Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis	Systematic review & Meta-analysis	22	Post-Covid	**Pooled Total** 64% **Quality of life** OR 1.06	.001
Nasserie et al. (2021)	Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review	Systematic review	45	2 months	Median 39.8% (IQR, 31.4-59.0%) 25 studies	
Poudel et al. (2021)	Impact of Covid-19 on health-related quality of life of patients: A structured review	Rapid review	12	> 4 weeks post-discharge	-	
Rao et al. (2021)	Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; a systematic review and meta-analysis	Systematic review & Meta-analysis	41	1-6 months Post-infection	**1-2 months** 52.7% ER 0.517 **2-3 months** 47.8% ER 0.527 **Female Gender** OR 1.782	
Rogers et al. (2020)	Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: A systematic review and meta-analysis with comparison to the COVID-19 pandemic	Meta-analysis	4	Post-illness	61 (19.3%)	
Sanchez-Ramirez et al. (2021)	Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis	Systematic review & Meta-analysis	24	4 months	38% 15 articles	
Shanbehzadeh et al. (2021)	Physical and mental health complications post-Covid-19: Scoping review	Scoping Systematic Review	34	3 months	-	

Author	Title	Study Design	Included Articles N.	Follow-up time	Fatigue Prevalence & Associations	*p*
Wong et al. (2021)	Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology	Narrative systematic review	21	> 1 month	-	

Supplementary file 4. CASP quality assessments for all study designs

Cohort & cross-sectional

Study	Did the study address a clearly focused issue?	Was the cohort recruited in acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have authors taken account of confounding factors in the design and/or analysis?	Was the follow up of participants complete enough?	Was the follow-up of participants long enough?	Are results precise?	Can the results be applied to the local population?	Do the results fit with other available evidence?	Are results relevant for clinical practice?	Grade
Albu et al. 2021	Y	?	Y	Y	N	N	-	Y	?	?	Y	?	3
Amin-Chowdhury et al. 2021	Y	Y	Y	N	Y	Y	?	Y	y	y	Y	Y	2
Anaya et al. 2021	Y	Y	Y	N	N	?	-	Y	?	Y	Y	?	3
Andrade Barreto et al. 2021	Y	Y	Y	N	?	?	-	Y	Y	Y	Y	Y	2
Aparisi et al. 2021	Y	Y	N	Y	N	?	Y	Y	Y	Y	Y	Y	2
Aranda et al. 2021	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Arnold et al. 2020	Y	?	Y	Y	N	N	?	Y	Y	Y	Y	Y	2
Asadi-Pooya et al. 2021	Y	Y	Y	N	Y	Y	-	Y	?	Y	Y	?	2
Augustin et al. 2021	Y	?	Y	N	?	N	N	Y	Y	Y	Y	Y	2
Aul et al. 2021	Y	Y	Y	Y	Y	Y	-	?	Y	Y	Y	Y	2
Aydin et al. 2021	Y	Y	Y	N	N	N	Y	Y	?	Y	Y	?	2
Bai et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	?	Y	Y	N	2
Bardakci et al 2021	Y	Y	Y	Y	N	N	Y	Y	?	Y	Y	Y	2
Barizien et al. 2021	Y	Y	Y	Y	?	?	Y	Y	?	Y	Y	Y	2
Becker et al. 2021	Y	?	Y	N	Y	Y	N	Y	Y	Y	Y	N	3
Bek et al. 2021	Y	Y	Y	Y	?	?	Y	Y	Y	Y	Y	?	2
Bottemanne et al. 2021	Y	Y	?	N	Y	Y	Y	Y	Y	Y	Y	?	2
Chen, Li et al. 2020	Y	Y	Y	Y	?	Y	-	Y	Y	?	N	?	2
Bell et al. 2021	Y	Y	Y	N	?	Y	N	Y	Y	Y	Y	Y	2
Bliddal et al. 2021	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	?	2
Boari et al. 2021	Y	Y	Y	N	?	?	Y	Y	Y	Y	Y	Y	2
Boesl et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	Y	2
Boscolo-Rizzo et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Bozzetti et al. 2021	Y	Y	Y	N	N	N	N	Y	?	Y	Y	Y	2
Cao et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1
Carfi et al. 2020	?	Y	N	?	N	N	Y	Y	?	Y	Y	Y	3
Carvalho-Schneider et al. 2021	Y	Y	Y	N	?	N	Y	Y	Y	Y	Y	Y	2
Catalan et al. 2021	Y	Y	Y	Y	?	?	Y	Y	Y	Y	?	?	2
Chen et al. 2020	Y	Y	Y	Y	Y	Y	?	Y	?	Y	N	?	2
Chopra et al. 2021	Y	Y	Y	N	?	Y	Y	Y	Y	Y	Y	Y	2
Clavario et al. 2020	Y	Y	Y	N	Y	Y	Y	Y	?	Y	Y	?	2
Creamer et al. 2021	Y	Y	Y	?	N	N	?	Y	Y	Y	Y	N	2
Daher et al. 2020	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	?	2
Dalbosco-Salas et al. 2021	Y	Y	Y	?	Y	Y	Y	Y	Y	?	?	Y	2
Danesh et al. 2021	Y	?	Y	N	?	?	-	Y	?	Y	Y	Y	3
Darley et al. 2021	Y	Y	Y	Y	?	Y	Y	Y	N	Y	Y	Y	2
Daugherty et al. 2021	Y	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	1
Daynes et al. 2021	Y	?	?	Y	N	N	Y	Y	Y	?	Y	?	2
D'Cruz et al. 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	2
Dennis et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1
Desgranges et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	?	2
Dini et al. 2021	Y	Y	Y	N	?	?	-	Y	?	Y	Y	Y	2

Study	Did the study address a clearly focused issue?	Was the cohort recruited in acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have authors taken account of confounding factors in the design and/or analysis?	Was the follow up of participants complete enough?	Was the follow-up of participants long enough?	Are results precise?	Can the results be applied to the local population?	Do the results fit with other available evidence?	Are results relevant for clinical practice?	Grade
Donaghy et al. 2021	Y	Y	Y	Y	N	N	Y	Y	?	?	?	N	3
Eloy et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Evans et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1
Fang et al. 2021	Y	?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	2
Fatima et al. 2021	Y	Y	Y	N	N	N	Y	Y	?	Y	Y	?	3
Fernandez-de-Las-Penas et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1
Ferraro et al. 2020	Y	?	Y	Y	N	N	Y	?	Y	?	N	N	3
Fortini et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	?	Y	Y	Y	2
Froidure et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	2
Frontera et al. 2021	Y	Y	Y	?	?	Y	Y	Y	Y	Y	Y	Y	2
Gamberini et al. 2021	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	Y	N	2
Ganesh et al. 2021	Y	Y	Y	Y	?	N	-	Y	?	Y	Y	Y	2
Garcia-Abellan et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Garrigues et al. 2020	Y	Y	Y	N	N	N	-	Y	Y	Y	Y	Y	2
Gautam et al. 2021	Y	Y	Y	N	N	N	Y	Y	?	Y	Y	Y	2
Gebhard et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	?	2
Goertz et al. 2019	Y	Y	Y	N	Y	Y	Y	Y	?	Y	N	y	3
Gonzalez-Hermosillo et al. 2021	Y	Y	Y	N	?	Y	Y	Y	Y	Y	Y	Y	2
Graham et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y	?	2
Guo et al. 2020	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	?	2
Gupta et al. 2021	Y	Y	Y	N	N	N	Y	Y	?	Y	Y	Y	2
Halpin et al. 2020	Y	Y	Y	N	N	N	-	Y	Y	Y	Y	Y	2
Heightman et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	2
Hellemons et al. 2021	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	2
Henneghan et al. 2021	Y	Y	Y	Y	N	N	-	-	Y	Y	Y	Y	2
Hossain et al. 2021	Y	Y	Y	N	Y	Y	N	Y	?	Y	Y	Y	2
Horwitz et al. 2021	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Y	Y	2
Iqbal et al. 2021	Y	Y	Y	N	?	N	-	Y	?	Y	Y	Y	2
Jacobs et al. 2020	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	2
Kanberg et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	?	Y	Y	Y	2
Karaarslan et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Kashif et al. 2021	Y	Y	Y	N	?	N	Y	Y	?	?	Y	Y	2
Kayaaslan et al. 2021	Y	Y	Y	N	Y	Y	?	Y	?	Y	Y	?	2
Kedor et al. 2021	Y	?	Y	Y	N	N	Y	Y	Y	?	Y	?	3
Khalaf et al. 2021	Y	?	Y	N	?	Y	-	Y	?	Y	Y	Y	2
Kozak et al. 2021	Y	Y	Y	N	Y	N	-	Y	Y	Y	Y	Y	2
Labarca et al. 2021	Y	Y	Y	Y	Y	Y	-	Y	Y	Y	Y	Y	2
Latronico et al. 2021	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	?	2
Lemhofer et al. 2021	Y	Y	Y	Y	N	N	-	Y	?	Y	Y	?	2
Leth et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	?	Y	Y	Y	2
Liang et al. 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	?	2
Lindahl et al. 2021	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	2
Liu, Wu et al. 2021	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Y	2
Liu, Lee et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Liyanage-Don et al. 2021	Y	Y	?	N	Y	Y	-	Y	Y	Y	Y	Y	3

Study	Did the study address a clearly focused issue?	Was the cohort recruited in acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have authors taken account of confounding factors in the design and/or analysis?	Was the follow up of participants complete enough?	Was the follow-up of participants long enough?	Are results precise?	Can the results be applied to the local population?	Do the results fit with other available evidence?	Are results relevant for clinical practice?	Grade
Logue et al. 2021	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	?	2
Lombardo et al. 2021	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	2
Maamar et al. 2021	Y	Y	Y	Y	Y	Y	-	?	Y	Y	Y	?	2
Mahmud et al. 2021	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	?	2
Mancini et al. 2021	Y	Y	Y	Y	?	?	Y	Y	?	Y	Y	Y	2
Mandal et al. 2020	Y	Y	Y	N	N	N	-	Y	Y	Y	Y	Y	2
Mantovani et al. 2021	Y	Y	Y	Y	N	N	N	Y	?	Y	?	?	2
Mazza et al. 2021	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	2
Menges et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1
Mirfazeli et al. 2021	Y	Y	Y	N	Y	Y	N	Y	?	Y	Y	?	2
Miyazato et al. 2020	Y	Y	Y	N	N	N	-	?	Y	Y	N	N	3
Molnar et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	?	2
Moradian et al. 2020	Y	Y	Y	N	Y	Y	-	?	?	Y	Y	?	2
Moreno-Perez et al. 2021	Y	Y	Y	N	?	Y	Y	Y	Y	Y	Y	?	2
Morin et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	?	2
Munblit et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	?	2
Naik et al. 2021	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	?	3
Nehme et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Novak et al. 2021	Y	?	Y	Y	Y	?	-	Y	Y	Y	Y	Y	2
Nune et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	2
O'Keefe et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Pauley et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	1
Peghin et al. 2021	Y	Y	Y	N	?	?	Y	Y	Y	Y	Y	?	2
Pérez-González et al. 2021	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	?	3
Pilotto et al. 2021	Y	?	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	2
Poyraz et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	?	2
Qin et al. 2021	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	?	2
Raman et al. 2020	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	Y	2
Rass et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	2
Rauch et al. 2021	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	?	2
Righi et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Romero-Duarte et al. 2021	Y	Y	Y	N	Y	Y	-	Y	?	Y	Y	?	2
Rosales- Castillo et al. 2021	Y	?	Y	Y	N	N	-	Y	?	Y	Y	?	3
Sami et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Sathyamurthy et al. 2021	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	2
Savarraj et al. 2021	Y	Y	Y	Y	N	N	?	?	?	N	Y	?	3
Schandl et al. 2021	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	?	2
Scherlinger et al. 2021	Y	Y	Y	Y	N	N	Y	Y	?	Y	Y	?	2
Seeßle et al. 2021	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	2
Senjam et al. 2021	Y	Y	Y	N	?	Y	N	Y	?	Y	Y	Y	2
Shang et al. 2021	Y	?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Shendy et al. 2021	Y	?	Y	Y	N	N	Y	Y	Y	Y	Y	Y	3
Shoucri et al. 2021	Y	Y	Y	N	N	N	-	Y	Y	Y	N	N	2
Sigfrid et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	1
Silva et al. 2021	Y	Y	Y	Y	?	Y	-	?	?	Y	Y	?	2
Smet et al. 2021	Y	?	Y	N	N	N	Y	Y	Y	Y	Y	Y	3

Study	Did the study address a clearly focused issue?	Was the cohort recruited in acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have authors taken account of confounding factors in the design and/or analysis?	Was the follow up of participants complete enough?	Was the follow-up of participants long enough?	Are results precise?	Can the results be applied to the local population?	Do the results fit with other available evidence?	Are results relevant for clinical practice?	Grade
Soraas et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	?	2
Staudt et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Stavem et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	2
Steinbeis et al. 2022	Y	Y	Y	N	Y	Y	Y	Y	?	Y	Y	Y	2
Strumiliene et al. 2021	Y	Y	Y	?	N	N	?	Y	Y	Y	Y	Y	2
Suarez-Robles 2020	Y	Y	Y	N	N	N	-	Y	?	Y	Y	Y	2
Sultana et al. 2021	Y	Y	Y	N	Y	Y	-	Y	Y	?	?	N	3
Sun et al. 2021	Y	Y	Y	N	Y	Y	-	Y	Y	Y	Y	Y	2
Sykes et al. 2021	Y	Y	Y	N	?	Y	-	Y	?	Y	Y	Y	3
Szekely et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Taboada et al. 2021	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	2
Taylor et al. 2021	Y	Y	?	N	N	N	?	Y	Y	Y	Y	Y	2
Tessitore et al. 2021	Y	Y	Y	Y	?	n	Y	Y	?	Y	Y	Y	2
Tleyjeh et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Tiwari et al. 2021	Y	Y	Y	N	N	N	-	Y	?	Y	Y	Y	3
Tomasoni et al. 2021	Y	Y	Y	N	Y	Y	-	Y	Y	Y	Y	Y	2
Tosato et al. 2021	Y	Y	?	N	Y	Y	Y	Y	Y	N	Y	Y	2
Townsend et al. 2020	Y	Y	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	2
Valent et al. 2020	Y	Y	?	Y	N	N	-	Y	Y	y	Y	y	2
van den Borst et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Y	?	Y	Y	2
Vanichkachorn et al. 2021	Y	?	Y	?	N	N	Y	Y	Y	Y	Y	?	3
van der Sar-van der Brugge et al. 2021	Y	Y	Y	Y	N	N	?	Y	Y	Y	Y	Y	2
van Veenendaal et al. 2021	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	2
Varghese et al. 2021	Y	Y	Y	N	N	N	Y	Y	?	Y	Y	Y	2
Venturelli et al. 2021	Y	Y	Y	Y	N	N	-	Y	Y	Y	Y	Y	2
Voruz et al. 2021	Y	Y	Y	Y	Y	Y	-	Y	Y	?	Y	?	2
Wang et al. 2021	Y	?	Y	?	N	N	?	Y	Y	Y	Y	N	3
Weerahandi et al. 2020	Y	Y	Y	N	N	N	Y	?	Y	Y	Y	?	3
Wong-Chew et al. 2022	Y	Y	Y	N	?	Y	N	Y	Y	Y	Y	Y	2
Wu et al. 2021	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	3
Yildirim et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	?	2
Yomogida et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Zayat et al. 2021	Y	Y	Y	N	N	N	-	Y	Y	?	Y	Y	2
Zhang et al. 2021	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	2
Zhao et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Y	?	Y	Y	2
Zulu et al. 2021	Y	Y	Y	N	Y	Y	-	Y	Y	?	Y	?	2

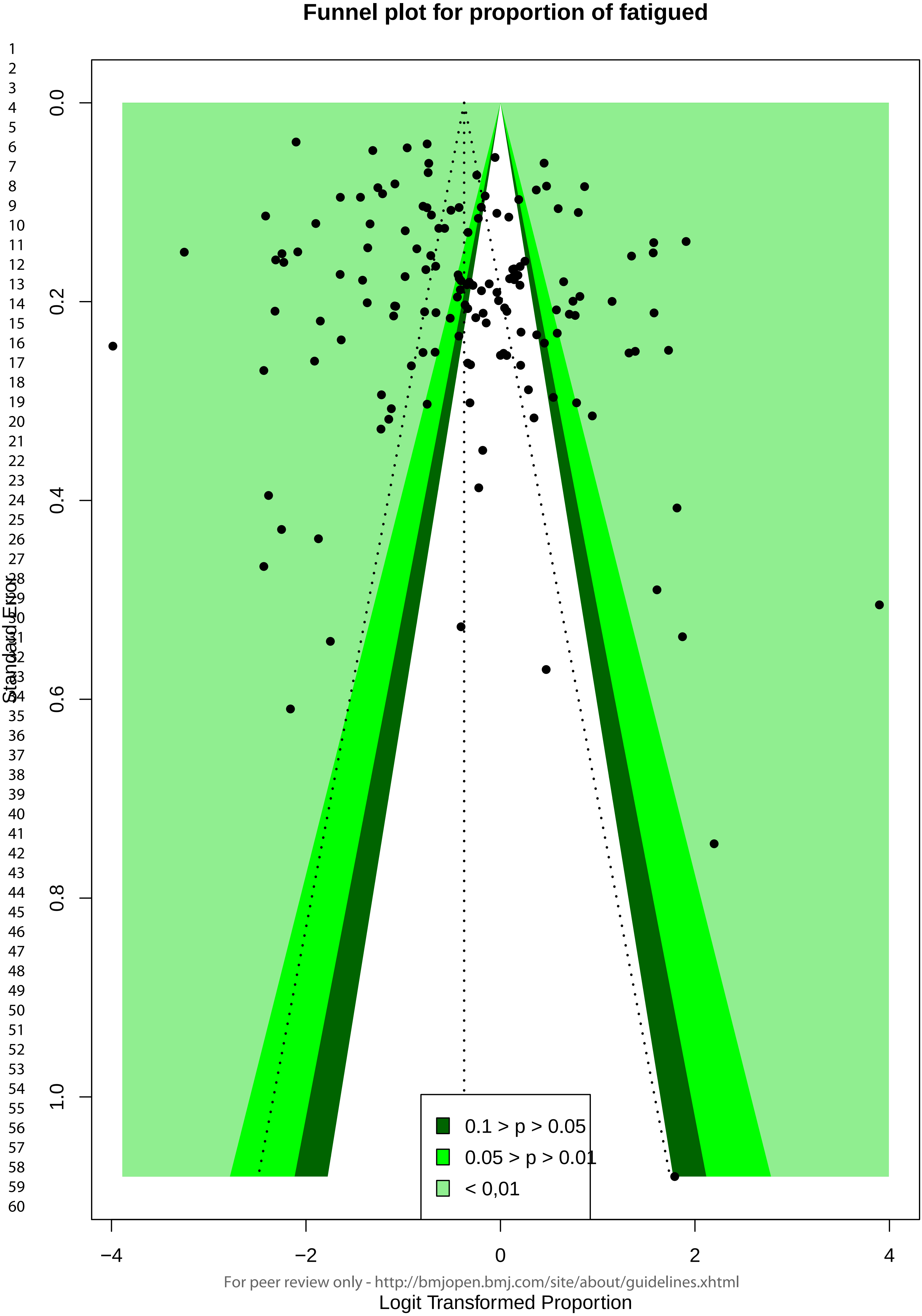
Case-control studies

Study	Did the study address a clearly focused question?	Was the method appropriate to answer the question?	Were the cases recruited in an acceptable way?	Were controls selected in an acceptable way?	Was the exposure measured to minimise bias?	Were the groups treated equally?	Were potential confounding factors taken account of in the design/analysis?	Are the results credible?	Can the results be applied to the local population?	Do the results fit with existing evidence?	Grade

Agergaard et al. 2021	Y	Y	Y	?	N	Y	Y	Y	Y	Y	2
Castro et al. 2021	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	3
Elanwar et al. 2021	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	2
Elkan et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	2
Noviello et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	2
Ortelli et al. 2021	Y	Y	Y	?	Y	Y	N	Y	Y	?	2
Sollini et al. 2021	Y	Y	?	Y	Y	Y	N	Y	Y	N	3
Zhou et al. 2021	Y	Y	Y	?	Y	Y	N	Y	Y	?	3

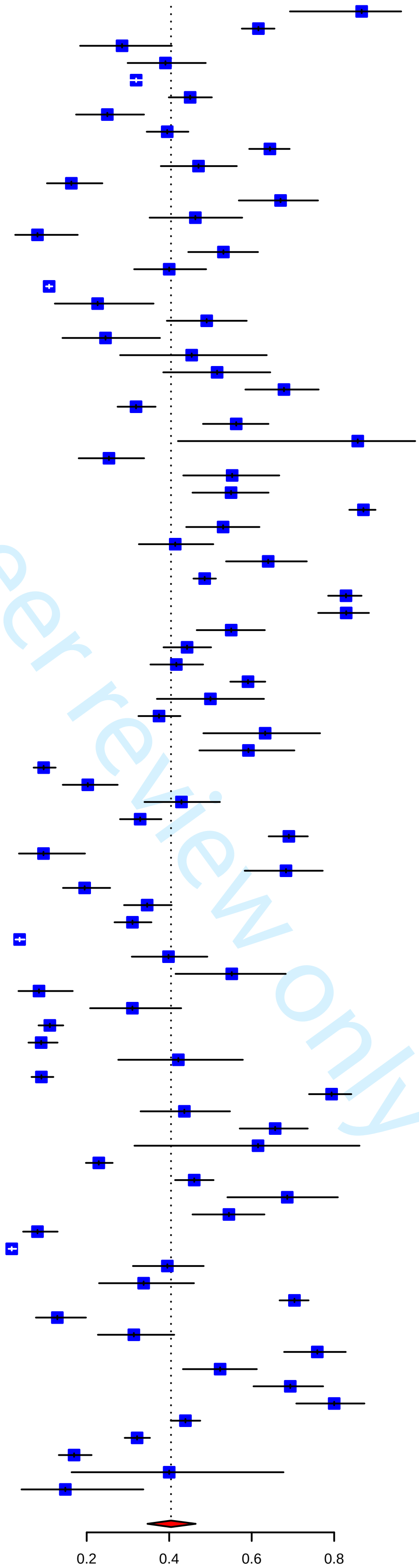
Randomised Controlled Trials

Study	Did the study address a clearly focused research question?	Was the assignment of participants to interventions randomised?	Were all participants who entered the study accounted for at its conclusion?	Were the participants, investigators &assessors 'blind' to the intervention ?	Were the study groups similar at the start of the randomised controlled trial?	Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	Were the effects of intervention reported comprehensively?	Was the precision of the estimate of the intervention or treatment effect reported?	Do the benefits of the experimental intervention outweigh the harms/costs?	Can the results be applied to your local population/in your context?	Would the experimental intervention provide greater value to people in your care than any existing interventions?	QA
Chen et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	2
Chudzik et al. 2021	Y	Y	?	?	Y	Y	Y	N	?	?	?	3
Liu et al. 2020	Y	Y	Y	N	Y	Y	Y	Y	?	Y	?	2

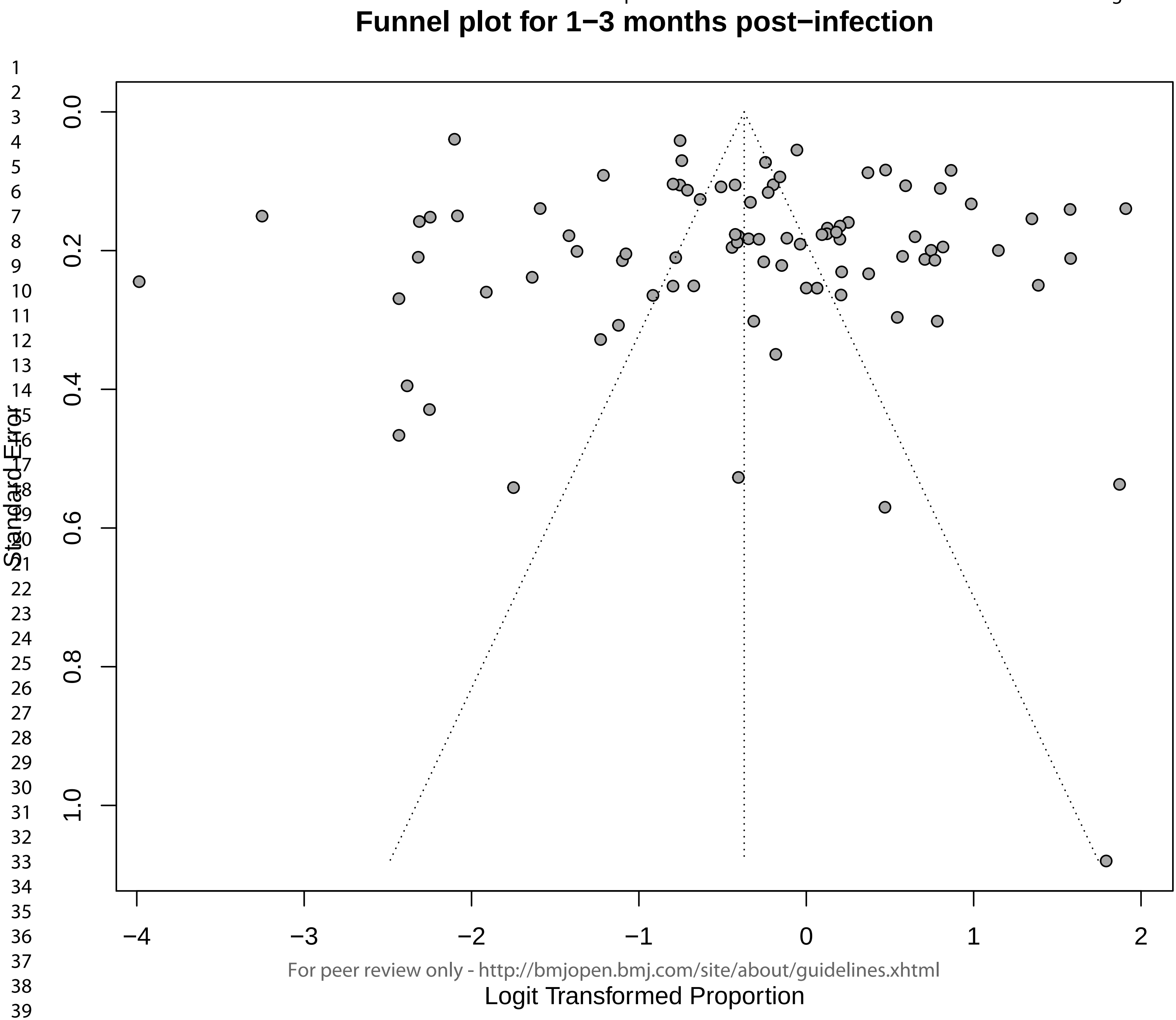

Funnel plot for proportion of fatigued
Standard Error
0.0
0.2
0.4
0.6
0.8
1.0
−4
−2
0
2
4
Logit Transformed Proportion
0.1 > p > 0.05
0.05 > p > 0.01
< 0,01

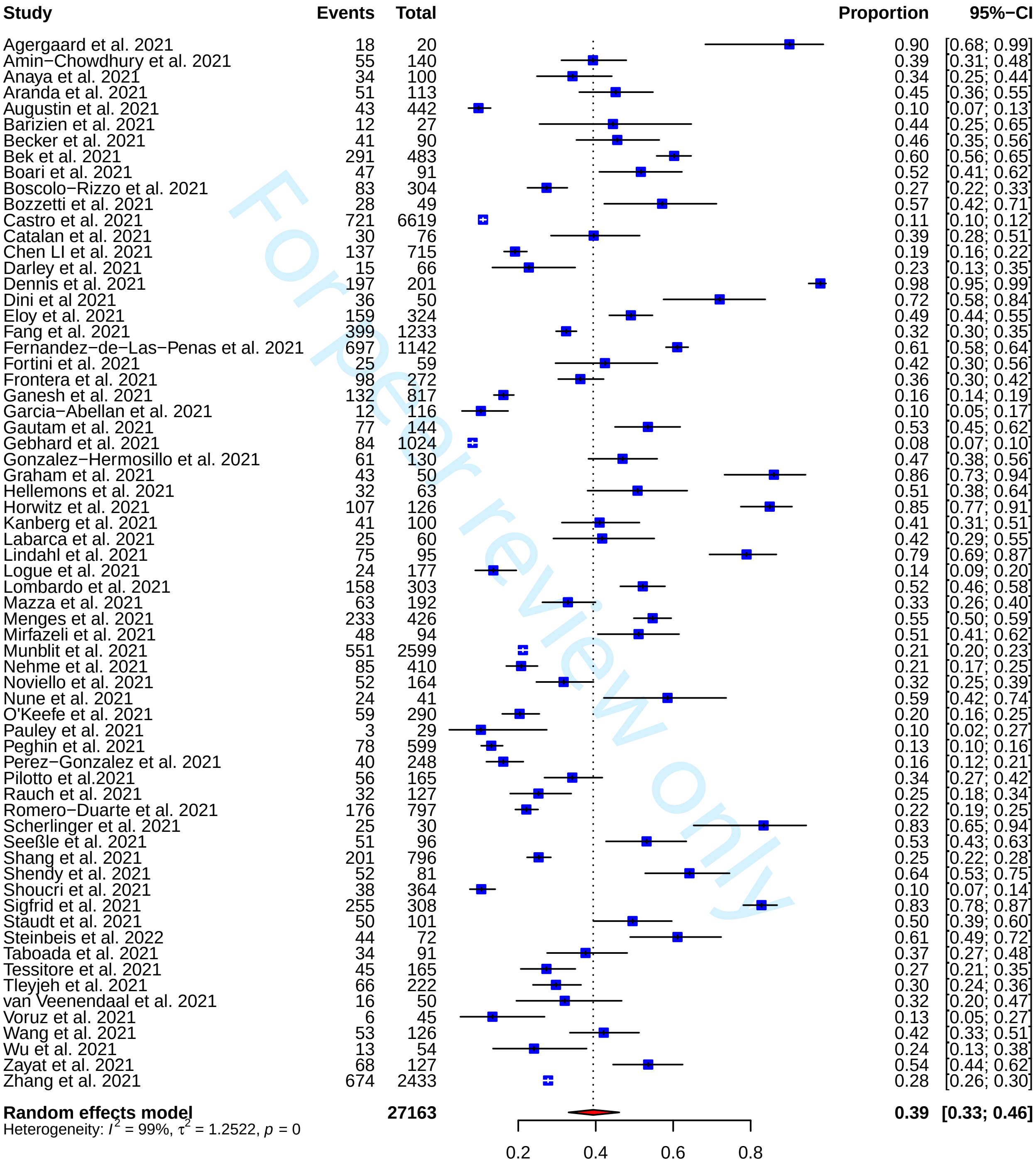
Study	Events	Total	Proportion	95%−CI
Albu et al. 2021	26	30	0.87	[0.69; 0.96]
Andrade Barreto et al. 2021	371	602	0.62	[0.58; 0.66]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi−Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Bek et al. 2021	248	385	0.64	[0.59; 0.69]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boesi et al. 2021	67	100	0.67	[0.57; 0.76]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carfi et al. 2020	76	143	0.53	[0.45; 0.62]
Carvalho−Schneider et al 2021	52	130	0.40	[0.32; 0.49]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Creamer et al. 2021	14	57	0.25	[0.14; 0.38]
Daher et al. 2020	15	33	0.45	[0.28; 0.64]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
D'Cruz et al. 2020	78	115	0.68	[0.58; 0.76]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Fatima et al. 2021	90	160	0.56	[0.48; 0.64]
Ferraro et al. 2020	6	7	0.86	[0.42; 1.00]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Garcia−Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Garrigues et al. 2020	66	120	0.55	[0.46; 0.64]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez−Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Heightman et al. 2021	644	1325	0.49	[0.46; 0.51]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Jacobs et al. 2021	82	149	0.55	[0.47; 0.63]
Karaarslan et al. 2021	133	300	0.44	[0.39; 0.50]
Kashif et al. 2021	101	242	0.42	[0.35; 0.48]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Liyanage−Don et al. 2021	31	153	0.20	[0.14; 0.28]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Miyazato et al. 2020	6	63	0.10	[0.04; 0.20]
Molnar et al. 2021	69	101	0.68	[0.58; 0.77]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno−Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Morin et al. 2021	134	431	0.31	[0.27; 0.36]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Raman et al. 2020	32	58	0.55	[0.42; 0.68]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Rosales−Castillo et a. 2021	23	74	0.31	[0.21; 0.43]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Sathyamurthy et al. 2021	25	279	0.09	[0.06; 0.13]
Savarraj et al. 2021	19	45	0.42	[0.28; 0.58]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Senjam et al. 2021	204	257	0.79	[0.74; 0.84]
Silva et al. 2021	38	87	0.44	[0.33; 0.55]
Smet et al. 2021	90	137	0.66	[0.57; 0.74]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Stavem et al. 2021	211	458	0.46	[0.41; 0.51]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez−Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sun et al. 2021	17	932	0.02	[0.01; 0.03]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Szekely et al. 2021	24	71	0.34	[0.23; 0.46]
Taylor et al. 2021	475	675	0.70	[0.67; 0.74]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
van den Borst et al. 2021	86	124	0.69	[0.60; 0.77]
Vanichkachorn et al. 2021	80	100	0.80	[0.71; 0.87]
Venturelli et al. 2021	337	767	0.44	[0.40; 0.48]
Wong−Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Zulu et al. 2020	4	27	0.15	[0.04; 0.34]
Random effects model		**29947**	**0.40**	**[0.35; 0.46]**

Heterogeneity: $I^2 = 99\%$, $\tau^2 = 1.2882$, $p = 0$



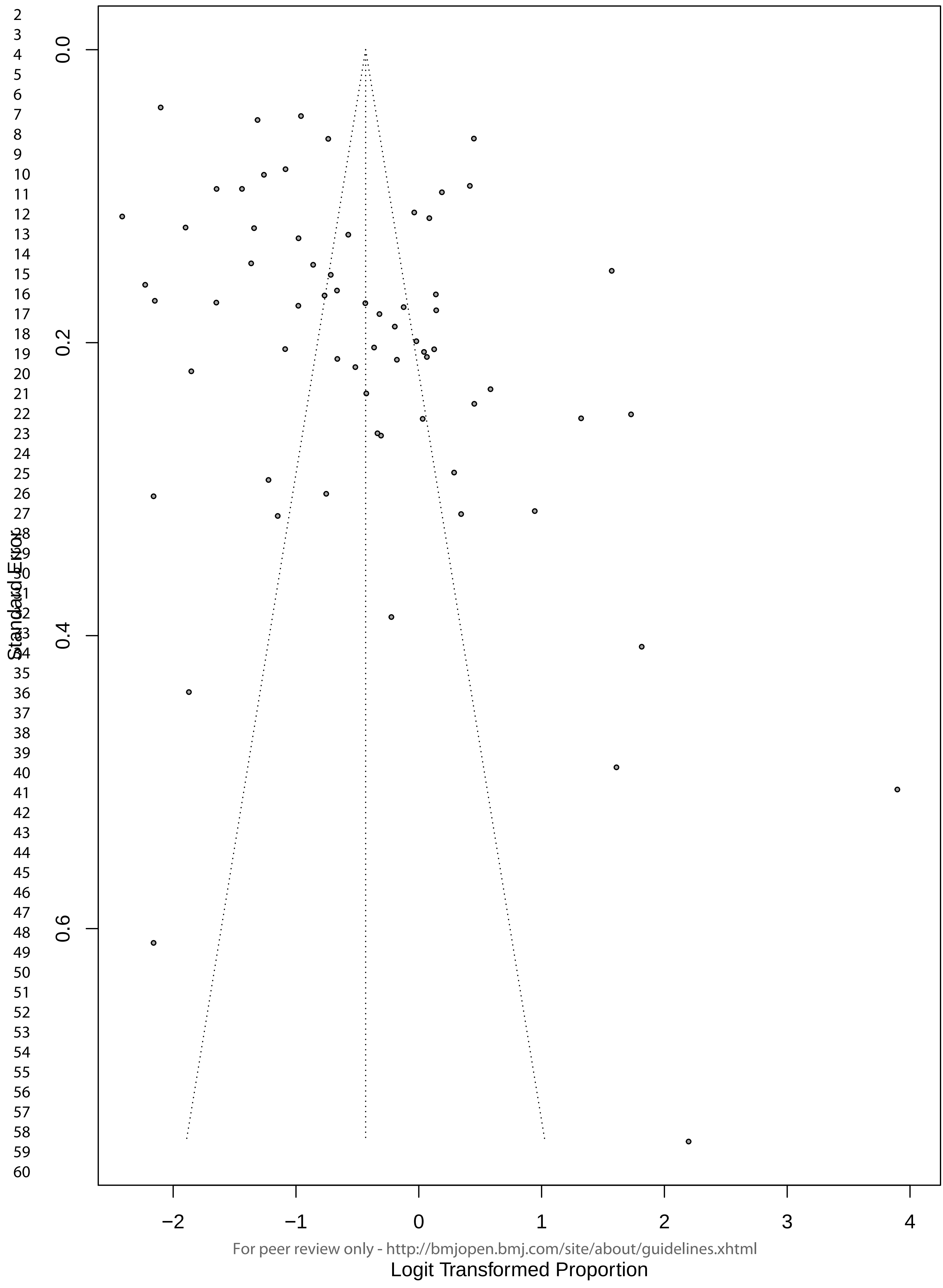
Forest plot 1−3 months fatigue proportion

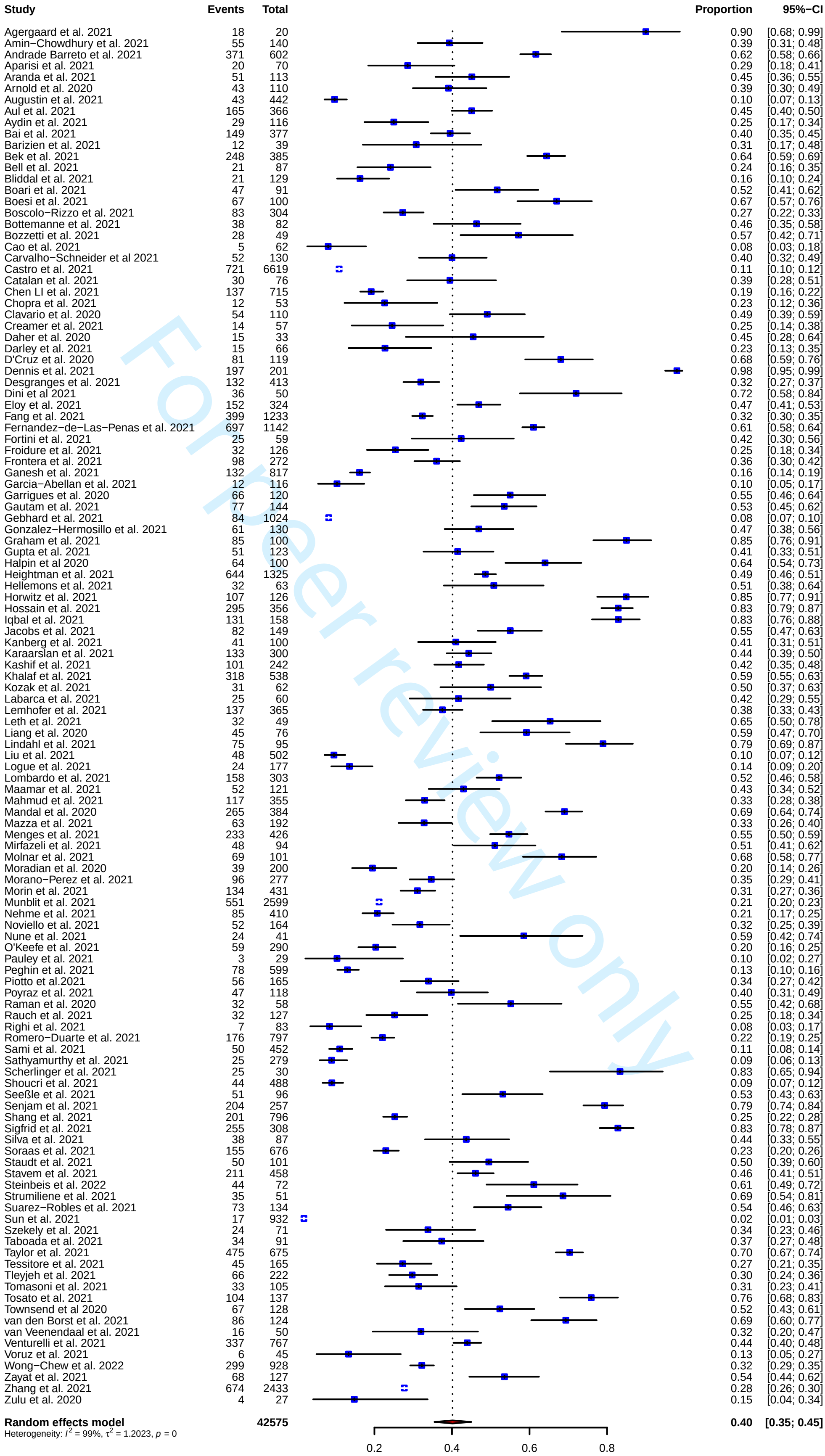

Funnel plot for 1−3 months post−infection
Standard Error
0.0
0.2
0.4
0.6
0.8
1.0
−4
−3
−2
−1
0
1
2
Logit Transformed Proportion



Forest plot for > 3 months fatigue proportion

Funnel plot for >3 months fatigue proportion





Forest plot for sensitivity analysis

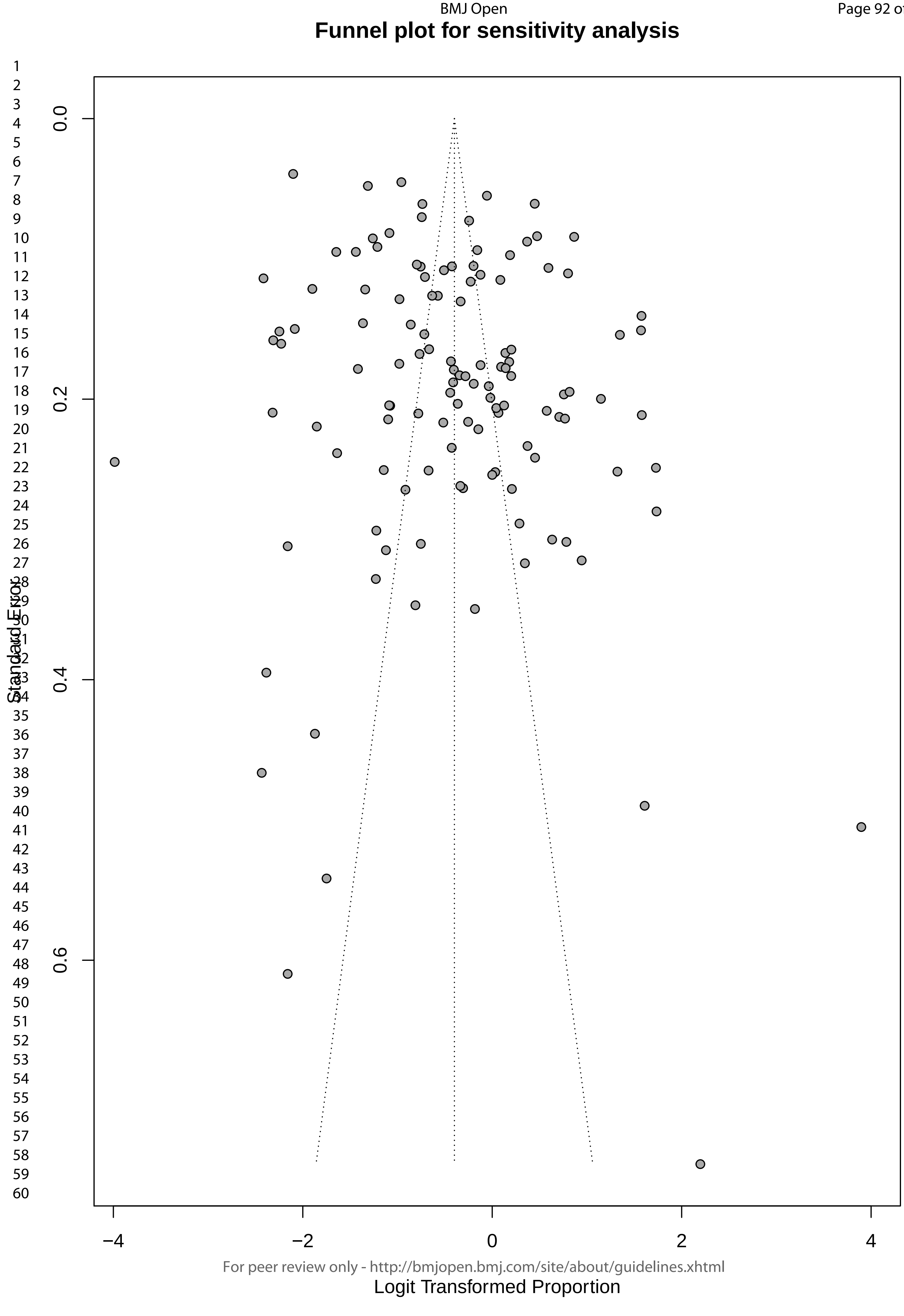

Funnel plot for sensitivity analysis
Standard Error
0.0
0.2
0.4
0.6
−4
−2
0
2
4
Logit Transformed Proportion

Table of reported risk factors for fatigue

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Agergaard et al. (2021) Denmark	Outpatients	Case-control	20	77-255 days	Questionnaire	Myopathy	11 (100)	
						No myopathy	3 (33)	< .05
							RR 3.27	
Albu et al. (2021) Spain	Outpatients	Cross-sectional	30	≥ 3 months	MFIS	**ICU**		
						Overall Fatigue	13 (81.2)	
						Physical activities	80.55	*0.28*
						Cognitive activities	72.5	*0.28*
						Psychosocial activities	20	*0.40*
						No ICU		
						Overall Fatigue	13 (92.8)	
						Physical activities	81.9	
						Cognitive activities	73.75	
						Psychosocial activities	35	
						Depression		
						Physical fatigue	r = .490	*<.001*
						Cognitive fatigue	r = .490	*<.001*
						Social fatigue	r = .540	*<.001*
						Anxiety		
						Physical fatigue	r = .270	*NS*
						Cognitive fatigue	r = .270	*NS*
						Social fatigue	r = .340	*NS*
						Sleep quality		
						Physical fatigue	r = .640	*<.001*
						Cognitive fatigue	r = .640	*<.001*
						Social fatigue	r = .620	*<.001*
Amin-Chowdhury et al. (2021) UK	Survey	Prospective cohort	1,671	7 months	ADQ	**Gender (F)**	OR = 2.22	*<.001*
						Comorbidities	OR = 1.98	*<.001*
Anaya et al. (2021) Colombia	Survey	Case series	100	219 days	Questionnaire	**Disease severity**		
						Ambulatory	9 (25.7)	0.407
						Severe	15 (36.6)	
						Critical	10 (41.7)	
Andrade Barreto et al. (2021) Brazil	Outpatients	Cross-sectional	602	> 1 month	Questionnaire	**Mild disease**		
						Female	133 (73.5)	
						Male	33 (55.9)	*.011*
						Moderate disease		
						Female	59 (62.1)	
						Male	30 (41.1)	*.007*
						Severe disease		
						Female	53 (67.1)	*.086*
						Male	63 (54.8)	
						Quality of life (Total)	β = -8.28	*<.001*
Aparisi et al. (2021) Italy	Outpatients	Prospective cohort	70	3 months	Clinical assessment for symptom burden	**Persistent dyspnoea**	17 (41.5)	*0.005*
						Residual dyspnoea	3 (10.3)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Arnold et al. (2020) UK	Outpatients	Prospective cohort	110	8-12 weeks	ADQ	**Disease severity & excessive Fatigue**		
						Mild	7/27 (26%)	*NR*
						Moderate	26/65 (40%)	
						Severe	10/18 (56%)	
						Disease severity & vitality	**M (SD)**	
						Mild	43 (20)	
						Moderate	49 (22)	
						Severe	36 (24)	
Aul et al. (2021) UK	Survey	Cross-sectional	387	6 weeks	Questionnaire	**Age**		
						Fatigue	61 (49-72)	*0.12*
						No fatigue	64 (50-76)	
						Gender (M)		
						Fatigue	89 (42.8)	*0.40*
						No fatigue	119 (57.2)	
						BMI		
						Fatigue	26.5 (23.5-30)	*.035*
						No fatigue	28.9 (23.9-32.7)	
						ICU		
						Fatigue	49 (59)	*.003*
						No fatigue	34 (41)	
						Intubated		
						Fatigue	40 (67.8)	*<.001*
						No fatigue	19 (32.2)	
						Days intubated		
						Fatigue	22 (11-45)	*.097*
						No fatigue	17 (7-26)	
						Lymphocytes (10^9/L)		
						Fatigue	0.7 (0.5-1.0)	*0.64*
						No fatigue	0.7 (0.5-1.0)	
						Peak WBC (10^9/L)		
						Fatigue	10.1 (7.1-15.6)	*0.37*
						No fatigue	9.8 (7.2-13.7)	
						Peak CRP (mg/L)		
						Fatigue	147 (81-276)	*.081*
						No fatigue	133 (73-212)	
						Peak ferritin (µg/L)		
						Fatigue	999 (562-2053.5)	*.68*
						No fatigue	961.5 (559-1625)	
						Peak D-dimer (ng/ml)		
						Fatigue	1122 (326-3821)	*.138*
						No fatigue	657.5 (328-2473)	
						High risk inpatient CXR		
						Fatigue	83 (55.7)	*NS*
						No fatigue	78 (47.9)	
							OR 7.04	
						Post-COVID fibrosis		*.167*
						Ethnicity	-	*NS*
								.001
Augustin et al. (2021)	Outpatients	Prospective	958	4, 7 months	ADQ	**IgG Levels**		

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Germany		cohort				Low < 1.1 Medium 2-4 High > 4 **Gender** Male Female	NR NR NR 13/353 (8.6%) 37/353 (18.3%)	*NR* *NR* *NR* *NR*
Aydin et al. (2021) Turkey	Outpatients	Cohort	116	44 days	ADQ	**Gender (F)**	OR = 1.8	*.008*
Bai et al. (2021) Italy	Outpatients	Prospective cohort	377	102 days	Clinical interview	**Gender** Females Males **Long-Covid** No Yes	 75/137 (54.7) 74/240 (30.8) 20/117 (17.1) 39/260 (15)	 .001 .732
Barizien et al. (2021) France	Outpatients	Prospective cohort	39	7 months	Clinician assessment	**Fatigued v Not fatigued** Age Gender (F) Physical comorbidities Loss of taste & smell Weight (before & current) Height BMI (before & current) Loss of weight Heartrate (BPM) Blood pressure NJIMEGEN score PTSD score 30 s of up & down test O^2 saturation (%) Months since diagnosis Systolic & diastolic BP		 *.085* *.059* *NS* *.951* *NS* *.499* *NS* *.632* *.708* *NS* *.002* *.001* *.192* *.663* *.157* *NS*
Becker et al. (2021) Switzerland	Outpatients	Prospective cohort	90	12 months	ADQ VAS	Psychological distress No psychological distress	**9 (23.1)** **30 (76.9)**	**.288**
Bek et al. (2021) Netherlands	Outpatients	Prospective cohort	492	3, 6, 12 months	FAS	Gender Comorbidity (Y) Employment (N) Employment Retired	**OR 2.76** **OR 2.19** **OR 0.57** **OR** 0.38	**<.001** **.007** **.009** **<.001**
Bell et al. (2021) USA	Survey	Prospective cohort	303	> 30 days	ADQ	**Follow-up** ≥ 30 days 30-59 days ≥ 60 days	 78 (37.5) 21 (24.1) 57 (47.1)	 -
Boesl et al. (2021) Italy	Outpatients	Cohort	100	≥ 12 weeks	FSS	 **No impairment due to fatigue (1-4 on FSS)** Total Female Male	**N (%)** 18 (19.8) 13 (20.3) 5 (18.5)	 *NR*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Impairment due to fatigue (4-7 on FSS) Total Female Male	 73 (80.2) 51 (79.7) 22 (81.5)	 *NR*
Bottemanne et al. 2021 France	Outpatients Telephone	Prospective cohort	84	1, 3 months	Clinical interview	**3-month outcomes** Anxiety @ 1 month Physical symptoms @ 1 month Depression	- aOR 0.81 aOR 4.00 aOR 0.84	 .250 .236 .307
Bozzetti et al. (2021) Italy	Outpatients	Prospective cohort	49	6 months	Questionnaire	[illegible] **< 50% reduction of serum NfL level**	4/14 (33) 4/15 (27)	 *.999*
Carvalho-Schneider et al. (2021) France	Survey	Prospective cohort	150	30-60 days	WHO Performance Status Classification	**Severe asthenia** Day 30 Day 60	 11 (7) 4 (3.1)	-
Castro et al. (2021) USA	EHR	Retrospective case-control	6,619	31-90 days 91-150 days	Reported symptoms	**Positive test v Negative test**	aOR = 0.98	*.761*
Catalan et al. (2021) Spain	Survey	Cohort	76	12 months	Questionnaire SF-36	**No Steroids** Asthenia Vitality **Steroids** Asthenia Vitality	 19 (43.2) 62.5 (IQR 40–85) 11 (34.4) 80 (56.2–85)	 *.440* *.120*
Chen, Li et al. (2021) China	Telephone	Longitudinal cohort	715	Median 225 days	Questionnaire	Mechanical ventilation (ICU) Re-admission after discharge Hypertension	OR 5.52 OR 3.41 OR 1.65	.001 .001 .0016
Chudzik et al. (2021) Poland	Outpatients	RCT	50	4 weeks	FAS	**Phase 0** 1-MNA supplementation No supplement **Phase 1** 1-MNA supplementation No supplement	**M (SD)** 4.23 4.53 4.42 4.94	 *.008*
Clavario et al. (2020) Italy	Outpatients	Prospective cohort	110	3 months	Questionnaire	**% predicted VO2 below 85%** **% predicted VO2 above 85%**	21/38 (55.3) 33/72 (45.8)	.459
Daugherty et al. (2021) USA	EHR	Retrospective cohort	27,074	1-6 months	ICD10	**Fatigue** **Age > 50**	HR = 2.20 -	 *<.001*
D'Cruz et al. (2020) UK	Outpatients	Prospective cohort	119	61 days	NRM	**Breathlessness** **Post-COVID-19 function** **Positive mental health** **Psychological impairment** **Age** **Pre-existing comorbidities**	OR = 3.19 OR = 4.66 OR = 3.58 NR NR NR	*.002* *.000* *.012* *NS* *NS* *NS*
Dennis et al. (2021 UK	Outpatients	Prospective cohort	201	Median 141 days	NR	**Not hospitalised** **Hospitalised**	**159/163 (97.5)** **37 (100)**	 *1.0*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Moderate PCS **Severe PCS**	**73/77 (96.1)** **115/116 (99.1)**	 *.302*
Desgranges et al. (2021) Switzerland	Survey	Cohort	418	3-10 months	Questionnaire	 **Overweight/Obese** **Female** **Age** **Smoker** **Physical comorbidities** **Time of phone survey**	- OR = 1.70 OR = 1.61 OR = 1.08 OR = 1.79 - -	*.006* *.001* *.001* *NS* *NS* *NS* *NS*
Dini et al. (2021) Italy	Outpatients	Cross-sectional	50	5 months	Questionnaire	**Fatigue** None Minimal Moderate Severe Very Severe **Lower resilience**	 14 (28) 16 (32) 13 (26) 6 (12) 1 (2) -2.51	 *.015*
Fang et al. 2021 China	Telephone	Prospective cohort	1233	12 months	Physician interview	Severe disease Non-severe disease	166/438 (37.9) 234/795 (29.4)	.002
Fatima et al. (2021) India	Survey	Cohort	160	40 days	ADQ	Fatigue on 'daily routine'	33 (20.6)	-
Fernandez-de-Las-Penas et al. (2021) Spain	Survey	Cohort	1142	7 months	FIC ADQ	**Gender** Male Female **Persistent fatigue (F)** **ICU Admission** **Medical comorbidity**	 329 (54.7) 367 (67.8) OR 1.80 OR 0.98 NR	 *.05* *.001* *.963* *NS*
Froidure et al. (2021) Italy	Outpatients	Cohort	126	3 months	Questionnaire	**Pulmonary functions** **Age** **Sex** **Dyspnoea**	NR NR NR NR	*NS* *NS* *NS* *NS*
Frontera et al. (2021) USA	Survey	Prospective cohort	272	6 months	ADQ	 **Neurologic COVID v controls** **Return to work**	**Median (IQR)** 45.6 (38.2–54.4) r = .118	 *.760* *.160*
Garrigues et al. (2020) France	Outpatients	Cross-sectional	120	110.9 days	Questionnaire	**Ward Group** Fatigue **ICU Group** Fatigue	 52(54.2) 14(58.3)	 *NS*
Gebhard et al. (2021) Switzerland	Survey	Cohort	1024	6.5 months	ADQ	**Gender** Women Men	 44 (8) 40 (8)	 -
Gonzalez-Hermosillo et al. (2021) Mexico	Survey	Prospective cohort	130	3 months 6 months	Questionnaire	**CFS** **Female** **Age >40** **Anxiety** Fatigued Not fatigued **Depression**	17 (17.2) OR = 1.95 OR = 2.5 39 (56.3) 15 (24.6)	*.07* *.03* *.001* *.004*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Fatigued	31 (44.9)	*.05*
						Not fatigued	13 (21.3)	
						Fatigue (3 mths v. 6 mths)		*.01*
						Dyspnoea on effort	-	*.53*
						Resting dyspnoea	-	*.05*
						Gastrointestinal symptoms	-	*.05*
						Neurocognitive symptoms	-	*.05*
						Sleep	-	*.05*
						Autonomic dysregulation	-	
						Pain	-	
Graham et al. (2021) USA	Survey	Cohort	100	7 months	PROMIS	**Processing speed**	r = .450	.02
						Executive function	r = .430	.02
						Working memory	r = .440	.02
						Attention		
						SARS-CoV+	r = −.070	.79
						SARS-CoV-	r = −.760	.02
Halpin et al. (2020) UK	Outpatients	Cross-sectional	100	4-8 weeks	Fatigue	**New fatigue**		
						Ward	41 (60.3)	*NR*
						ICU	23 (72)	
						Fatigue Severity Severe		
						Ward	10 (14.7)	*NR*
						ICU	4 (12.5)	
						Fatigue severity moderate		
						Ward	14 (20.6)	*NR*
						ICU	13 (40.6)	
						Fatigue Severity mild		
						Ward	17 (25)	*NR*
						ICU	6 (18.8)	
						Gender		
						Moderate/Severe fatigue		
						Women	46 (61)	*NR*
						Men	54 (26.6)	
						PTSD		
						Severe fatigue	(43.9)	*NR*
						No fatigue	(18.6)	
						Cognitive problems		
						Moderate/Severe fatigue	(41.4)	*NR*
						Less severe fatigue	(18.6)	
						Breathlessness		
						Moderate/Severe fatigue	(65.9)	*NR*
						Less severe fatigue	(39)	
						Age	NR	*NS*
						Ethnicity (severe v. non severe fatigue)	NR	*NS*
						BMI (severe v. non severe fatigue)	NR	*NS*
Heightman et al. (2021) UK	Outpatients	Cohort	1325	≥ 6 weeks	FAS	**Total fatigue**		
						Post-Hospitalised	24 (16-34)	
						Non-Hospitalised	30 (24-38)	
						Post-Emergency	28 (23-36)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						CFS	10 (0.8)	
						Return to full-time work		
						Hospitalised	OR = 0.29	
						Non-Hospitalised	OR = 0.67	
						Functional recovery		
						Hospitalised	OR = 0.47	
						Non-Hospitalised	OR = 0.49	
						Post-Emergency	OR = 0.40	
Hellemons et al. (2021) Netherlands	Outpatients Survey	Prospective cohort	92	3-6 months	FAS	**Post -Covid Time**		
						6 weeks to 3 months	-	*.863*
						3 months to 6 months	-	*.006*
						Gender (F)	β = 4.05	.027
						Physical functioning	β = -2.88	<.001
Hossain et al. 2021 Bangladesh	Outpatients	Prospective cohort	2198	12 weeks	ADQ	**Gender**		
						Female	96 (27)	*.763*
						Male	199 (55.9)	
						Age	X^2 5.59	*.241*
						Marital status	X^2 2.95	*.304*
						Education	X^2 2.59	*.659*
						Rural/Urban location	X^2 1.17	*.351*
						Occupation	X^2 1.48	*.928*
						Disease severity	X^2 0.51	*.540*
						Post-covid functional status score	B 0.094	*.001*
Iqbal et al. (2021) Pakistan	Survey	Cross-sectional	158	38 days	ADQ	**Female**	92 (58)	*.05*
						Days since recovery		
						Fatigued	33.98 (15.62)	*<.001*
						Not fatigued	58.07 (26.37)	
						Disease severity		
						Mild	86 (65.6)	*.005*
						Moderate	33 (25.2)	
						Severe	12 (9.2)	
Jacobs et al. (2020) USA	Survey	Cohort	149	35 days	PROMIS	**Physical health rating**		
						Poor/fair	OR = 0.128	*<.001*
						Quality of life rating		
						Moderate	OR = 0.785	*NS*
						Mild to none	OR = 0.104	*NS*
Kanberg et al. (2021) Sweden	Outpatients	Prospective cohort	100	6 months	KEDS	**Disease severity**		
						Mild	9 (38)	0.59
						Moderate	11 (42)	
						Severe	20 (42)	
Karaarslan et al. (2021) Turkey	Survey	Cohort	300	1 month	ADQ	**Fatigue severity**		
						Mild	93 (31.0)	
						Moderate	30 (10.0)	
						Severe	9 (3.0)	
						Very severe	1 (0.3)	
						None	167 (55.7)	
						Multivariate		
						Age	OR = 0.98	*.060*
						Female	OR = 1.42	*.145*
						BMI	OR = 1.08	*.003*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						LOS	OR = 0.98	*.468*
Kashif et al. 2021 Pakistan	Telephone	Cohort	242	3 months	Questionnaire	**Gender**		
						Female	38 (51)	.039
						Male	63 (38)	
						Comorbidities		
						With	13/29 (44.8)	.647
						Without	88/213 (41.3)	
Labarca et al. (2021) Chile	Outpatients	Cross-sectional	60	4 months	CFQ	**Disease severity**		
						Mild	5 (11.1)	*.05*
						Moderate	10 (47)	
						Severe	10 (36)	
Liang et al. (2020) China	Outpatients	Prospective cohort	76	3 months	Questionnaire	**3 months fatigue**		
						TN1 at acute phase	r = . 782	*.008*
Lindahl et al. (2021) Finland	Survey	Cohort	101	6 months	SF-36		**M (SD)**	
						54.2 (23.6)		
						Gender		
						Women		.033
						Men	36 (83.7)	
						Mild fatigue	39 (7)	
						Women		
						Men	26 (60.5)	
						Severe fatigue	32 (61)	
						Women		
						Men	17 (39.5)	
							7 (13)	
Liu et al. (2021) China	Outpatients	Prospective cohort	594	3, 6, 12 months	Questionnaire	**3 months**		
						Total	48/502 (9.6)	
						Moderate	7/63 (11.1)	
						Severe	34/378 (9.0)	
						Critical	7/61 (11.5)	
						6 months		
						Total	27/422 (6.4)	
						Moderate	5/52 (9.6)	
						Severe	20/313 (6.4)	
						Critical	2/57 (3.5)	
						12 months		
						Total	18/486 (3.7)	
						Moderate	0 (0)	
						Severe	16/379 (4.2)	
						Critical	2/55 (3.6)	
Liyanage-Don et al. 2021 USA	Survey	Cross-sectional	153	3 months	ADQ	**Depression v No Depression**	NR	*<.01*
						Anxiety v. No Anxiety	NR	*<.01*
Lombardo et al. (2021) Italy	Telephone	Prospective cohort	303	12 months	ADQ	**Age**		
						18-47	OR =1.52	*<.001*
						47-58	OR = 3.30	*<.001*
						59-90	OR = 0.78	*.044*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Gender (F) **Hospitalised**	OR = 0.57 OR = −0.069	*.022* *.801*
Maamar et al. (2021) Spain	Outpatients	Cross-sectional	121	3 months	Interview	**Neutrophil count (x103/µL)** Post-Covid fatigue No fatigue Post-Covid Men	 OR = 4.68 OR = 3.37 OR = 4.07	 *.041* *.047*
Mazza et al. 2021 Italy	Outpatients Online	Prospective cohort	402	1, 6, 12 months	FSS	Age LOS Severity of Depression at 6 months Severity of PTSD at 6 months Severity of Anxiety at 6 months Severity of Depression at 12 months Severity of PTSD at 12 months Severity of Anxiety at 12 months **FSS M (SD)** Men Women Comorbid Psychiatric history No psychiatric history	r = .01 r = -.06 r = .47 r = .32 r = .37 r = .56 r = .52 r = .48 3.17 ± 1.42 3.88 ± 1.73 4.05 (1.62) 3.18 (1.48)	*NS* *NS* *NS* q = .05 q = .05 q = .05 q = .05 q = .05 q = .004 **q =.001**
Menges et al. (2021) Switzerland	Survey	Prospective cohort	431	6-8 months	FAS	**Age** 18-39 40–64 65+ **Gender** Female Male **Not hospitalised** **Hospitalised** **Healthcare utilisation** **Age 18-39** **Female** **Initial symptoms (v severe)** **ICU admission** **Ex-smoker** **BMI** **Comorbidities** **Time since diagnosis**	 105 (64.0) 104 (51.0) 24 (41.4) 125 (59.2) 108 (50.2) 195 (55.9) 38 (49.4) OR = 1.61 OR = 0.59 OR = 1.38 OR = 1.36 OR = 4.63 OR = 1.58 OR = 1.04 OR = 1.27 OR = 1.00	 *NS* *NS* *NR* *NR* *NR* *NR* *NR* *NR* *NR* *NR* *NR*
Mirfazeli et al. (2021) Iran	Survey Interview	Prospective cohort	94	9 months	CDC Criteria for Fatigue Scale	**Chronic fatigue syndrome** Total 21 (22.9) Female Age Constitutional neuropsychiatric symptoms in the acute phase Initial Covid severity	 - - - -	 *.02* *NS* *.01* *NS*
Molnar et al. (2021) Hungary	Outpatients	Prospective cohort	101	> 4 weeks	CFQ-11	 Total fatigue score 4-12 weeks	**M (SD)** 15.7 (5.9) 15.8 (5.5)	 *.951*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						> 12 weeks **Fatigue severity** Age **Antibody levels** Total CFQ-11 score	5.6 (6.7) OR = 1.18 OR = 9.03	 *.178* *.003*
Morin et al. (2021) France	Telephone	Prospective cohort	478	3-4 months	MFI	 MFI Score Mental fatigue score Intubated Non-intubated	**M (IQR)** 4.5 (I3.0-5.0) 3.7 (3.0-4.5 **N (%)** 110 (29.9) 24 (38.1)	
Munblit et al. (2021) Russia	Telephone	Longitudinal cohort	2599	218 days	Questionnaire	**Chronic fatigue** Chronic pulmonary disease Female Hypertension RT- PCR "+"	 OR = 1.68 OR = 1.67 OR = 1.27 OR = 1.23	 *.05* *.05* *.05* *.05*
Nehme et al. (2021) Switerland	Survey	Cohort	410	7-9 months	Questionnaire	**Female** **Male** **Age** 18-39 40-59 > 60	65 (23.6) 20 (14.8) 30 (17.3) 43 (21.7) 12 (30.8)	- -
Noviello et al. (2021) Italy	Survey	Case control	164 patients 184 controls	4.8 months	SAGIS	**Chronic fatigue** Patients **Disease severity** Mild Moderate Severe **Diarrhoea** **Somatisation** Fatigued Not fatigued	 RR = 2.24 (33.3) (25.9) (40.1) - **M (SD)** 61.7 (10.8) 50.9 10.9)	*<.001* *.41* *.05* *<.001*
Nune et al. (2021) UK	Telephone	Prospective cohort	271	3, 6, 9 months	ADQ VAS	**3 months** Evidence of pneumonia in CXR ITU/HDU admission	 OR = 3.22 OR = 5.58	 *.008* *.020*
O'Keefe et al. (2021) USA	Survey	Cross-sectional	290	1-6 months	ADQ	**Fatigue post-acute** Median 61 days Median 139 days **Worse physical health (than before Covid)** **Physical health affects daily activities** **Emotional health affects daily activities**	 17 (19.3) 42 (21.2) OR = 10.48 OR = 10.35 OR = 2.56	 *.710*
Pauley et al. (2021) UK	Telephone/ Outpatients	Prospective cohort	332	3 months 12 months	VAS	**Fatigue severity** **Age** Male 50-69 Male > 70	β = 0.09 β = 1.33 β = 0.96	*.242* *.101* *.295*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Female < 50	β = 2.56	*.037*
						Female 50 - 69	β = 1.32	*.101*
						≥ 1 comorbidities	β = 1.20	*.037*
						Ventilated (ICU)	OR = 0.50	*NR*
Peghin et al. 2021 Italy	Telephone	Prospective cohort	599	6 months	PRO	**Disease Severity @ Onset**	**N (%)**	
						Asymptomatic	1/55 (1.8)	
						Mild	45/409 (11.0)	*<.001*
						Moderate	21/93 (22.6)	
						Severe	5/24 (20.8)	
						Critical	6/15 (40.0)	
Pérez-González et al. (2021) Spain	Telephone	Prospective cohort	284	6 months	Questionnaire	**Hospitalised**	36 (20.9)	
						Not hospitalised	4 (5.3)	*.001*
						Gender		
						Female	22 (22)	*.00*
						Male	18 (12.2)	
						COPD v No COPD	-	*NS*
Pilotto et al. (2021) Italy	Outpatients	Cohort	165	6 months	Questionnaire	**Disease severity**		
						Moderate/Severe	OR = 2.1	*NR*
Rass et al. (2021) Austria	Outpatients	Prospective cohort	90	3 months	NR	**Quality of life (SF-36)**		
						MCS ≥ 40	13 (19.7)	*.009*
						MCS < 40	9 (40.9)	
						PCS ≥ 40	12 (15.8)	*.001*
						PCS < 40	9 (81.8)	
Rauch et al. (2021) Germany	Survey	Prospective cohort	127	3, 6, 12 months	ADQ	**Disease severity**		
						Mild	3 (8)	
						Moderate	19 (31)	.004
						Severe	10 (39)	
						Age		
						18 - 19	8 (28)	*.471*
						40 - 59	13 (21)	
						> 60	11 (31)	
						Gender		
						Female	24 (28)	*.390*
						Male	8 (20)	
Righi et al. (2021) Italy	Outpatients Telephone	Prospective cohort	448	4-12 weeks	Questionnaire	**Duration of fatigue**		
						Inpatients	22 days	*<.001*
						Outpatients	14 days	
Romero-Duarte et al. (2021) Spain	EHR	Retrospective cohort	797	6 months	Reported symptoms	**Gender**		
						Men	81 (18.9)	*.021*
						Women	95 (25.7)	
Sami et al. (2020) Iran	Telephone	Cohort	452	4 weeks	Questionnaire	**Disease severity**		
						Non-Severe	43/400 (10.75)	*.320*
						Severe	7/52 (13.46)	
Sathyamurthy et al. (2021) India	Telephone	Prospective cohort	279	90 days	Questionnaire	**Gender**		
						Men	16/101 (9)	*.277*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Women **Disease Severity** Mild/moderate Severe/critical	9/178 (8.9) 9/163 (5.5) 16/116 (13.8)	 *.077*
Scherlinger et al. (2021) France	Outpatients	Prospective cohort	30	152 days	VAS	**Immunised** **Not immunised**	13 (86.7) 12 (80)	*NS*
Seeßle et al. (2021) Germany	Outpatients	Prospective cohort	96	5/12 months	Questionnaire			*.043*
Shang et al. (2021) China	Telephone	Cohort	796	6 months	Questionnaire	**Disease Severity** Severe Critical **Gender** Men Women **Age** < 65 > 65	 183 (25.3) 18 (24.7) 86 (21.3) 115 (29.3) 125 (26.1) 76 (24.0)	 *.902* *.009* *.500*
Shendy et al. (2021) Egypt	Telephone	Cohort	81	3-5 months	MFIS	**Fatigued v Not fatigued** **Gender** **Age** **BMI** **Smoking status** **O^2 supplementation** **Hospitalised** **Dyspnoea level** None Mild Moderate Severe **NRS Scores** Physical MFIS Cognitive MFIS Psychosocial MFIS	 - - - - - - - - - - r = 0.44 r = 0.31 r = 0.27	 *.40* *.80* *.44* *.89* *.53* *.52* *.04* *<.001* *.005* *.01*
Sigfrid et al. (2021) UK	Outpatients Survey	Prospective cohort	308	222 days	VAS	 **Gender** Men Women **Women** < 50 years > 50 years > 70 years **Males** < 70 years > 70 years **≥ 1 comorbidity** **Age**	**M (IQR)** 4.0 (2.0 – 6) 6.0 (2.0 - 7.0) OR = 2.06 OR = 1.20 OR= 0.29 OR = 0.44 OR = 0.38 OR = 0.95 -	 *<.001* *.001* *.012* *.362* *.194* *.194* *.272* *.001* *NS*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Disease severity	**VAS Score**	
						WHO Scale 4	OR = -0.26	*.266*
						WHO Scale 5	OR = -0.20	*.354*
						WHO Scale 6/7	OR = -0.18	*.354*
Silva et al. (2021) Brazil	Outpatients	Cross-sectional	87	54 days	Questionnaire CFQ-11	**CFQ-11 Score**	15 (0-32)	
						Sleep	r = .440	<.001
						Depression	r = .470	<.001
Staudt et al. 2021 Germany	Outpatients	Prospective cohort	101	10 months	Questionnaire	Age	OR = 1.00	*NS*
						Gender	OR = 0.52	*NS*
						Smoking	OR = 0.80	*NS*
						SpO_2	OR = 0.99	*NS*
						BMI	OR = 1.02	*NS*
						FEV_1	OR = 0.97	*NS*
						TLC/RV	OR = 1.00	*NS*
						6MWT	OR = 1.02	*NS*
						Depression PHQ-9	OR = 1.27	*.05*
						Respiratory symptoms SGRQ	OR = 1.06	*.05*
						Haemoglobin levels (g/dL)	OR = 1.26	*NS*
						Somatization index SOMS-SAD	OR = 0.90	*NS*
Stavem et al. (2021) Norway	Survey	Cohort	458	1.5-6 months	CFQ-11 RAND-36		**M (SD)**	
						CFQ Physical	10.1 (3.8)	
						CFQ Mental	5.0 (1.8)	
						Vitality	56.8 (23.9)	
						CFQ-11		
						Age		
						Marital status	OR = 1.02	*.081*
						Female gender	OR = 0.56	*.022*
						Education (university)	OR = 0.49	*.002*
						No. comorbidities >2	OR = 1.17	*.070*
						Previous depression	OR = 1.52	*.230*
						Symptoms during COVID	OR = 1.10	*.840*
						No. covid symptoms (10-23)	OR = 3.66	*.001*
						Dyspnoea	OR = 1.56	*.069*
						Confusion	OR = 2.25	*.022*
						BMI	OR = 1.03	*.130*
						Smoking	OR = 1.34	*.210*
						Days since symptom onset (128-200)	OR = 0.55	*.034*
						RAND-36 (Vitality)		
						Age	β = 1.51	*.057*
						Gender (f)	β = 9.63	*<.001*
						Marital status	β = 3.53	*<.001*
						Education (university)	β = 4.42	*.230*
						Previous depression	β = -12.05	*.005*
						Covid symptoms (#10-23)	β = −15.59	*<.001*
						Confusion during covid	β = -7.35	*.018*
						BMI	β = -0.50	*.010*
						Days since symptom onset (128-200)	β = 6.09	*.015*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Sun et al (2021) China	Telephone	Retrospective cohort	932	3 months	Questionnaire	**Disease Severity**		
						Non severe	15 (1.7)	.262
						Severe	2 (3.8)	
Sykes et al. (2021) UK	Outpatients	Retrospective cohort	134	113 days	Questionnaire	**Gender**		
						Males	27 (30)	*.004*
						Females	26 (56.5)	
						ICU/Ward		
						Ward	44/107 (41.1)	NR
						ICU	9/27 (33.3)	
						Follow-up days		
						47-75	5 (71.4)	NR
						76-100	13 (50)	
						101-125	26(33.3)	
						126-167	9 (39.1)	
						BMI (>)	NR	*.046*
Taboada et al. (2021) Spain	NR	Prospective cohort	91	6 months	Questionnaire	**With a decrease in functional status v. no decrease**	OR = 12.321	*.01*
						With a decrease in QoL v. no decrease	OR = 15.448	*.01*
Taylor et al. (2021) UK	Telephone Survey	Cohort	675	> 12 weeks	Amplitude Questionnaire	**High risk for post-covid healthcare needs**	169 (50.3)	-
						Low risk for post-covid healthcare needs	376 (46.8)	
Tomasoni et al. (2021) Italy	Outpatients	Cross-sectional	105	1-3 months	Questionnaire	**HADS Anxiety Scores**		
						‘Normal’	18/70 (25.7)	.044
						‘Pathological’	15/30 (30)	
Townsend et al. (2020) Ireland	Outpatients	Prospective cohort	128	10 weeks	CFQ	**Physical fatigue**	11.38 (4.22)	
						Psychological fatigue	4.72 (1.99)	
						Severe fatigue group:		
						Female	45 (52.3)	*.002*
						Anxiety/Depression/anti-depressant history	-	*.002*
						Days since onset		*NS*
						Critical care		*NS*
						LOS		*NS*
						BMI		*NS*
						Lab tests (NLR, LDH, CRP)		*NS*
						COVID severity		*NS*
van den Borst et al. (2021) Netherlands	Outpatients	Prospective cohort	124	3 months	NCSI	**Disease severity**	NR	*.05*
Venturelli et al. (2021) Italy	Telephone	Cohort	767	49 days 81 days	BFI	**Male**	93 (18.1)	*NR*
						Female	93 (36.9)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Voruz et al. (2021) Switzerland	Outpatients Survey	Cohort	75	6-9 months	FIS SF-36	**Disease Severity**		
						Mild	2/15 (13.3)	*.088*
						Moderate	3/15 (20)	
						Severe	1/15 (6.6)	
						Quality of Life	-	*.040*
						Vitality Score		
						Mild	38.66	*.039*
						Moderate	49.00	
						Severe	56.00	
Wu et al. (2021) China	Outpatients	Cohort	54	6 months	ADQ	**Disease Severity**	**N(%)**	
						Severe	6/23 (19.4)	*NR*
						Moderate	7/31 (30.4)	
Yomogida et al. (2021) USA	Telephone	Prospective cohort	366	1, 2, 6 months	Questionnaire	Gender (F)	aOR = 3.90	<.001
						≥ 1 comorbidity	aOR = 4.39	<.001
						Age ≥40	aOR = 2.25	0.01
Zhang et al. (2021) China	Telephone	Cohort	2433	1 year	ADQ	**Disease Severity**		
						Severe v. Not severe	OR = 1.36	.004
						Oder age	OR = 1.02	< .001
						Gender (F)	OR = 1.27	.008
						Severe disease during hospital-stay	OR = 1.43	< .001
Zhou et al. (2021) China	Outpatients	Case-control	15 patients 14 controls	3 months	NR	Intestinibacter bartlettii	r = 0.545	.036
						Escherichia unclassified	r = 0.567	.028

Table 1 continued - Continuous fatigue outcomes

Author (year), Country	**Setting**	**Study Design**	**Sample (n)**	**Follow-up Time**	**Fatigue Scale**	**Risk Factors for Fatigue**	**Risk Factors M (SD) Median (IQR)**	***P***
Bardakci et al. (2021) Turkey	Outpatients	Cohort	65	6-7 months	SF-36	**6MWT** **Pulmonary functions** FVC% FEV_1%	r = .526 r = .242 r = .290	*<.001* *.064* *.026*
Chen et al. (2020) China	Outpatients	Cross-sectional	361	1 month	SF-36	**Gender** Women Men **Multivariate** LOS Age	 81.80 (16.32) 83.25 (16.13) β .113 β .128	 <.001 .040 .04
Dalbosco-Salas et al. (2021) Chile	Outpatients	Prospective cohort	115	30 days	SF-36 VAS Fatigue	**Pre-rehabilitation (VT)** Total Hospitalised Not hospitalised **Post-rehabilitation (VT)** Total Hospitalised Not hospitalised Post intervention intergroup **Non-ICU (VAS)** Pre-rehabilitation Post-rehabilitation **ICU** Pre-rehabilitation Post-rehabilitation Post-intervention intergroup	 40.7 38.3 42.9 58.5 58.3 58.7 - 3 (0–4) 1 (0–3.25) 3 (1.75–5) 1.5 (0–2.75) -	 *.001* *.001* *.001* - - - *.912* *.053* *.004* *.473*
Elanwar et al. (2021) Egypt	Outpatients	Case control	46 fatigue 46 no fatigue	6 months	CFQ	**Fatigue** Physical Mental **Fatigued v. no fatigue** Duration of acute illness Increased ferritin (ng/mL Mean consecutive difference for ECD Decremental response in ADM (Y/N) Decremental response in trapezius (Y/N)	 4 (2-7) 2 (0-3) β = 0.099 R = .425 40.7 (36.7,44.8) 9 (13%) 20 (43%)	 .05 .003 <.001 .011 <.001

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Elkan et al. (2021) Israel	Survey	Case control	42 cases 42 controls	9 months	SF-36	**Age**		.914
						Gender		
						Males	55 (27.5-87.5)	.720
						Females	60 (30-70)	
						Smoking		
						Never	55 (30-75)	.992
						Ever	60 (10.0-87.5)	
						Physical comorbidities	-	NS
						Obesity		
						No	60 (30-81.2)	.197
						Yes	50 (27.5-63.7)	
						BMI	r = -0.13	.310
						LOS	r = 0.03	.798
						Disease Severity		
						Mild	55 (30-75)	.440
						Moderate	60 (50-78.7)	
						Severe	45 (25-85)	
						O^2 support		
						Yes	47.5 (21.2-81.2)	.435
						No	60 (33.7-76.2)	
						Follow-up (months)	r = 0.138	.270
Evans et al. (2021) UK	Outpatients	Prospective cohort	1077	5 months	FACIT	**Disease severity**		
						WHO Class 3-4	18·5 (14·3)	NR
						WHO Class 5	14·6 (12·1)	
						WHO Class 6	16·4 (13·1)	
						WHO Class 7-9	18·5 (13·4)	
Gamberini et al. (2021) Italy	Telephone	Prospective cohort	205	3, 12 months	15D	**Full Recovery**	0.931(0.125)	
						Partial Recovery Mental	0.718 (0.160)	
						Partial Recovery Physical	0.806 (0.227)	<.001
						Bad Recovery	0.499 (0.185)	
Guo et al. (2020) China	Outpatients	Prospective cohort	259	1 month	SF-36	**Positive nucleic-acid duration > 14 days (Age 46-69)**		*.047*
						Gender		
						Age	NR	*NS*
						Smoking	NR	*NS*
						Corticosteroids	NR	*NS*
							NR	*NS*
Henneghan et al. (2021) USA	Survey	Cross-sectional	52	4 months	PROMIS	**Younger age**	r = .280	*<.05*
						Total symptoms (n.)	r = .300	*<.05*

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Kedor et al. (2021) Germany	Outpatients	Prospective cohort	42	6 months	CFQ	**Covid-19 Syndrome**	7 (2-10)	*.687*
						CFS v. CCS		
						Stress intolerance	-	*.042*
						Post-exertional malaise	-	*.007*
						Temperature sensitivity	-	*.024*
						Sensitivity to light	-	*.014*
						Sensitivity to noise	-	*.029*
						Autonomic dysfunction	-	*NS*
Liu et al. (2020) China	Outpatients	RCT	72	6 weeks	SF-36	**Intervention Group**		
						Pre-rehab	60.6 (6.9)	*< .05*
						Post-rehab	75.6 (7.1)	
						Control Group		
						Pre-rehab	60.5 (7.1)	*NS*
						Post-rehab	61.2 (6.3)	
Mantovani et al. (2021) Italy	Outpatients	Cohort	37	6 months	Clinical interview BORG	**MFI - FG - General fatigue**		
						All	9.5 (4.8)	.002
						CFS	13.6 (4.6)	
						No CFS	7.9 (3.9)	
						MFI-FF Physical Fatigue		
						All	8.7 (4.7)	.001
						CFS	13.1 (5.0)	
						No CFS	7.0 (3.4)	
						MFI-RA Reduced Activity		
						All	8.7 (4.8)	<.001
						CFS	13.6 (4.7)	
						No CFS	6.9 (3.4)	
						MFI-RM Reduced Motivation		
						All	7.5 (3.8)	.001
						CFS	10.9 (4.1)	
						No CFS	6.3 (2.9)	
						MFI-FM Mental Fatigue		
						All	8.0 (4.3)	<.001
						CFS	13.2 (3.5)	
						No CFS	6.0 (2.7)	
						Between CFS +Ve and CFS -Ve		
						Lung functions (all)	-	NS
						6MWT	-	NS
						BORG dyspnoea (baseline)	-	.014
						Subjective neuropsychological complaints (Y/N)	-	<.001
						Anxiety	-	.11
						Depression	-	.002
						SARS-CoV-2 Inflammatory markers	-	NS
						Hospitalisation	-	NS
						ICU	-	NS

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Qin et al. (2021) USA		Cross-sectional	55	30 days	PROMIS 7a	**Gender (F)** **Anxiety** **Depression** **Age > 65** **Initial symptoms (n.)** **Longer LOS** **ICU admission** **Each day of hospitalisation**	β = 5.4 β = 1.47 β = 0.89 OR = 0.36 OR = 1.33 OR = 1.15 OR = 5.18 OR = 1.2	*.05* *.05* *.05* *.05* *.04* *.03* *.02* *.08*
van der Sar -van der Brugge (2021) Netherlands	Outpatients	Prospective cohort	101	6 weeks	SF-36	**Disease severity v. Pop Norms** Moderate (lowest VT)	NR	*.001*
Yildirim et al. (2021) Turkey	Outpatients	Prospective cohort	70	6 months	SF-36	**Vitality Score** ICU Non-ICU	**Median (IQR)** 65 (40-80) 60 (45-80)	*.680*
Zhao et al. (2021) China	Outpatients	Prospective cohort	94	1 year	SF-36 Questionnaire	**Disease severity (VT)** Mild/moderate Severe/critical **Muscle fatigue (MF)** Total **Disease Severity (MF)** Mild/moderate Severe/critical **Age** < 60 > 60	80 (65, 90) 70 (60, 85) 37/94 (39.36) 15/51 (29.41) 22/43 (51.16) 34/81 (41.98) 3/13 (23.08)	*.108* .032 .195

NA = Not analysed; NR = Not reported; NS = not significant; r = Pearson's correlation; OR = Odds Ratio; CFS = chronic fatigue syndrome; 6MWT = 6-minute walking test; FEV_1 = forced expiratory volume; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for CO^2; KCO = carbon monoxide transfer coefficient; TLco = gas transfer capacity; ECLA = extracorporeal lung assist; ARDS = acute respiratory distress syndrome; FMA = fibromyalgia; BFHX = Bufei Huoxue supplement, PTSD = post-traumatic stress disorder; CXR = chest X-ray; WBC – white blood cell; CRP = c-reactive protein; ADQ = author designed questionnaire; BFI = Brief Fatigue Inventory; BORG = Borg rating of perceived exertion scale; BRAF-NRS, V2 Revised = Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale-Revised; CFQ = Chalder Fatigue Scale; ECOG = Eastern Cooperative Oncology Group performance scale; EHR = electronic health records; FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue; FAI = Fatigue Assessment Inventory; FIC = Functional Impairment Checklist; FSS = Fatigue Severity Scale; FAS = Fatigue Assessment Scale; FIS = Fatigue Impact Scale; FRS = Fatigue Rating Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; KEDS = Karolinska Exhaustion Disorder Scale; NCSI = Nijmegen Clinical Screening Instrument; NRS = Numeric Rating Score; PCL-5 = Post-Traumatic Stress Disorder Checklist; PRO = Patient reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS-7a = short-form Fatigue; SAGIS = Structured Assessment of Gastrointestinal Symptoms Scale; SF-36 = 36-Item Short-Form Survey; SPHERE-34 = Somatic & Psychological Health Report; VAS-F = Visual Analogue Scale- Fatigue.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 1-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 1-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplemental
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5 & 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6 &7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pages 6-7
Study characteristics	17	Cite each included study and present its characteristics.	Pages 8-19 & supplemental
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplemental
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8-19
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 20
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 20-21 & 21-25 for Risk factors
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 21 & supplemental
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 21 & supplemental
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 21 & supplemental
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 25-26
	23b	Discuss any limitations of the evidence included in the review.	Page 27-28
	23c	Discuss any limitations of the review processes used.	Page 27-28
	23d	Discuss implications of the results for practice, policy, and future research.	Page 27
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5 Supplemental
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplemental
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 28
Competing interests	26	Declare any competing interests of review authors.	Page 28

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 28

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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Fatigue outcomes following COVID-19: A systematic review and meta-analysis

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Title **Fatigue outcomes following COVID-19: A systematic review and meta-analysis**

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ABSTRACT

Objectives

Fatigue is a pervasive clinical symptom in coronaviruses and may continue beyond the acute phase, lasting for several months or years. This systematic review and meta-analysis aimed to incorporate the current evidence for post-infection fatigue among survivors of SARS-CoV-2 and investigate associated factors.

Methods

Embase, PsyINFO, Medline, CINAHL, CDSR, Open Grey, BioRxiv and MedRxiv were systematically searched from January 2019 to December 2021. Eligible records included all study designs in English. Outcomes were fatigue or vitality in adults with a confirmed diagnosis of SARS-CoV-2 measured at $\geq$ 30 days post-infection. Non-confirmed cases were excluded. JBI risk of bias was assessed by 3 reviewers. Random-effects model was used for the pooled proportion with 95% CIs. A mixed-effects meta-regression of 35 prospective articles calculated change in fatigue overtime. Subgroup analyses explored specific group characteristics of study methodology. Heterogeneity was assessed using Cochran's Q and I^2 statistic. Egger's tests for publication bias.

Results

Database searches returned 14262 records. Following deduplication and screening, 178 records were identified. 147 (n=48,466 participants) were included for the meta-analyses. Pooled prevalence was 41% (95% CI: 37-45%, k=147, I^2=98%). Fatigue significantly reduced over time (-0.057, 95% CI: -107 - -0.008, k=35, I^2=99.3%, p=0.05). A higher proportion of fatigue was found in studies using a

valid scale (51%, 95% CI: 43- 58%, k=36, I^2=96.2%, p=.004). No significant difference was found for fatigue by design study (p=0.272). Egger's test indicated publication bias for all analyses except valid scales. Quality assessments indicated 4% at low risk of bias, 77% at moderate risk and 19% at high risk. Frequently reported associations were female gender, age, physical functioning, breathlessness and psychological distress.

Conclusion This study revealed that a significant proportion of survivors experienced fatigue following SARS-CoV-2 and their fatigue reduced overtime. Non-modifiable factors and psychological morbidity may contribute to ongoing fatigue and impede recovery.

Prospero Registration No. CRD42020201247

Strengths &Limitations

- This review and meta-analysis was conducted using a significant sample size from a comprehensive search of the literature, including only confirmed cases;
- Substantial unexplained heterogeneity between studies limits generalisability of our findings;
- Only one reviewer screened and extracted the data from each study leaving the potential for missing articles and selection errors;
- Outcome measures of fatigue were unvalidated in the majority of studies, limiting confidence in our estimates;

- Total point-prevalence was likely impacted by predominance of hospitalised patients with potentially more severe disease.

INTRODUCTION

Fatigue may be characterised as tiredness or exhaustion as a result of physical or mental exertion or as a result of an illness or disease.[1] The experience of fatigue is common and is usually short-lived but, for a small number of people, it can become long-lasting, associated with a number of impairments in daily living and quality of life.[1] It is one of the most common presenting symptoms of coronaviruses.[2] The current pandemic has also revealed a considerable burden of lasting symptoms [3–12] with approximately 1 in 4 people experiencing fatigue by one estimate.[13] Systematic reviews indicate a pooled-prevalence of post-COVID-19 fatigue to vary between 45% [14], 52% [15] and 64%.[16] In previous epidemics, fatigue was enduring. In a follow-up of 90 SARS survivors 30 months post-illness, for instance, 1 study found significantly lower vitality scores compared to Hong Kong population norms.[17] A small study of Middle East Respiratory Syndrome patients, revealed 32.7% had clinically relevant chronic fatigue, according to their FSS scores, at 18 months follow-up.[18] Likewise, for a considerable number of COVID-19 patients, tiredness symptoms extend beyond 3 months and represent a larger burden of post-infection symptomology.[19–41]. A large study of 1,142 hospitalised patients found that 61% had fatigue 7 months post-COVID-19.[42] Similarly, those who perceived themselves as experiencing 'poor recovery' had lower vitality on the 15D instrument, compared to those making a 'full recovery' ($p<.001$) 1 year post-illness.[43]

More severe disease, associated with being hospitalised or ICU admission, has been related to post-illness fatigue.[44–55] In a small cohort of 55 people, 30 days post-discharge for COVID-19, each additional day of hospitalisation increased fatigue by 1.2.[56] Apart from hospitalised patients, among non-hospitalised or those treated for milder disease, fatigue is persistent.[57–65] In 359 patients 63.4% reported significant fatigue up to 12 months post-infection and were more likely than admitted patients to require referral for fatigue symptomology.[66]

Determinants of post-illness fatigue include female gender, [67–71] and older age, although the latter relationship was not consistent. Being over 50 years was associated with fatigue severity in some studies,[56,72,73] but not in others.[74–76] Exercise impairments are a common feature of post-Covid sequelae.[77–83] Poorer performance on the six-minute walk test (6MWT) was associated with fatigue and lower vitality at 6 months despite no concomitant impairments in pulmonary functions.[84] Indeed, impairments in lung functions have not thus far fully explained worse fatigue in COVID-19.[84–87] Nevertheless, patients often report persistent dyspnoea, which was consistently related to their fatigue,[88–91] suggestive of multi-dimensional functional consequences. For instance, quality of life,[92] functional status[93] and an increased risk for post-infection healthcare needs [94] were all related to fatigue. Anxiety, post-traumatic stress and depressive symptoms are prevalent in survivors of respiratory viral infections.[91,95–100] A meta-analysis of 36 COVID-19 articles found high rates of anxiety (29%) and depressive symptoms (23%) 4-12 weeks post-illness.[101] The relationship between mental health outcomes and fatigue is consistent among convalescing COVID-19 patients. Depressive symptoms for example were associated with lower vitality [102] and fatigue.[85,103] In a retrospective study of 55 patients, baseline anxiety was related to higher fatigue 30 days after hospitalisation.[56] Moreover, these relationships can be present at 12 months follow-up. Mazza et al. (2021) found depression ($r=0.56$, $q=0.05$) and PTSD ($r=0.52$, $q=0.05$) were related to fatigue severity in 402 post-Covid patients. Neuropsychiatric symptoms comprising anxiety, mood swings, irritability and depression and others, predicted chronic fatigue 9 months later for those with mild/moderate disease ($p=0.01$).[104]

Summary and aims

For the majority of patients acute fatigue diminishes during the course of a virus, but current evidence suggests some experience longer lasting symptoms, and these affect functional and psychological recovery. Other meta-analyses have focused on post-acute sequelae of Covid-19 (PASC) or clusters of symptoms and therefore fewer studies have investigated solely fatigue outcomes. Moreover, a proportion of these reviews were narrative in design, which did not provide a pooled estimate for fatigue. Furthermore, fatigue is reported as the most prominent factor of post-infection symptomology indicative of its importance in understanding recovery. Therefore, the objectives of this systematic review were to a) investigate the prevalence of persistent fatigue among survivors of COVID-19; b) integrate the findings by conducting a meta-analysis and c) investigate current evidence for factors associated with fatigue outcomes in this context.

METHODS

Search strategy

The protocol and PICO framework for this study (supplementary file 1) was developed utilising the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[105] Embase, PsyINFO, Medline, CINAHL, Cochrane Database of Systematic Reviews, Open Grey, MedRxiv and BioRxiv were systematically searched from January 2019 to 31 December 2021. Search terms: severe acute respiratory syndrome or severe acute respiratory adj2 syndrome or coronavirus or corona virus or corona adj1 virus or COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV or nCoV19 or nCoV2 or covid19 or covid-19 or covid and "chronic fatigue" or fatigue or tired or exhaust or quality adj2 life or QoL or health related quality) adj2 life or HRQoL. We incorporated ‘health related quality of life’ into our search terms in order to capture ‘vitality’, which we used as proxy for fatigue. Reference lists of the review studies were manually searched for additional articles. Full search protocols for each database are available in supplementary file 2. Duplicate references were removed electronically and imported into Rayyan [106] for screening and inclusion decisions.

Inclusion and exclusion criteria

Included were original articles with primary data, published in English between January 2019-December 2021. Adult patients (≥18 years) must have had a diagnosis of SARS-CoV-2 confirmed by RT-PCR, IgM/IgG serology or clinical assessment (e.g. chest X-ray, CT scan). ‘Probable’ or self-reported cases were excluded. All study designs were incorporated except qualitative and case reports. Main outcomes were fatigue/vitality reported as 'post-discharge', 'post-hospitalisation', 'post-acute', 'post-illness' or 'post-onset'. Outcomes were included if measured at a median/mean time of $\geq$ 30 days post-infection as defined. All associations with fatigue/vitality were included if reported/quantified (e.g. anxiety, dyspnoea). We excluded pandemic fatigue (defined as 'worn out' by pandemic warnings, government safety instructions, media coverage or compliance requirements), healthcare worker fatigue in the context of their work (e.g. burnout, compassion fatigue), comorbid physical disease or pregnant populations. We excluded 'muscle fatigue', 'leg fatigue' and fatigue combined with 'malaise' or 'muscle weakness'. Protocols, vaccination studies, newspaper articles, conference papers, commentaries, opinions or editorials were also omitted.

Data extraction

Titles and abstracts were screened by 1 reviewer (KPW). Full texts were screened by KPW. A data spreadsheet was created to record extracted data from the included studies. Spreadsheet variables were citation, population, sample size, control group, location, virus type and diagnostic method, follow-up period, study design, inclusion/exclusion criteria, objectives, outcome variable of interest (e.g. fatigue, vitality), associated variables (e.g. PTSD, dyspnoea), scales/measures employed, results, power calculation (Y/N). The senior researcher (TC) reviewed 10% of the final included studies. Discrepancies were resolved via discussion and consensus. A PRISMA flow diagram is available in Figure 1.

Figure 1. PRISMA 2020 flow diagram

Quality Assessments

Risk of bias was assessed by the JBI Critical Appraisal Tools.[107] Items demand a 'yes', 'no', 'unclear' or 'not applicable'. An overall assessment was made by assigning a grade of low quality, moderate quality or good quality. Three researchers (KPW, OS, CC) independently graded 13%, 14%

and 73% each of the total articles and, for the purposes of interrater estimation, researchers graded the same 10% of the articles. Interrater agreement was assessed by Fleiss' kappa, which indicated moderate agreement (k=0.534, p=.004).

Statistical analysis

We computed pooled mean prevalence for fatigue outcomes with 95% confidence intervals using a random effects model as high heterogeneity was anticipated. A number of studies investigated fatigue across multiple time points. Therefore, in order to maintain the independence of observations for the pooled prevalence, we selected 1 time-point with accompanying prevalence from each study using 1 of 3 methods: (a) fatigue reported at the stated mean/median time of the follow-up assessment, e.g. 127 days post-illness, (b) fatigue at the 3-month follow-up (being the mode for all 147 studies), or (c) for studies investigating fatigue > 4 months, we selected the shortest timepoint. Studies with missing data were excluded from analyses. Where studies investigated both 'fatigue' and CFS outcomes, we incorporated the 'fatigue' data only. This was because a confirmed diagnosis of CFS could not be established. To determine the trend for fatigue, 35 prospective studies, with available data for $\geq$ 2 follow-up times, were included in a meta-regression using the mixed-effects framework for meta-analyses developed by Sera et al. (2019).[108] Meta-regression coefficients were estimated using a Restricted Maximum Likelihood (REML) estimator. To determine the proportion of fatigued participants by study design, and to increase the power, we categorised studies into 2: 'cross-sectional' and 'prospective'. The latter included longitudinal and retrospective designs. The cross-sectional category comprised the remaining designs. Two categories were used to investigate proportions for 'ongoing symptomatic COVID-19'(1-3 months) and 'post-Covid-19 syndrome' (>3 months) following NICE guidelines (nice.org.uk). The robustness of the main pooled prevalence was checked by controlling for the presence of outliers. Studies with 95% confidence intervals falling outside the 95% confidence interval of the total pooled effect were defined as 'outliers'. Sensitivity analysis was performed on the mean pooled prevalence by excluding high risk of bias studies. Meta-analyses were conducted using R Studio, Version 1.3.1073,[109] using packages meta, metafor, dmetar, metareg, mixmeta and irr. Heterogeneity was assessed using Cochran Q statistic. We obtained the I^2 statistic with the degree of heterogeneity categorised as 'not important' (0-40%), 'moderate' (30-60%), 'substantial' (50-90%) and 'considerable' (75-100%).[110] We conducted Egger's tests and produced funnel plots to explore potential publication bias for all proportional analyses. For 'vitality' outcomes, lack of comparable controls and missing data precluded a means difference analysis.

Patient and public involvement: No patient was involved in this study.

RESULTS

Search results

A total of 14,262 articles were identified using the database search protocols. Following the removal of duplicates 13,210 articles remained for title and abstract screening. Of these a total of 3,222 were selected for full text screening producing a final total of 178 studies and 22 systematic reviews. We identified 147 as eligible for a quantitative analysis. A summary of the 147 included articles is available as supplementary Table 1. The studies are tabulated according to categorical and continuous fatigue outcome measures. Summary table of systematic reviews is available in supplementary file 3.

Study characteristics

A total of 178 articles comprising 48,466 participants and 22 systematic reviews were included.[13–16,97,101,111–126] 14(8%) were pre-prints, 30(17%) used a fatigue scale and 27(15%) used a validated measure with a fatigue item(s). 13(7%) utilised the 'vitality' subscale of the SF-36 and 108(61%) employed a questionnaire, interview or health records. The most common countries were Italy with 25 studies and USA with 23 studies. UK had 19 studies and China 14 studies. Spain had 12 and France had 9 studies. Germany had 8 and Switzerland had 7 studies. The Netherlands and Turkey had 6 studies each and India had 5. Iran had 4 studies. Bangladesh, Denmark, Egypt and

Pakistan had 3 studies each. Brazil, Chile, Israel, Mexico, Norway and Sweden all had 2 studies. Austria, Australia, Belgium, Canada, Colombia, Finland, Ireland, Hungary, Japan, Lithuania, Mexico, Nepal, Poland, Russia, Saudi Arabia and Zambia each had 1 study. There were 80 prospective and 11 retrospective cohort deigns. Six longitudinal studies, 29 cross-sectional, 8 case-controls, 5 case series, 36 cohort, 3 randomised-controlled trials and 22 systematic reviews. The most frequent follow-up times were 3 months (46 studies), 6 months (22 studies), 1 month (20 studies), 12 months (12 studies) and 2 months (12 studies). All other time-points had $\leq$ 8 studies. JBI quality assessments resulted in most studies receiving a moderate rating. Full ratings are available as supplementary file 4. In summary, 30 were assigned a 'high' risk of bias, 139 received a 'moderate' risk assessment and only 9 were considered 'low' risk. Lower grades were assigned for selection bias, lack of adequate control groups, small samples, study design and methodological bias (employment of unvalidated/unreliable scales).

Meta-analyses

A total of 48,466 participants were included for the meta-analysis of proportions using a random-effects model. A pooled prevalence from 147 studies was found to be 41% (95% CI: 37-45%, I^2 =98%). A forest plot of this analysis is available in Figure 2. Fatigue was present between 1 month to 1-year post-infection with a median time of 3 months (IQR=2-6). An Egger's test was conducted to assess possible publication bias for our proportional analysis. The results indicated funnel plot asymmetry (bias=3.35, p=0.001) (supplementary file 5).

Figure 2 Forest plot for proportion of fatigued

To explore potential origins of heterogeneity and to test the robustness of our pooled prevalence, outliers were controlled for. A 1% difference was found once n=84 outlier studies were removed 42% (95% CI: 40-45%, I^2= 67%), although heterogeneity was reduced to 'substantial'. Given the range of post-infection assessment periods, the effect of time on fatigue was investigated by a linear mixed-effects model meta-regression. The outcome variable was the proportion of individuals reporting fatigue, with 'Months' (number of months since infection) and 'Hospitalisation' (whether someone was hospitalised) as predictors. 36 studies with available fatigue data and multiple time points ($\geq$ 2 follow-ups) were included. We found an effect of time, with the proportion of fatigued participants decreasing by 5.7% per month (95% CI: 1-10%, p=0.05). There was no effect of Hospitalisation and no interaction between Hospitalisation and time (Table 1).

Table 1 Results of linear mixed-effect meta-regression of time and hospitalisation

Parameter	*Estimate*	*SE*	*AIC*	*p*	*95% CI*	
					Lower	*Upper*
Months	-0.0577	0.0252	501.933	.05	-0.1070	-0.0084
Hospitalisation	-0.0871	0.1088	-	.445	-0.3013	0.1326
Months: Hospitalised	0.0324	0.0674	505.680	.630	-0.0997	0.1645

AIC Akaike Information Criterion

We conducted 2 subgroup analyses to explore the origins of heterogeneity arising from study methodology and investigate between group differences. No significant difference in fatigue was found between n=67 cross-sectional studies (44%, CI: 38-50%,!^{2}=97.6%) and n=80 prospective studies (39%, CI: 33-45%, !^{2}=98%), p=0.272.

A higher proportion of fatigued participants was found in n=36 studies using a scale (51%, 95% CI: 43-58%,I^2= 96.2%) compared to n=111 studies using an unvalidated questionnaire (38%, 95% CI: 33-43%, I^2=98%), p=0.004. To assess fatigue occurring at (a) 1-3 months ('ongoing symptomatic COVID-19') and (b) > 3 months ('post-COVID-19 syndrome'), 2 random effects subgroup analyses were conducted. Between 1-3 months the proportion of fatigued was 41% (95% CI: 36-47%, k=86, I^2=98.3%). At > 3 months, the proportion was 41% (95% CI: 34-48%, k=61, I^2= 97.4%). Sensitivity analysis was performed by excluding n=30 quality assessments (graded 'low') and removing unpublished results from the main analysis (n=8). Results found the pooled prevalence to be 40% (95% CI: 36-45%, I^2 =98.3%) and 41% (95% CI: 37-46%, k=139, I^2 =98%) respectively, indicating little impact on the main results. Egger's tests indicated publication bias for both time categories and sensitivity. Plots available in supplementary files 6-15.

Factors associated with fatigue

Not all studies investigated or reported factors associated with fatigue. For some, the available data for each risk factor were too few to conduct a quantified analysis. Studies also used diverse outcome measures or non-validated scales. In addition, some risk factors were reported but not accompanied by quantified data making comparisons between studies problematic. Consequently, reported associations were arranged in tabular form illustrating the direction of the association with fatigue (Table 2). A positive symbol (+) indicated a positive association, a negative symbol (-) indicated a negative association and a zero (0) indicated no significant association between the investigated variable and fatigue.[127] Associations with fatigue measured in prospective cohort designs were demonstrated by superscript figures contained within parentheses, representing the time period the relationships were examined. Where a risk factor was examined with another (e.g. ICU admission with age), one set of results was included. Full details of the associations are available in supplementary file 16.

Table 2. Variables associated with fatigue

Factor	Cross-sectional		Prospective Cohort	
	Bivariate	*Multivariate*	*Bivariate*	*Multivariate*
PTSD ↑	+ +		+ +	
Anxiety symptoms ↑	+ 0 +	0	+	
Depression ↑	+ + + + + +	0 0	+ (0^6 $+^{12}$)	+
Psychiatric morbidity ↑			+	
Physical comorbidities	0 0 0	+	0	+ + + + + + +
Psychological distress			0	
Somatisation				0
Pulmonary functions	+ 0 0			0

Pneumonia (CXR)		+		
Disease Severity ↑	+ 0 - + 0 0 0 0	+	+ 0 + 0 0 0 + 0 0 0 0 + + + 0 0	0 0
Age ↑	0 - 0 + - 0 0 -	- + 0 0 0 +	0 0 + 0 0 0 0 0 0 --	+ 0 – + 0 +
ICU Admission	0 0 + + + +	0 0	+ 0	
Female gender	+ + + 0 + + + + + + 0 + + + + 0 + + + +	+ + + +	+ + 0 + 0 + + 0 + 0 0 + +	+ + + + 0 0
Ethnicity	0 0			
Marital status			0	
Rural/Urban habitat			0	
Occupation type			0	
BMI/obesity/weight↑	0 + + 0	0 0 +	0 0	0
Returned to work	+	+	0	
Employed				+
Retired				-
Exercise capacity <	+ + +			0 0
Intubated/IMV	+		+	+ +
Serum troponin-1 (TN1)			+	
Nucleic-acid test (> 14 days, 46-69 years old)	+	+		
Reduction of serum NfL levels			0	
Blood (e.g. lymphocytes10⁹/L, IgG)	0 + +	+	0	0
SpO²				0
Gut microbiota	+			
% Predicted VO2			0	
Mean consecutive difference (MCD) in extensor digitorum communis (EDC)	+			
Alcohol consumption	0	0		
Smoking history	0 0 0 0	0 0		0 0
Response to follow-up <				
Length of stay (LOS) >	0 + + 0 0	+	0	
Hospital readmission				+
Education ↑	0	0		
Physical health ↓	0 +			+
Post functional status/daily functioning ↓	+ + +			
Frailty ↑			+	
Sleep (quality & quantity)	+ +		+	
Steroid treatment	0 0			
Days since onset ↑	0	+		
Cognitive problems ↑	+ + +		+	

1

Breathlessness/Dyspnoea ↑	+ 0	+	+ +	+
Post Covid-19 functioning↓			+	+

Non-modifiable factors

Older age was reported in 31 studies with mixed results. Six reported an association with, or an increased likelihood of fatigue (OR=1.02) in participants >50.[45,56,70,72,73,128] Two reported higher fatigue in > 60 year olds [129] and > 40-year olds.[89] Some, however, reported that younger age related to fatigue [130–133] or no difference in fatigue severity between <65 and >65 year olds.[134] The remaining 18 studies did not find a relationship to fatigue.[44,74,75,85,86,90,91,102,104,134–142] However, studies reporting non-significant results had small to modest sample sizes and were therefore potentially underpowered. Gender was investigated by 43 studies. Twenty-six reported a significant association with fatigue or found higher fatigue in women.[42,45,56,67–70,73,102,104,129,134,137,139,141–153] Females (54.3%) reported more severe/moderate fatigue than males (29.6%),[92,133] and had significantly lower vitality scores (M=81.80) compared to men (M=83.25).[128] However, 16 utilised an unvalidated instrument potentially affecting results. Those finding no association [44,75,85,89,90,135,136,140,141,154,155] had small sample sizes and only 3 used a fatigue scale.

Physical factors

The key physical factors associated with fatigue were dyspnoea, pulmonary functions, exercise capacity, comorbidities and ICU admission. Positive correlations between breathlessness and fatigue were found in 7 studies.[85,88–91,133,156] At ≥ 6 months post-infection 2 did not find a relationship,[86,102] suggestive of improvements over time. Although Staudt et al. (2022) found that 'respiratory symptoms' on the SGRQ were related to fatigue in multivariate analyses at 10 months post-infection (OR=1.06, p=0.05). However, only 2 used a dyspnoea scale or a fatigue scale. All had small sample sizes, therefore potentially underpowered. Pulmonary functions were reported in 4 studies. FEV_1 related to higher vitality in 1 (r=.0.23, p<.05),[84] but non-significant in the others.[85,86,156] These studies assessed survivors > 3 months, suggesting results are indicative of functional improvements overtime. Exercise capacity was generally poor in survivors[157] and 7 studies examined its relationship with fatigue, with mixed results. Better exercise performance was associated with vitality ($r = 0.526$, $p<.001$)[84] but not with 4-meter gait speed test [91] or 6MWT.[85] Two others found improved fatigue following a physical rehabilitation programme.[103,158] At 3 months post-infection, fatigue was cited as the reason for halting a cardiopulmonary performance test or limiting exercise in 3 studies.[159–161] Myopathy was associated with fatigue in another small study of 20 people [162] suggestive of poor conditioning contributing to limited capacity. Generally, fatigue had an inverse relationship with exercise capacity in the early months. Where the relationship remained beyond 3 months,[84] patients were overweight/obese, which possibly affected performance. Also all studies had small sample sizes limiting generalisability.

Physical comorbidities such as hypertension, asthma and diabetes were related to fatigue in 8 studies.[67,73,130,132,139,150,152,163] Four found no relationship.[136,137,140,151]. A large study of 4,755 participants found hypertension increased the likelihood (OR=1.27, $p=0.05$) of persistent fatigue > 6 months.[152] Yomogida et al. (2021) reported that having at least 1 comorbidity increased the risk for fatigue (aOR=4.39, $p<.001$). Moreover, worse physical health and its effects of daily living were related to an increased likelihood of fatigue (OR = 10.48) in 3 studies,[164–166] implying general poorer functioning among survivors.

For those admitted to ICU, some experienced high fatigue (8 studies),[133,135,163] and lower vitality,[167,168] or had an increased likelihood for fatigue (OR=4.63).[56,132,169] While 4 found no association between ICU admission and worse fatigue or vitality.[42,156,170,171] Patients who received mechanical ventilation had lower vitality (M=50, 95% CI: 44- 57) than a sex and age matched group (M=68, 95% CI: 67-69).[172] Similarly, more intubated patients had fatigue (38.1%) than non-intubated(29.9%).[173] One study found the proportion of fatigued was higher in the ward group (74%) compared to ICU (33%).[147] Disease severity also had an inconsistent impact on fatigue, with most studies finding no association with severe acute disease.[76,92,99,134,139,140,155,174–179] Five studies found a significant association with critical illness.[44,45,180–182] Two studies found a relationship between severity of acute illness and vitality,[48,49] although both had small samples and were single-centre designs. Interestingly, moderately severe COVID-19 related to fatigue (OR=2.1) in 2 studies.[181,183] Even after a longer hospital stay, the relationship with fatigue was inconsistent with 2 finding significance,[56,128] while 4 did not.[74,140,142,184] Taken together these results indicate an uncertain contribution of critical illness to fatigue, although the non-significant results chiefly occurred > 6 months. However, the classification of disease severity varied between studies and countries making comparisons difficult.

Psychological factors

A relationship with anxiety was found up to 6 months post-infection in 6 studies.[56,89,184,185] The fatigued had higher anxiety (56.3%) compared to non-fatigued (24.6%, p<.001)[89,184] In contrast, no significant interaction between anxiety and fatigue at 1 month related to later fatigue.[186] Similar results were found for depression. Previous depression was associated with lower vitality (-12.05, p=0.005) in 1 study.[102] and a higher proportion of fatigued had depressive symptoms in 2 other studies (p =.004).[89,96] Other studies found consistently moderate positive correlations (r=0.470).[142,187,188] or increased likelihood of fatigue (OR=0.24, p=0.05) in those with depressive symptoms.[56] The relationship continued up until 12 months.[85,142] Four studies found that those with PTSD symptoms reported higher fatigue [96,133] and PTSD was associated with fatigue at 6 and 12 months after infection.[142] Barizien et al. (2021) found higher scores on the PCL-5 (PTSD Checklist for DSM-5) in those with fatigue (M=31, IQR=18) compared to those without fatigue (M=18, IQR=19, p<.001). Generalisability of these results, however, are likely limited due to modest sample sizes and single-centre designs. In addition only 3 studies used a valid fatigue scale.

DISCUSSION

This review investigated the prevalence of persistent fatigue in survivors who had a confirmed diagnosis of SARS-CoV-2, using a mean of $\geq$ 30 days post-infection. We found a considerable proportion of patients continued to experience fatigue up to 12 months after their initial illness, which was associated with some non-modifiable factors including gender, age and modifiable factors such as anxiety, depression and post-traumatic stress. Our findings support other research indicating that fatigue is an important symptom in persistent post-acute sequelae.[14,114,189–196] Rates of fatigue may depend on when it was measured and, in this respect, we found overall rates of fatigue decreased by 6% per month. Fatigue did not differ by hospitalisation status, indicating that the contribution of severe disease was not related to fatigue recovery for most people. This is consistent with previous reviews, which did not find support for the effects of critical illness on fatigue outcomes.[119,197] Respiratory impairments, a key clinical indicator, were associated with worse vitality (r=0.290, p=0.026) post-recovery,[84] although at 10 months, FEV_1 was not associated[85] implying that, as lung function improved, fatigue diminished. Indeed, rehabilitation aimed at improving functioning by incorporating aerobic exercises, improved vitality scores.[103,168,198] Some survivors, however, continued to experience dyspnoea, which was associated with their fatigue,[88–91] despite normal pulmonary tests.[86,160] Similarly, reduced exercise capacity, as a result of critical illness, is thought to contribute to reduced HRQoL and fatigue outcomes in recovered patients.[199] However, our review did not find a consistent relationship between exercise performance and worse fatigue in those who had more severe disease. It is possible that these limitations are related to diminished muscle function [199] and deconditioning as rehabilitation programmes have led to improved vitality [158,198] and lower fatigue.[103,158] In a 9-week telerehabilitation study of 115 participants, incorporating 2/3 aerobic exercises per week to improve physical capacity, reported significantly increased vitality scores from pre = 40.7(SD=21.7)to post = 58.5(SD=21.2), p=0.001.[168] While deconditioning could explain fatigue, persistent fatigue may be related to other variables including psychological factors.

Depression and anxiety were found to be correlated with fatigue in our review.[56,185,187] Moreover, these relationships were found some distance from the initial infection.[142,156] In a prospective study of 402 participants using a fatigue scale, Mazza et al. (2021) found that both anxiety (r=0.48) and PTSD (r=0.52) were moderately correlated with fatigue at 6 and 12 months, post-illness. These findings accord with critical illness studies[200] and systematic reviews suggesting that symptoms of depression, anxiety, PTSD and fatigue persist long after discharge.[197] For COVID-19, we cannot be certain of the longevity of psychological factors or their relationship to fatigue because the body of evidence is too small, but current literature indicates the relationship remains up to 6 months later.[89,136,185] This fits with previous coronavirus research indicating those with chronic fatigue were more likely to have psychiatric morbidity 4 years following a SARS infection.[201] Similarly, those with psychiatric illness reported higher fatigue than those without ($p<.05$) in survivors of SARS.[202]

Theoretical implications

Our results found that persistent fatigue was associated with physical functioning several months after the initial infection. The origins of fatigue persistence are multidimensional, likely linked to physical factors in the shorter term and psychological factors in the long term. Both possibly as a result of stress and distress resulting from the pandemic or infection.[203,204] These factors, alongside other mechanisms such as skeletal muscle deficits,[205] could lead to poorer global functioning and lower engagement in activities or exercise thus prolonging fatigue. We have illustrated diagrammatically our findings post-coronavirus fatigue (Figure 3).

Figure 3 Diagram of post-COVID-19 fatigue findings

Practical implications

Our review suggests post-coronavirus fatigue is complex, affecting multiple domains of physical and psychological well-being. While there were small improvements in fatigue over time, our review indicates that fatigue remains a significant problem for patients beyond their anticipated recovery time.[206] Pulmonary and exercise programmes have shown promise.[103,168,198] Our results also suggest that psychological interventions may benefit some survivors. Given fatigue is one of a number of post-Covid symptoms,[207–210] an integrated management approach has been suggested.[211] Care pathways should identify those most at risk for long-term symptoms such as women and older people with comorbidities.

Future directions

Few studies have examined correlates between fatigue, physical and pulmonary functioning, psychological and social functioning in hospitalised and outpatients. Some research concerns symptom 'clusters' or 'post-covid syndrome'[212–215] limiting understanding of fatigue processes. Future studies should interrogate risk factors further to help inform the development of clinical interventions to address persistent fatigue. Furthermore, fatigue is the principal symptom for post-illness patients, but there is little research into what mechanisms may ameliorate distress resulting from infection, and thus protect against long symptoms. Severity of the illness, for instance, was not conclusive in our study and nor was length of stay pointing to the importance of individual differences.

Limitations

The generalisability of our results should be applied with caution due to a number of limitations. Firstly, the considerable and unexplained between-study heterogeneity. Measurement error was not found to explain the inconsistency. However, diverse tools were used to measure fatigue in different populations. Non-validated questionnaires were unlikely to capture fatigue dimensions accurately given most had 1-2 fatigue-related items. Moreover, scoring and cut-offs were underreported, contributing to variability. Included studies could not adequately exclude 'pandemic fatigue' in their selections or definitions therefore, we recognise that our results cannot completely exclude such fatigue and its potential influence on participants in the included studies. Some studies used particular populations, including older age or only those admitted to ICU, meaning they were not representative.

Furthermore, our sample comprised primarily of hospitalised patients with potentially more severe disease. This was complicated by different admission and discharge protocols across countries, with some admitting all confirmed patients regardless of disease severity, explaining why there was no difference between hospitalised and non-hospitalised survivors. We also encountered missing data, which reduced the reliability of our results. Moreover, Egger's tests suggested all but one analyses were asymmetric representing a high likelihood of publication bias. Small study effects were likely to affect precision. Larger studies, with more precise confidence intervals are likely to be a more reliable indicator of fatigue proportions. Moreover, sample bias probably occurred due to recruitment from single-centre post-covid clinics[216–218] for persistent symptoms and therefore could be expected to have higher fatigue than controls or population norms. Different admission and discharge protocols and lung function reference ranges vary between countries.[219] Our results, therefore, should be viewed with this in mind. Methodologically, our study had only one reviewer for screening and data extraction and we did not contact authors for missing data meaning our study was at higher risk for excluding relevant data. Other limitations include the inclusion of non-peer reviewed articles and those limited to English. For the meta-analysis, given the multiple assessment times, we incorporated one median follow-up time obtained from each study, which may not denote actual fatigue prevalence. Despite these limitations, we incorporated as substantial sample size likely to be a reasonable estimate of fatigue in this population.

CONCLUSION

This large review provides a broad illustration of fatigue outcomes and complements the growing body of information for persistent symptoms in those recovering from COVID-19. We report that fatigue decreases over time, but recovery pathways are potentially impeded by a number of risk factors, independent of disease severity or hospitalisation. Our study indicates the need for long-term clinical and psychological rehabilitation support for survivors of COVID-19.

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TC is the author of several self-help books on chronic fatigue for which she has received royalties. TC(KCL) has received ad hoc payments for workshops carried out in long-term conditions. TC acknowledges financial support from NIHR. TC is on the Expert Advisory Panel for Covid-19 Rapid Guidelines. She is also in receipt of grants related to long Covid from the United Kingdom Research and Innovation (UKRI) and Guy's and St Thomas' Charity. TC collaborates with The Post-hospitalisation Covid-19 Study (PHOSP-COVID). TC is the Director of the Persistent Physical

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References

1 Dittner A., Wessely S., Brown R. The assessment of fatigue. *J Psychosom Res* 2004;**56**:157–70. doi:10.1016/S0022-3999(03)00371-4

2 Grant MC, Geoghegan L, Arbyn M, *et al.* The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. *PLoS One* 2020;**15**:e0234765. doi:http://dx.doi.org/10.1371/journal.pone.0234765

3 Lemhöfer C, Sturm C, Loudovici-Krug D, *et al.* The impact of Post-COVID-Syndrome on functioning – results from a community survey in patients after mild and moderate SARS-CoV-2-infections in Germany. *J Occup Med Toxicol* 2021;**16**:1–9. doi:10.1186/s12995-021-00337-9

4 Leth S, Gunst JD, Mathiasen V, *et al.* Persistent Symptoms in Patients Recovering From COVID-19 in Denmark. *Open forum Infect Dis* 2021;**8**:ofab042. doi:https://dx.doi.org/10.1093/ofid/ofab042

5 Liang L, Yang B, Jiang N, *et al.* Three-Month Follow-Up Study of Survivors of Coronavirus Disease 2019 after Discharge. *J Korean Med Sci* 2020;**35**. doi:10.3346/jkms.2020.35.e418

6 Miyazato Y, Akashi M, Osanai Y, *et al.* Prolonged and late-onset symptoms of coronavirus disease 2019. *Open Forum Infect Dis* 2020;**7**:ofaa507. doi:10.1093/ofid/ofaa507

7 Ortelli P, Ferrazzoli D, Sebastianelli L, *et al.* Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *J Neurol Sci* 2021;**420**:117271.

doi:http://dx.doi.org/10.1016/j.jns.2020.117271

8 Rosales-Castillo A, García de los Ríos C, Mediavilla García JD. Persistent symptoms after acute COVID-19 infection: importance of follow-up. *Med Clin (Barc)* 2021;**156**:35–6. doi:10.1016/j.medcli.2020.08.001

9 Shoucri SM, Purpura L, DeLaurentis C, *et al.* Characterising the long-term clinical outcomes of 1190 hospitalised patients with COVID-19 in New York City: a retrospective case series. *BMJ Open* 2021;**11**:e049488. doi:10.1136/bmjopen-2021-049488

10 Søraas A, Kalleberg KT, Dahl JA, *et al.* Persisting symptoms three to eight months after non-hospitalized COVID-19, a prospective cohort study. *PLoS One* 2021;**16**:e0256142. doi:10.1371/journal.pone.0256142

11 Sultana S, Islam MT, Salwa M, *et al.* Duration and Risk Factors of Post-COVID Symptoms Following Recovery Among the Medical Doctors in Bangladesh. *Cureus* 2021;**13**:e15351. doi:https://dx.doi.org/10.7759/cureus.15351

12 Zhou Y, Zhang J, Zhang D, *et al.* Linking the gut microbiota to persistent symptoms in survivors of COVID-19 after discharge. *J Microbiol* 2021;**59**:941–8. doi:https://dx.doi.org/10.1007/s12275-021-1206-5

13 Badenoch JB, Rengasamy ER, Watson CJ, *et al.* Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.30.21256413. doi:10.1101/2021.04.30.21256413

14 Hoshijima H, Mihara T, Seki H, *et al.* Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. *medRxiv* 2021;:2021.04.08.21255109. doi:10.1101/2021.04.08.21255109

15 Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, *et al.* Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chron Respir Dis* 2021;**18**:147997312110022. doi:10.1177/14799731211002240

16 Malik P, Patel K, Pinto C, *et al.* Post-acute COVID-19 syndrome (PCS) and health-related

quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* Published Online First: 2021. doi:https://dx.doi.org/10.1002/jmv.27309

17 Mak IWC, Chu CM, Pan PC, *et al.* Long-term psychiatric morbidities among SARS survivors. *Gen Hosp Psychiatry* 2009;**31**:318–26. doi:10.1016/j.genhosppsych.2009.03.001

18 Lee SH, Shin H-S, Park HY, *et al.* Depression as a Mediator of Chronic Fatigue and Post-Traumatic Stress Symptoms in Middle East Respiratory Syndrome Survivors. *Psychiatry Investig* 2019;**16**:59–64. doi:10.30773/pi.2018.10.22.3

19 Becker C, Beck K, Zumbrunn S, *et al.* Long COVID 1 year after hospitalisation for COVID-19: a prospective bicentric cohort study. *Swiss Med Wkly* 2021;**151**:w30091. doi:https://dx.doi.org/10.4414/smw.2021.w30091

20 Khalaf M, Bazeed SE, Abdel-Gawad M, *et al.* Prevalence and Predictors of Persistent Symptoms after Clearance of SARS-CoV-2 Infection: A Report from Egypt. *SSRN Electron J* Published Online First: 2020. doi:10.2139/ssrn.3727954

21 Arnold DT, Hamilton FWFW, Morley MA, *et al.* Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. *medRxiv* 2020;:2020.08.12.20173526. doi:10.1101/2020.08.12.20173526

22 Bozzetti S, Ferrari S, Zanzoni S, *et al.* Neurological symptoms and axonal damage in COVID-19 survivors: are there sequelae? *Immunol Res* Published Online First: 7 August 2021. doi:10.1007/s12026-021-09220-5

23 Steinbeis F, Thibeault C, Doellinger F, *et al.* Severity of respiratory failure and computed chest tomography in acute COVID-19 correlates with pulmonary function and respiratory symptoms after infection with SARS-CoV-2: An observational longitudinal study over 12 months. *Respir Med* 2021;**191**:106709. doi:https://dx.doi.org/10.1016/j.rmed.2021.106709

24 Tleyjeh IM, Saddik B, AlSwaidan N, *et al.* Prevalence and predictors of Post-Acute COVID-19 Syndrome (PACS) after hospital discharge: A cohort study with 4 months median follow-up. *PLoS One* 2021;**16**:e0260568. doi:https://dx.doi.org/10.1371/journal.pone.0260568

25 van Veenendaal N, van der Meulen IC, Onrust M, *et al.* Six-Month Outcomes in COVID-19

ICU Patients and Their Family Members: A Prospective Cohort Study. Healthc. . 2021;**9**. doi:10.3390/healthcare9070865

26 Wu Q, Li H, Guo J, *et al.* A Follow-Up Study of Lung Function and Chest Computed Tomography at 6 Months after Discharge in Patients with Coronavirus Disease 2019. *Can Respir J* 2021;**2021**:6692409. doi:http://dx.doi.org/10.1155/2021/6692409

27 Zayet S, Zahra H, Royer P-YY, *et al.* Post-COVID-19 Syndrome: Nine Months after SARS-CoV-2 Infection in a Cohort of 354 Patients: Data from the First Wave of COVID-19 in Nord Franche-Comte Hospital, France. *Microorganisms* 2021;**9**. doi:https://dx.doi.org/10.3390/microorganisms9081719

28 Evans RA, McAuley H, Harrison EM, *et al.* Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* Published Online First: 2021. doi:https://dx.doi.org/10.1016/S2213-2600(21)00383-0

29 Kayaaslan B, Eser F, Kalem AK, *et al.* Post-COVID syndrome: A single-center questionnaire study on 1007 participants recovered from COVID-19. *J Med Virol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/jmv.27198

30 Fatima G, Bhatt D, Idrees J, *et al.* Elucidating Post-COVID-19 manifestations in India. *medRxiv* 2021;:2021.07.06.21260115. doi:10.1101/2021.07.06.21260115

31 Catalan IP, Marti CR, Sota DP de la, *et al.* Corticosteroids for COVID-19 symptoms and quality of life at 1 year from admission. *J Med Virol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/jmv.27296

32 Scherlinger M, Felten R, Gallais F, *et al.* Refining “Long-COVID” by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection. *Infect Dis Ther* 2021;**10**:1747–63. doi:10.1007/s40121-021-00484-w

33 Poyraz BÇ, Poyraz CA, Olgun Y, *et al.* Psychiatric morbidity and protracted symptoms after COVID-19. *Psychiatry Res* 2021;**295**:113604. doi:10.1016/j.psychres.2020.113604

34 Ganesh R, Ghosh AK, Nyman MA, *et al.* PROMIS scales for assessment of the impact of post-

COVID syndrome: A Cross Sectional Study. *medRxiv* 2021;:2021.05.25.21257817. doi:10.1101/2021.05.25.21257817

35 Eloy P, Tardivon C, Martin-Blondel G, *et al.* Severity of self-reported symptoms and psychological burden 6-months after hospital admission for COVID-19: a prospective cohort study. *Int J Infect Dis* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.ijid.2021.09.011

36 Fortini A, Torrigiani A, Sbaragli S, *et al.* COVID-19: persistence of symptoms and lung alterations after 3-6 months from hospital discharge. *Infection* 2021;**49**:1007–15. doi:http://dx.doi.org/10.1007/s15010-021-01638-1

37 García-Abellán J, Padilla S, Fernández-González M, *et al.* Antibody Response to SARS-CoV-2 is Associated with Long-term Clinical Outcome in Patients with COVID-19: a Longitudinal Study. *J Clin Immunol* 2021;**41**:1490–501. doi:10.1007/s10875-021-01083-7

38 Mahmud R, Rassel MA, Rahman MM, *et al.* Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. *PLoS One* 2021;**16**:e0249644. doi:http://dx.doi.org/10.1371/journal.pone.0249644

39 Moreno-Perez O, Merino E, Boix V, *et al.* Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect* 2021;**82**:378–83. doi:http://dx.doi.org/10.1016/j.jinf.2021.01.004

40 Righi E, Mirandola M, Mazzaferri F, *et al.* Long-Term Patient-Centred Follow-up in a Prospective Cohort of Patients with COVID-19. *Infect Dis Ther* 2021;**10**:1579–90. doi:http://dx.doi.org/10.1007/s40121-021-00461-3

41 Seesle J, Hippchen T, Lim A, *et al.* Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. *Clin Infect Dis* Published Online First: 2021. doi:http://dx.doi.org/10.1093/cid/ciab611

42 Fernandez-De-Las-Penas C, Palacios-Cena D, Palacios-Cena M, *et al.* Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously Hospitalized Patients: Related Functional Limitations and Disability. *Respiration* Published Online First: 2021.

doi:http://dx.doi.org/10.1159/000518854

43 Gamberini L, Mazzoli CA, Prediletto I, *et al.* Health-related quality of life profiles, trajectories, persistent symptoms and pulmonary function one year after ICU discharge in invasively ventilated COVID-19 patients, a prospective follow-up study. *Respir Med* 2021;**189**:106665. doi:10.1016/j.rmed.2021.106665

44 Rauch B, Kern-Matschilles S, Haschka SJ, *et al.* COVID-19-related symptoms 6 months after the infection - Update on a prospective cohort study in Germany. *medRxiv* 2021;:2021.02.12.21251619. doi:10.1101/2021.02.12.21251619

45 Zhang X, Wang F, Shen Y, *et al.* Symptoms and Health Outcomes among Survivors of COVID-19 Infection 1 Year after Discharge from Hospitals in Wuhan, China. *JAMA Netw Open* 2021;**4**:e2127403. doi:http://dx.doi.org/10.1001/jamanetworkopen.2021.27403

46 Kozak R, Armstrong SM, Salvant E, *et al.* Recognition of Long-COVID-19 Patients in a Canadian Tertiary Hospital Setting: A Retrospective Analysis of Their Clinical and Laboratory Characteristics. *Pathogens* 2021;**10**:1246. doi:10.3390/pathogens10101246

47 Liu T, Wu D, Yan W, *et al.* Twelve-month systemic consequences of COVID-19 in patients discharged from hospital: a prospective cohort study in Wuhan, China. *Clin Infect Dis* Published Online First: 2021. doi:https://dx.doi.org/10.1093/cid/ciab703

48 Van Den Borst B, Van Hees HWH, Van Helvoort H, *et al.* Comprehensive Health Assessment 3 Months after Recovery from Acute Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis* 2021;**73**:E1089–98. doi:http://dx.doi.org/10.1093/cid/ciaa1750

49 van der Sar - van der Brugge S, Talman S, de Mol M, *et al.* Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respir Med* 2021;**176**:106272. doi:https://dx.doi.org/10.1016/j.rmed.2020.106272

50 Boari GEM, Bonetti S, Braglia-Orlandini F, *et al.* Short-Term Consequences of SARS-CoV-2-Related Pneumonia: A Follow Up Study. *High Blood Press Cardiovasc Prev* 2021;**28**:373–81. doi:https://dx.doi.org/10.1007/s40292-021-00454-w

51 Creamer AW, Alaee S, Iftikhar H, *et al.* Clinico-radiological recovery following Severe covid-19

pneumonia. *Thorax* 2021;**76**:A185. doi:http://dx.doi.org/10.1136/thorax-2020-BTSabstracts.320

52 Horwitz LI, Garry K, Prete AM, *et al.* Six-Month Outcomes in Patients Hospitalized with Severe COVID-19. *J Gen Intern Med* Published Online First: 2021. doi:https://dx.doi.org/10.1007/s11606-021-07032-9

53 Naik S, Haldar SN, Soneja M, *et al.* Post COVID-19 sequelae: A prospective observational study from Northern India. *Drug Discov Ther* 2021;**15**:254–60. doi:10.5582/ddt.2021.01093

54 Frontera JA, Yang D, Lewis A, *et al.* A Prospective Study of Long-Term Outcomes Among Hospitalized COVID-19 Patients with and without Neurological Complications. *medRxiv* 2021;:2021.03.18.21253881. doi:10.1101/2021.03.18.21253881

55 Gupta A, Garg I, Iqbal A, *et al.* Long-Term X-ray Findings in Patients With Coronavirus Disease-2019. *Cureus* 2021;**13**:e15304. doi:https://dx.doi.org/10.7759/cureus.15304

56 Qin ES, Gold LS, Hough CL, *et al.* Patient-Reported Functional Outcomes Thirty Days after Hospitalization for COVID-19. *PM R* Published Online First: 2021. doi:https://dx.doi.org/10.1002/pmrj.12716

57 Bell ML, Catalfamo CJ, Farland L V, *et al.* Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT. *medRxiv* 2021;:2021.03.29.21254588. doi:10.1101/2021.03.29.21254588

58 Carvalho-Schneider C, Laurent E, Lemaignen A, *et al.* Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021;**27**:258–63. doi:10.1016/j.cmi.2020.09.052

59 Graham EL, Clark JR, Orban ZS, *et al.* Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 'long haulers'. *Ann Clin Transl Neurol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/acn3.51350

60 Savarraj JPJ, Burkett AB, Hinds SN, *et al.* Three-month outcomes in hospitalized COVID-19 patients. *medRxiv* 2020;:2020.10.16.20211029. doi:10.1101/2020.10.16.20211029

61 Senjam SS, Balhara YPS, Kumar P, *et al.* Assessment of Post COVID-19 Health Problems

and its Determinants in North India: A descriptive cross section study. *medRxiv* 2021;:2021.10.03.21264490. doi:10.1101/2021.10.03.21264490

62 Boscolo-Rizzo P, Guida F, Polesel J, *et al.* Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol* 2021;**11**:1685–8. doi:10.1002/alr.22832

63 Bliddal S, Banasik K, Pedersen OB, *et al.* Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. *Sci Rep* 2021;**11**:13153. doi:10.1038/s41598-021-92045-x

64 Castro VM, Rosand J, Giacino JT, *et al.* Case-control study of neuropsychiatric symptoms in electronic health records following COVID-19 hospitalization in 2 academic health systems. *Mol Psychiatry* 2022;**27**:3898–903. doi:10.1038/s41380-022-01646-z

65 Logue JK, Franko NM, McCulloch DJ, *et al.* Sequelae in Adults at 6 Months After COVID-19 Infection. *JAMA Netw Open* 2021;**4**:e210830. doi:10.1001/jamanetworkopen.2021.0830

66 Heightman M, Prashar J, Hillman TE, *et al.* Post-COVID assessment in a specialist clinical service: a 12-month, single-centre analysis of symptoms and healthcare needs in 1325 individuals. *medRxiv* 2021;:2021.05.25.21257730. doi:10.1101/2021.05.25.21257730

67 Amin-Chowdhury Z, Harris RJ, Aiano F, *et al.* Characterising post-COVID syndrome more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. *medRxiv* 2021;:2021.03.18.21253633. doi:10.1101/2021.03.18.21253633

68 Bai F, Tomasoni D, Falcinella C, *et al.* Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.cmi.2021.11.002

69 Hellemons ME, Huijts S, Bek L, *et al.* Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for SARS-CoV-2; A Longitudinal Study of Respiratory, Physical and Psychological Outcomes. *Ann Am Thorac Soc* Published Online First: 2021. doi:https://dx.doi.org/10.1513/AnnalsATS.202103-340OC

70 Lombardo MDM, Foppiani A, Peretti GM, *et al.* Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. *Open forum*

Infect Dis 2021;**8**:ofab384. doi:https://dx.doi.org/10.1093/ofid/ofab384

71 Augustin M, Schommers P, Stecher M, *et al.* Recovered not restored: Long-term health consequences after mild COVID-19 in non-hospitalized patients. *medRxiv* 2021;:2021.03.11.21253207. doi:10.1101/2021.03.11.21253207

72 Daugherty SE, Guo Y, Heath K, *et al.* Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021;**373**:n1098. doi:https://dx.doi.org/10.1136/bmj.n1098

73 Yomogida K, Zhu S, Rubino F, *et al.* Post-Acute Sequelae of SARS-CoV-2 Infection Among Adults Aged ≥18 Years — Long Beach, California, April 1–December 10, 2020. *MMWR Morb Mortal Wkly Rep* 2021;**70**:1274–7. doi:10.15585/mmwr.mm7037a2

74 Karaarslan F, Demircioğlu Güneri F, Kardeș S. Postdischarge rheumatic and musculoskeletal symptoms following hospitalization for COVID-19: prospective follow-up by phone interviews. *Rheumatol Int* 2021;**41**:1263–71. doi:10.1007/s00296-021-04882-8

75 Hossain MA, Hossain KMA, Saunders K, *et al.* Prevalence of Long COVID symptoms in Bangladesh: a prospective Inception Cohort Study of COVID-19 survivors. *BMJ Glob Heal* 2021;**6**. doi:https://dx.doi.org/10.1136/bmjgh-2021-006838

76 Zhao Y, Yang C, An X, *et al.* Follow-up study on COVID-19 survivors one year after discharge from hospital. *Int J Infect Dis* 2021;**112**:173–82. doi:https://dx.doi.org/10.1016/j.ijid.2021.09.017

77 Cao J, Chen X, Zheng X, *et al.* Three-month outcomes of recovered COVID-19 patients: prospective observational study. *Ther Adv Respir Dis* 2021;**15**. doi:http://dx.doi.org/10.1177/17534666211009410

78 Aranda J, Oriol I, Martín M, *et al.* Long-term impact of COVID-19 associated acute respiratory distress syndrome. *J Infect* Published Online First: August 2021. doi:10.1016/j.jinf.2021.08.018

79 Szekely Y, Lichter Y, Sadon S, *et al.* Cardiorespiratory Abnormalities in Patients Recovering from Coronavirus Disease 2019. *J Am Soc Echocardiogr* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.echo.2021.08.022

80 Wang SY, Adejumo P, See C, *et al.* Characteristics of Patients Referred to a Cardiovascular Disease Clinic for Post-Acute Sequelae of SARS-CoV-2 Infection. *medRxiv* 2021;:2021.12.04.21267294. doi:10.1101/2021.12.04.21267294

81 Donaghy M, McKeegan D, Walker J, *et al.* Follow up for COVID-19 in Belfast City Hospital. *Ulster Med J* 2021;**90**:157–61.http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med19&NEWS=N&AN=34815594

82 Chudzik M, Kapusta J, Burzyńska M. Use of 1-MNA to Improve Exercise Tolerance and Fatigue in Patients After COVID-19. *medRxiv* 2021;:2021.07.14.21259081. doi:10.1101/2021.07.14.21259081

83 Chen Y, Liu C, Wang T, *et al.* Efficacy and safety of Bufei Huoxue capsules in the management of convalescent patients with COVID-19 infection: A multicentre, double-blind, and randomised controlled trial. *J Ethnopharmacol* 2022;**284**:114830. doi:https://dx.doi.org/10.1016/j.jep.2021.114830

84 Bardakci MI, Ozkarafakili MA, Ozturk EN, *et al.* Evaluation of long-term radiological findings, pulmonary functions, and health-related quality of life in survivors of severe COVID-19. *J Med Virol* 2021;**93**:5574–81. doi:http://dx.doi.org/10.1002/jmv.27101

85 Staudt A, Jorres RA, Hinterberger T, *et al.* Associations of Post-Acute COVID syndrome with physiological and clinical measures 10 months after hospitalization in patients of the first wave. *Eur J Intern Med* 2022;**95**:50–60. doi:https://dx.doi.org/10.1016/j.ejim.2021.10.031

86 Froidure A, Mahsouli A, Liistro G, *et al.* Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. *Respir Med* 2021;**181**:106383. doi:10.1016/j.rmed.2021.106383

87 Smet J, Stylemans D, Hanon S, *et al.* Clinical status and lung function 10 weeks after severe SARS-CoV-2 infection. *Respir Med* 2021;**176**:106276. doi:10.1016/j.rmed.2020.106276

88 Aparisi Á, Ybarra-Falcón C, García-Gómez M, *et al.* Exercise Ventilatory Inefficiency in Post-COVID-19 Syndrome: Insights from a Prospective Evaluation. *J Clin Med* 2021;**10**:2591.

doi:10.3390/jcm10122591

89 Gonzalez-Hermosillo JA, Martinez-Lopez JP, Carrillo-Lampon SA, *et al.* Post-Acute COVID-19 Symptoms, a Potential Link with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A 6-Month Survey in a Mexican Cohort. *Brain Sci* 2021;**11**. doi:https://dx.doi.org/10.3390/brainsci11060760

90 Shendy W, Elsherif AA, Ezzat MM, *et al.* Prevalence of fatigue in patients post Covid-19. *Eur J Mol Clin Med* 2021;**8**:1330–40.https://www.ejmcm.com/article_9929_c759b7fc62d11f801d43514cb73388c6.pdf

91 D'cruz RF, Waller MD, Perrin F, *et al.* Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res* 2020;**7**:00655–2020. doi:10.1183/23120541.00655-2020

92 Andrade Barreto AP, Duarte LC, Cerqueira-Silva T, *et al.* Post-Acute COVID Syndrome, the Aftermath of Mild to Severe COVID-19 in Brazilian Patients. *medRxiv* 2021;:2021.06.07.21258520. doi:10.1101/2021.06.07.21258520

93 Taboada M, Moreno E, Cariñena A, *et al.* Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. *Br J Anaesth* 2021;**126**:e110–3. doi:10.1016/j.bja.2020.12.007

94 Taylor RR, Trivedi B, Patel N, *et al.* Post-COVID symptoms reported at asynchronous virtual review and stratified follow-up after COVID-19 pneumonia. *Clin Med J R Coll Physicians London* 2021;**21**. doi:http://dx.doi.org/10.7861/CLINMED.2021-0037

95 Daher A, Balfanz P, Cornelissen C, *et al.* Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020;**174**:106197. doi:http://dx.doi.org/10.1016/j.rmed.2020.106197

96 Liyanage-Don NA, Cornelius T, Sanchez JE, *et al.* Psychological Distress, Persistent Physical Symptoms, and Perceived Recovery After COVID-19 Illness. *J Gen Intern Med* 2021;**36**:2525–7. doi:10.1007/s11606-021-06855-w

97 Rogers JP, Chesney E, Oliver D, *et al.* Psychiatric and neuropsychiatric presentations

associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry* 2020;**7**:611–27. doi:10.1016/S2215-0366(20)30203-0

98 Suarez-Robles M, Iguaran-Bermudez MDR, Garcia-Klepizg JL, *et al.* Ninety days post-hospitalization evaluation of residual covid-19 symptoms through a phone call check list. *Pan Afr Med J* 2020;**37**:1–4. doi:http://dx.doi.org/10.11604/pamj.2020.37.289.27110

99 Voruz P, Allali G, Benzakour L, *et al.* Long COVID neuropsychological deficits after severe, moderate or mild infection. *medRxiv* 2021;:2021.02.24.21252329. doi:10.1101/2021.02.24.21252329

100 Weerahandi H, Hochman KA, Simon E, *et al.* Post-discharge health status and symptoms in patients with severe COVID-19. *medRxiv* 2020;:2020.08.11.20172742. doi:10.1101/2020.08.11.20172742

101 Domingo FR, Waddell LA, Cheung AM, *et al.* Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review. *medRxiv* 2021;:2021.06.03.21258317. doi:10.1101/2021.06.03.21258317

102 Stavem K, Einvik G, Ghanima W, *et al.* Prevalence and determinants of fatigue after covid-19 in non-hospitalized subjects: A population-based study. *Int J Environ Res Public Health* 2021;**18**:1–11. doi:http://dx.doi.org/10.3390/ijerph18042030

103 Daynes E, Gerlis C, Chaplin E, *et al.* Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort study. *Chron Respir Dis* 2021;**18**:14799731211015692. doi:https://dx.doi.org/10.1177/14799731211015691

104 Mirfazeli FS, Sarabi-Jamab A, kordi A, *et al.* Acute phase clinical manifestation of COVID-19 is linked to long-COVID symptoms; A 9-month follow-up study. *medRxiv* 2021;:2021.07.13.21260482. doi:10.1101/2021.07.13.21260482

105 Page MJ, Moher D, Bossuyt PM, *et al.* PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;:n160.

doi:10.1136/bmj.n160

106 Ouzzani M, Hammady H, Fedorowicz Z, *et al.* Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;**5**:1–10. doi:10.1186/s13643-016-0384-4

107 Moola S, Munn Z, Tufanaru C, *et al.* Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. *JBI Manual for Evidence Synthesis*. 2020. https://synthesismanual.jbi.global

108 Sera F, Armstrong B, Blangiardo M, *et al.* An extended mixed-effects framework for meta-analysis. *Stat Med* 2019;**38**:5429–44. doi:10.1002/sim.8362

109 RStudio. RStudio: Integrated development environment for R. RStudio. 2020.www.rstudio.com

110 Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60. doi:10.1136/bmj.327.7414.557

111 Chen C, Haupert SR, Shi X, *et al.* Global prevalence of post-acute sequelae of COVID-19 (PASC) or long COVID: A meta-analysis and systematic review. *medRxiv* Published Online First: 2021. doi:https://dx.doi.org/10.1101/2021.11.15.21266377

112 Fernandez-de-Las-Penas C, Palacios-Cena D, Gomez-Mayordomo V, *et al.* Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021;**92**:55–70. doi:https://dx.doi.org/10.1016/j.ejim.2021.06.009

113 Garg M, Maralakunte M, Bhatia V, *et al.* The conundrum of 'long-covid-19': A narrative review. *Int J Gen Med* 2021;**14**:2491–506. doi:http://dx.doi.org/10.2147/IJGM.S316708

114 Jennings G, Monaghan A, Xue F, *et al.* A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: Ongoing symptomatic phase vs. post-COVID-19 syndrome. *medRxiv* 2021;:2021.06.25.21259372. doi:10.1101/2021.06.25.21259372

115 Gavriatopoulou M, Ntanasis-Stathopoulos I, Kastritis E, *et al.* Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. *J Infect* 2021;**83**:1–16. doi:http://dx.doi.org/10.1016/j.jinf.2021.05.004

3.

116 Long Q, Li J, Hu X, *et al.* Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis. *Front Med* 2021;**8**. doi:10.3389/fmed.2021.702635

117 Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw open* 2021;**4**:e2111417. doi:https://dx.doi.org/10.1001/jamanetworkopen.2021.11417

118 Poudel AN, Zhu S, Cooper N, *et al.* Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One* 2021;**16**:e0259164. doi:https://dx.doi.org/10.1371/journal.pone.0259164

119 Rao S, Benzouak T, Gunpat S, *et al.* Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.23.21256006. doi:10.1101/2021.04.23.21256006

120 Sanchez-Ramirez DC, Normand K, Zhaoyun Y, *et al.* Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis. *Biomedicines* 2021;**9**. doi:https://dx.doi.org/10.3390/biomedicines9080900

121 Shanbehzadeh S, Tavahomi M, Ebrahimi-Takamjani I, *et al.* Physical and mental health complications post-COVID-19: Scoping review. *J Psychosom Res* 2021;**147**:110525. doi:http://dx.doi.org/10.1016/j.jpsychores.2021.110525

122 Wong TL, Weitzer DJ. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-A Systemic Review and Comparison of Clinical Presentation and Symptomatology. *Medicina (Kaunas)* 2021;**57**. doi:http://dx.doi.org/10.3390/medicina57050418

123 Aiyegbusi OL, Hughes SE, Turner G, *et al.* Symptoms, complications and management of long COVID: a review. *J R Soc Med* 2021;**114**:428–42. doi:10.1177/01410768211032850

124 Falk RS, Amdal CD, Pe M, *et al.* Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review. *Qual Life Res* Published Online First: 2021. doi:http://dx.doi.org/10.1007/s11136-021-02908-z

125 Cabrera Martimbianco AL, Pacheco RL, Bagattini AM, *et al.* Frequency, signs and symptoms,

and criteria adopted for long COVID-19: A systematic review. *Int J Clin Pract* 2021;**75**:e14357. doi:http://dx.doi.org/10.1111/ijcp.14357

126 Cha C, Baek G. Symptoms and management of long COVID: A scoping review. *J Clin Nurs* 2021;:No-Specified. doi:https://dx.doi.org/10.1111/jocn.16150

127 Matcham F, Ali S, Hotopf M, *et al.* Psychological correlates of fatigue in rheumatoid arthritis: A systematic review. Clin. Psychol. Rev. 2015;**39**:16–29. doi:10.1016/j.cpr.2015.03.004

128 Chen Y, Li T, Gong FH, *et al.* Predictors of Health-Related Quality of Life and Influencing Factors for COVID-19 Patients, a Follow-Up at One Month. *Front Psychiatry* 2020;**11**:668. doi:http://dx.doi.org/10.3389/fpsyt.2020.00668

129 Nehme M, Braillard O, Chappuis F, *et al.* Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in an Outpatient Setting. *Ann Intern Med* 2021;**174**:1252–60. doi:http://dx.doi.org/10.7326/M21-0878

130 Pauley E, Drake TM, Griffith DM, *et al.* Recovery from Covid-19 critical illness: a secondary analysis of the ISARIC4C CCP-UK cohort study and the RECOVER trial. *medRxiv* 2021;:2021.06.15.21258879. doi:10.1101/2021.06.15.21258879

131 Henneghan AM, Lewis KA, Gill E, *et al.* Describing cognitive function and psychosocial outcomes of COVID-19 survivors: A cross-sectional analysis. *J Am Assoc Nurse Pract* Published Online First: 2021. doi:http://dx.doi.org/10.1097/JXX.0000000000000647

132 Menges D, Ballouz T, Anagnostopoulos A, *et al.* Burden of Post-COVID-19 Syndrome and Implications for Healthcare Service Planning: A Population-based Cohort Study. *medRxiv* 2021;:2021.02.27.21252572. doi:10.1101/2021.02.27.21252572

133 Halpin SJ, McIvor C, Whyatt G, *et al.* Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;**93**:1013–22. doi:10.1002/jmv.26368

134 Shang YF, Liu T, Yu JN, *et al.* Half-year follow-up of patients recovering from severe COVID-19: Analysis of symptoms and their risk factors. *J Intern Med* 2021;**290**:444–50. doi:https://dx.doi.org/10.1111/joim.13284

135 Aul DR, Gates DJ, Draper DA, *et al.* Complications after discharge with COVID-19 infection and risk factors associated with development of post-COVID pulmonary fibrosis. *Respir Med* 2021;**188**:106602. doi:http://dx.doi.org/10.1016/j.rmed.2021.106602

136 Barizien N, Le Guen M, Russel S, *et al.* Clinical characterization of dysautonomia in long COVID-19 patients. *Sci Rep* 2021;**11**:14042. doi:http://dx.doi.org/10.1038/s41598-021-93546-5

137 Desgranges F, Tadini E, Munting A, *et al.* Post-COVID-19 syndrome in outpatients: a cohort study. *medRxiv* 2021;:2021.04.19.21255742. doi:10.1101/2021.04.19.21255742

138 Molnar T, Varnai R, Schranz D, *et al.* Severe Fatigue and Memory Impairment Are Associated with Lower Serum Level of Anti-SARS-CoV-2 Antibodies in Patients with Post-COVID Symptoms. *J Clin Med* 2021;**10**. doi:https://dx.doi.org/10.3390/jcm10194337

139 Sigfrid L, Drake TM, Pauley E, *et al.* Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *medRxiv* 2021;:2021.03.18.21253888. doi:10.1101/2021.03.18.21253888

140 Elkan M, Dvir A, Zaidenstein R, *et al.* Patient-Reported Outcome Measures After Hospitalization During the COVID-19 Pandemic: A Survey Among COVID-19 and Non-COVID-19 Patients. *Int J Gen Med* 2021;**14**:4829–36. doi:https://dx.doi.org/10.2147/IJGM.S323316

141 Guo L, Lin J, Ying W, *et al.* Correlation Study of Short-Term Mental Health in Patients Discharged After Coronavirus Disease 2019 (COVID-19) Infection without Comorbidities: A Prospective Study. *Neuropsychiatr Dis Treat* 2020;**Volume 16**:2661–7. doi:10.2147/NDT.S278245

142 Mazza MG, Palladini M, De Lorenzo R, *et al.* One-year mental health outcomes in a cohort of COVID-19 survivors. *J Psychiatr Res* 2021;**145**:118–24. doi:https://dx.doi.org/10.1016/j.jpsychires.2021.11.031

143 Aydin S, Unver E, Karavas E, *et al.* Computed tomography at every step: Long coronavirus disease. *Respir Investig* 2021;**59**:622–7. doi:https://dx.doi.org/10.1016/j.resinv.2021.05.014

144 Lindahl A, Aro M, Reijula J, *et al.* Women report more symptoms and impaired quality of life: a survey of Finnish COVID-19 survivors. *Infect Dis (Auckl)* Published Online First: 2021. doi:http://dx.doi.org/10.1080/23744235.2021.1965210

145 Pérez-González A, Araújo-Ameijeiras A, Fernández-Villar A, *et al.* Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a prospective cohort study. *medRxiv* 2021;:2021.08.05.21261634. doi:10.1101/2021.08.05.21261634

146 Romero-Duarte Á, Rivera-Izquierdo M, Guerrero-Fernández de Alba I, *et al.* Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med* 2021;**19**. doi:10.1186/s12916-021-02003-7

147 Sykes DL, Holdsworth L, Jawad N, *et al.* Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It? *Lung* 2021;**199**:113–9. doi:10.1007/s00408-021-00423-z

148 Boesl F, Audebert H, Endres M, *et al.* A Neurological Outpatient Clinic for Patients With Post-COVID-19 Syndrome — A Report on the Clinical Presentations of the First 100 Patients. *Front Neurol* 2021;**12**:738405. doi:10.3389/fneur.2021.738405

149 Iqbal A, Iqbal K, Ali SA, *et al.* The COVID-19 Sequelae: A Cross-Sectional Evaluation of Post-recovery Symptoms and the Need for Rehabilitation of COVID-19 Survivors. *CUREUS* 2021;**13**. doi:10.7759/cureus.13080

150 Bek LM, Berentschot JC, Heijenbrok-Kal MH, *et al.* Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study. *medRxiv* 2021;:2021.12.11.21267652. doi:10.1101/2021.12.11.21267652

151 Kashif A, Chaudhry M, Fayyaz T, *et al.* Follow-up of COVID-19 recovered patients with mild disease. *Sci Rep* 2021;**11**:13414. doi:https://dx.doi.org/10.1038/s41598-021-92717-8

152 Munblit D, Bobkova P, Spiridonova E, *et al.* Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin Exp Allergy* 2021;**51**:1107–20. doi:10.1111/cea.13997

153 Maamar M, Artime A, Pariente E, *et al.* POST-COVID-19 SYNDROME, INFLAMMATORY

MARKERS AND SEX DIFFERENCES. *medRxiv* 2021;:2021.07.07.21260092. doi:10.1101/2021.07.07.21260092

154 Gebhard CE, Sütsch C, Bengs S, *et al.* Sex- and Gender-specific Risk Factors of Post-COVID-19 Syndrome: A Population-based Cohort Study in Switzerland. *medRxiv* 2021;:2021.06.30.21259757. doi:10.1101/2021.06.30.21259757

155 Sathyamurthy P, Madhavan S, Pandurangan V. Prevalence, Pattern and Functional Outcome of Post COVID-19 Syndrome in Older Adults. *Cureus* 2021;**13**:e17189. doi:https://dx.doi.org/10.7759/cureus.17189

156 Mantovani E, Mariotto S, Gabbiani D, *et al.* Chronic fatigue syndrome: an emerging sequela in COVID-19 survivors?. *J Neurovirol* 2021;**27**:631–7. doi:https://dx.doi.org/10.1007/s13365-021-01002-x

157 Latronico N, Peli E, Calza S, *et al.* Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax* 2021;:thoraxjnl-2021-218064. doi:10.1136/thoraxjnl-2021-218064

158 Ferraro F, Calafiore D, Dambruoso F, *et al.* COVID-19 related fatigue: Which role for rehabilitation in post-COVID-19 patients? A case series. *J Med Virol* 2020;:jmv.26717. doi:10.1002/jmv.26717

159 Clavario P, Marzo V De, Lotti R, *et al.* Assessment of functional capacity with cardiopulmonary exercise testing in non-severe COVID-19 patients at three months follow-up. *ERJ Open Res* 2020;**7**:2020.11.15.20231985. doi:10.1101/2020.11.15.20231985

160 Mancini DM, Brunjes DL, Lala A, *et al.* Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post-Coronavirus Disease. *JACC Heart Fail* 2021;**9**:927–37. doi:https://dx.doi.org/10.1016/j.jchf.2021.10.002

161 Raman B, Cassar MP, Tunnicliffe EM, *et al.* Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine* 2021;**31**:100683. doi:https://dx.doi.org/10.1016/j.eclinm.2020.100683

162 Agergaard J, Ostergaard L, Leth S, *et al.* Myopathic changes in patients with long-term fatigue after COVID-19. *Clin Neurophysiol* 2021;**132**:1974–81. doi:http://dx.doi.org/10.1016/j.clinph.2021.04.009

163 Chen X, Li Y, Shao T-R, *et al.* Some characteristics of clinical sequelae of COVID-19 survivors from Wuhan, China: A multi-center longitudinal study. *Influenza Other Respi Viruses* Published Online First: 2021. doi:https://dx.doi.org/10.1111/irv.12943

164 O'Keefe JB, Minton HC, Morrow M, *et al.* Postacute Sequelae of SARS-CoV-2 Infection and Impact on Quality of Life 1-6 Months After Illness and Association With Initial Symptom Severity. *Open forum Infect Dis* 2021;**8**:ofab352. doi:https://dx.doi.org/10.1093/ofid/ofab352

165 Dini M, Poletti B, Tagini S, *et al.* Resilience, Psychological Well-Being and Daily Functioning Following Hospitalization for Respiratory Distress Due to SARS-CoV-2 Infection. *Healthc (Basel, Switzerland)* 2021;**9**. doi:https://dx.doi.org/10.3390/healthcare9091161

166 Jacobs LG, Gupta A, Rasouli L, *et al.* Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS One* 2020;**15**:e0243882. doi:http://dx.doi.org/10.1371/journal.pone.0243882

167 Valent A, Dudoignon E, Ressaire Q, *et al.* Three-month quality of life in survivors of ARDS due to COVID-19: A preliminary report from a French academic centre. *Anaesth Crit Care Pain Med* 2020;**39**:740–1. doi:10.1016/j.accpm.2020.10.001

168 Dalbosco-Salas M, Torres-Castro R, Leyton AR, *et al.* Effectiveness of a primary care telerehabilitation program for post-covid-19 patients: A feasibility study. *J Clin Med* 2021;**10**:4428. doi:http://dx.doi.org/10.3390/jcm10194428

169 Nune A, Durkowski V, Titman A, *et al.* Incidence and risk factors of long COVID in the UK: a single-centre observational study. *J R Coll Physicians Edinb* 2021;**51**:338–43. doi:https://dx.doi.org/10.4997/JRCPE.2021.405

170 Garrigues E, Janvier P, Kherabi Y, *et al.* Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;**81**:e4–6. doi:10.1016/j.jinf.2020.08.029

171 Yildirim S, Ediboglu O, Kirakli C, *et al.* Do Covid-19 patients needing ICU admission have worse 6 months follow up outcomes when compared with hospitalized non-ICU patients? A prospective cohort study. *Intensive Care Med Exp* 2021;**9**. doi:http://dx.doi.org/10.1186/s40635-021-00415-6

172 Schandl A, Hedman A, Lynga P, *et al.* Long-term consequences in critically ill COVID-19 patients: A prospective cohort study. *Acta Anaesthesiol Scand* 2021;**65**:1285–92. doi:https://dx.doi.org/10.1111/aas.13939

173 Morin L, Savale L, Montani D, *et al.* Four-Month Clinical Status of a Cohort of Patients after Hospitalization for COVID-19. *JAMA - J Am Med Assoc* Published Online First: 2021. doi:http://dx.doi.org/10.1001/jama.2021.3331

174 Noviello D, Costantino A, Muscatello A, *et al.* Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: A controlled cohort study. *Neurogastroenterol Motil* 2021;:e14187. doi:10.1111/nmo.14187

175 Strumiliene E, Zeleckiene I, Bliudzius R, *et al.* Follow-Up Analysis of Pulmonary Function, Exercise Capacity, Radiological Changes, and Quality of Life Two Months after Recovery from SARS-CoV-2 Pneumonia. *Medicina (Kaunas)* 2021;**57**. doi:http://dx.doi.org/10.3390/medicina57060568

176 Rass V, Ianosi B-A, Zamarian L, *et al.* Factors associated with impaired quality of life three months after being diagnosed with COVID-19. *Qual Life Res* Published Online First: 28 September 2021. doi:10.1007/s11136-021-02998-9

177 Sami R, Soltaninejad F, Amra B, *et al.* A one-year hospital-based prospective COVID- 19 open-cohort in the Eastern Mediterranean region: The Khorshid COVID Cohort (KCC) study. *PLoS One* 2020;**15**:e0241537. doi:http://dx.doi.org/10.1371/journal.pone.0241537

178 Anaya J-M, Rojas M, Salinas ML, *et al.* Post-COVID Syndrome. A Case Series and Comprehensive Review. *medRxiv* 2021;:2021.07.17.21260655. doi:10.1101/2021.07.17.21260655

179 Kanberg N, Simrén J, Edén A, *et al.* Neurochemical signs of astrocytic and neuronal injury in

acute COVID-19 normalizes during long-term follow-up. *EBioMedicine* 2021;**70**:103512. doi:10.1016/j.ebiom.2021.103512

180 Peghin M, Palese A, Venturini M, *et al.* Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. *Clin Microbiol Infect* 2021;**27**:1507–13. doi:10.1016/j.cmi.2021.05.033

181 Pilotto A, Cristillo V, Piccinelli SC, *et al.* Long-term neurological manifestations of COVID-19: prevalence and predictive factors. *Neurol Sci* 2021;:2020.12.27.20248903. doi:10.1101/2020.12.27.20248903

182 Fang X, Ming C, Cen Y, *et al.* Post-sequelae one year after hospital discharge among older COVID-19 patients: A multi-center prospective cohort study. *J Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.jinf.2021.12.005

183 Labarca G, Henriquez-Beltran M, Lastra J, *et al.* Analysis of clinical symptoms, radiological changes and pulmonary function data 4 months after COVID-19. *Clin Respir J* 2021;**15**:992–1002. doi:https://dx.doi.org/10.1111/crj.13403

184 Townsend L, Dyer AH, Jones K, *et al.* Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020;**15**:e0240784. doi:http://dx.doi.org/10.1371/journal.pone.0240784

185 Tomasoni D, Bai F, Castoldi R, *et al.* Anxiety and depression symptoms after virological clearance of COVID-19: A cross-sectional study in Milan, Italy. *J Med Virol* 2021;**93**:1175–9. doi:10.1002/jmv.26459

186 Bottemanne H, Gouraud C, Hulot J-S, *et al.* Do Anxiety and Depression Predict Persistent Physical Symptoms After a Severe COVID-19 Episode? A Prospective Study. *Front psychiatry* 2021;**12**:757685. doi:https://dx.doi.org/10.3389/fpsyt.2021.757685

187 Albu S, Zozaya NR, Murillo N, *et al.* What's going on following acute COVID-19? Clinical characteristics of patients in an out-patient rehabilitation program. *NeuroRehabilitation* 2021;**48**:469–80. doi:http://dx.doi.org/10.3233/NRE-210025

188 Silva LS, Joao RB, Nogueira MH, *et al.* Functional and microstructural brain abnormalities,

fatigue, and cognitive dysfunction after mild COVID-19. *medRxiv* 2021;:2021.03.20.21253414. doi:10.1101/2021.03.20.21253414

189 Elanwar R, Hussein M, Magdy R, *et al.* Physical and mental fatigue in subjects recovered from covid-19 infection: A case-control study. *Neuropsychiatr Dis Treat* 2021;**17**:2063–71. doi:http://dx.doi.org/10.2147/NDT.S317027

190 Danesh V, Arroliga AC, Bourgeois JA, *et al.* Post-acute sequelae of COVID-19 in adults referred to COVID recovery clinic services in an integrated health system in Texas. *Baylor Univ Med Cent Proc* 2021;**34**:645–8. doi:10.1080/08998280.2021.1972688

191 Mandal S, Barnett J, Brill SE, *et al.* Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2020;**0**:1–3. doi:http://dx.doi.org/10.1136/thoraxjnl-2020-215818

192 Moradian ST, Parandeh A, Khalili R, *et al.* Delayed Symptoms in Patients Recovered from COVID-19. *Iran J Public Health* 2020;**49**:2120–7. doi:10.18502/ijph.v49i11.4729

193 Tiwari B, Ghimire M, Bhatta G, *et al.* Persistent Symptoms in Non-critical COVID-19 Patients at Two Months Follow-Up in a District Hospital: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc* 2021;**59**:550–3. doi:https://dx.doi.org/10.31729/jnma.6440

194 Tosato M, Carfi A, Martis I, *et al.* Prevalence and Predictors of Persistence of COVID-19 Symptoms in Older Adults: A Single-Center Study. *J Am Med Dir Assoc* 2021;**22**:1840–4. doi:http://dx.doi.org/10.1016/j.jamda.2021.07.003

195 Venturelli S, Benatti S V, Casati M, *et al.* Surviving COVID-19 in Bergamo Province: A post-Acute outpatient re-evaluation. *Epidemiol Infect* Published Online First: 2021. doi:http://dx.doi.org/10.1017/S0950268821000145

196 Zulu JE, Banda D, Hines JZ, *et al.* Two-Month Follow-up of Persons with SARS-CoV-2 Infection—Zambia, September 2020. *medRxiv* 2021;:2021.06.15.21258964. doi:10.1101/2021.06.15.21258964

197 Ahmed H, Patel K, Greenwood DC, *et al.* Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after

hospitalisation or ICU admission: A systematic review and meta-analysis. *J Rehabil Med* 2020;**52**:0. doi:10.2340/16501977-2694

198 Liu K, Zhang W, Yang Y, *et al.* Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. *Complement Ther Clin Pract* 2020;**39**:101166. doi:10.1016/j.ctcp.2020.101166

199 Herridge MS, Cheung AM, Tansey CM, *et al.* One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;**348**:683–93. doi:10.1056/NEJMoa022450

200 Hatch R, Young D, Barber V, *et al.* Anxiety, Depression and Post Traumatic Stress Disorder after critical illness: a UK-wide prospective cohort study. *Crit Care* 2018;**22**:310. doi:10.1186/s13054-018-2223-6

201 Lam M, Wing Y, Yu MWM, *et al.* Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: Long-term follow-up. *Arch Intern Med* 2009;**169**:2142–7. doi:10.1001/archinternmed.2009.384

202 Wing YK, Leung CM. Mental health impact of severe acute respiratory syndrome: a prospective study. *Hong Kong Med J = Xianggang yi xue za zhi / Hong Kong Acad Med J = Xianggang yi xue za zhi / Hong Kong Acad Med* 2012;**18 Suppl 3**:24–7.https://pubmed.ncbi.nlm.nih.gov/22865219/ (accessed 29 Jun 2020).

203 Morgul E, Jordan TR, Akyel S, *et al.* COVID-19 pandemic and psychological fatigue in Turkey. *Int J Soc Psychiatry* 2020;**67**:20764020941889. doi:http://dx.doi.org/10.1177/0020764020941889

204 Tessitore E, Handgraaf S, Poncet A, *et al.* Symptoms and quality of life at 1-year follow up of patients discharged after an acute COVID-19 episode. *Swiss Med Wkly* 2021;**151**:w30093. doi:https://dx.doi.org/10.4414/smw.2021.w30093

205 Soares MN, Eggelbusch M, Naddaf E, *et al.* Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J Cachexia Sarcopenia Muscle* 2022;**13**:11–22. doi:10.1002/jcsm.12896

206 Goertz YMJ, Van Herck M, J.M. D, *et al.* Persistent symptoms 3 months after a SARS-CoV-2

4.

infection: The post-COVID-19 syndrome? *ERJ Open Res* 2020;**6**:1–10. doi:http://dx.doi.org/10.1183/23120541.00542-2020

207 Carfì A, Bernabei R, Landi F, *et al.* Persistent Symptoms in Patients After Acute COVID-19. *JAMA - J Am Med Assoc* 2020;**324**:603–5. doi:http://dx.doi.org/10.1001/jama.2020.12603

208 Dennis A, Wamil M, Alberts J, *et al.* Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021;**11**:e048391. doi:https://dx.doi.org/10.1136/bmjopen-2020-048391

209 Gautam N, Goyal S, Qureshi H, *et al.* Medium-term outcome of severe to critically ill patients with SARS-CoV-2 infection. *Clin Infect Dis* Published Online First: 2021. doi:http://dx.doi.org/10.1093/cid/ciab341

210 Darley DR, Dore GJ, Byrne AL, *et al.* Limited recovery from post-acute sequelae of SARS-CoV-2 at 8 months in a prospective cohort. *ERJ Open Res* 2021;**7**:00384–2021. doi:10.1183/23120541.00384-2021

211 Roth A, Chan PS, Jonas W. Addressing the Long COVID Crisis: Integrative Health and Long COVID. *Glob Adv Heal Med* 2021;**10**:21649561211056596. doi:https://dx.doi.org/10.1177/21649561211056597

212 Asadi-Pooya AA, Akbari A, Emami A, *et al.* Risk Factors Associated with Long COVID Syndrome: A Retrospective Study. *Iran J Med Sci* 2021;**46**:428–36. doi:https://dx.doi.org/10.30476/ijms.2021.92080.2326

213 Chopra N, Chowdhury M, Kumar A, *et al.* Clinical predictors of long COVID-19 and phenotypes of mild COVID-19 at a tertiary care centre in India. *Drug Discov Ther* 2021;**15**:156–61. doi:http://dx.doi.org/10.5582/DDT.2021.01014

214 Wong-Chew RM, Rodríguez Cabrera EX, Rodríguez Valdez CA, *et al.* Symptom cluster analysis of long COVID-19 in patients discharged from the Temporary COVID-19 Hospital in Mexico City. *Ther Adv Infect Dis* 2022;**9**:204993612110692. doi:10.1177/20499361211069264

215 Novak P, Mukerji SS, Alabsi HS, *et al.* Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19. *Ann Neurol* Published Online First: 2021.

doi:https://dx.doi.org/10.1002/ana.26286

216 Sollini M, Morbelli S, Ciccarelli M, *et al.* Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. *Eur J Nucl Med Mol Imaging* 2021;**48**:3187–97. doi:https://dx.doi.org/10.1007/s00259-021-05294-3

217 Vanichkachorn G, Newcomb R, Cowl CT, *et al.* Post-COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at Mayo Clinic and Characteristics of the Initial Patient Cohort. *Mayo Clin Proc* 2021;**96**:1782–91. doi:https://dx.doi.org/10.1016/j.mayocp.2021.04.024

218 Kedor C, Freitag H, Meyer-Arndt L, *et al.* Chronic COVID-19 Syndrome and Chronic Fatigue Syndrome (ME/CFS) following the first pandemic wave in Germany – a first analysis of a prospective observational study. *medRxiv* 2021;:2021.02.06.21249256. doi:10.1101/2021.02.06.21249256

219 Chan JCK. Recovery pathway of post-SARS patients. Thorax. 2005;**60**:361–2. doi:10.1136/thx.2004.035972

Figure 1. PRISMA 2020 flow diagram

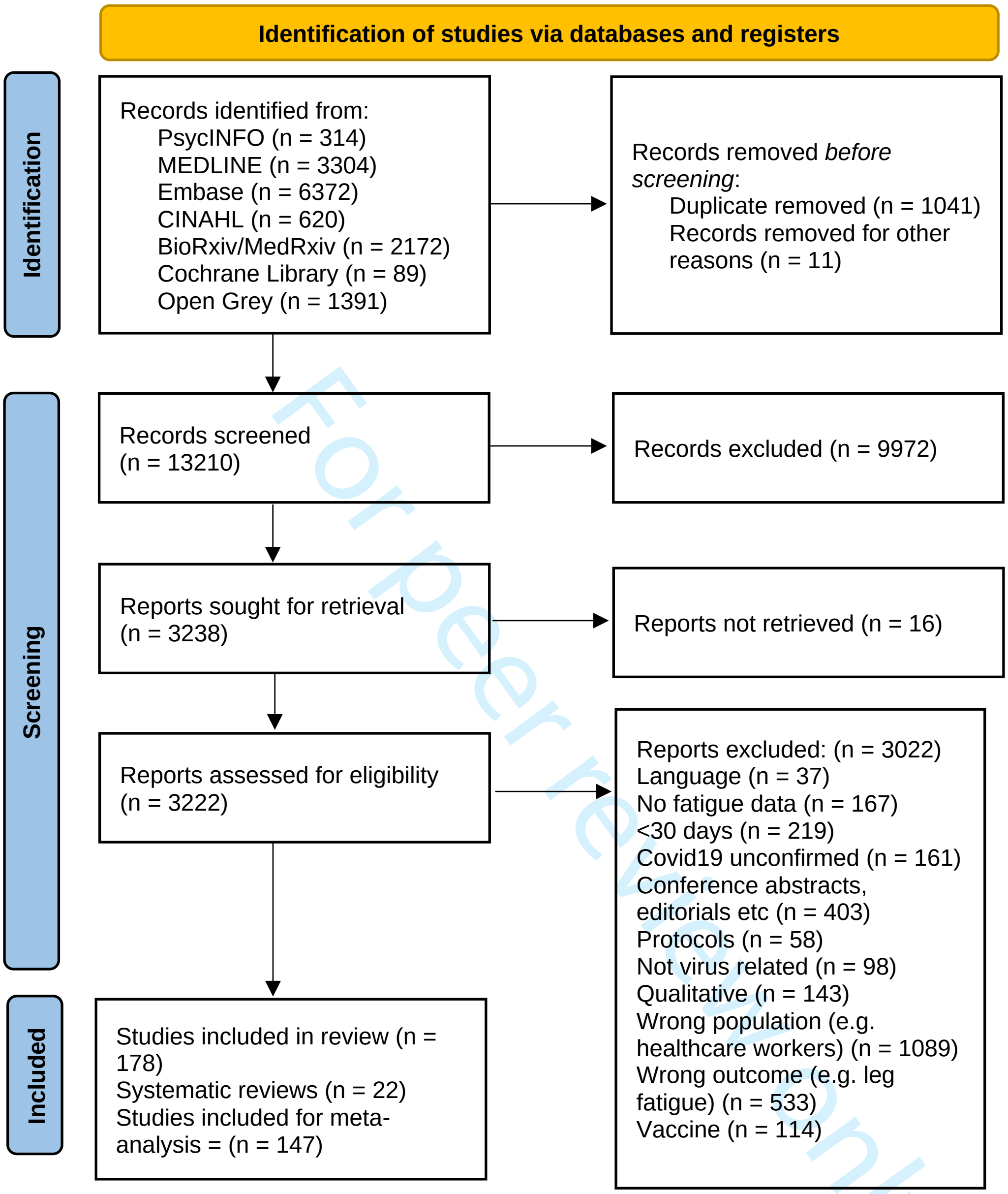


Figure 2. Forest plot for total fatigue proportions

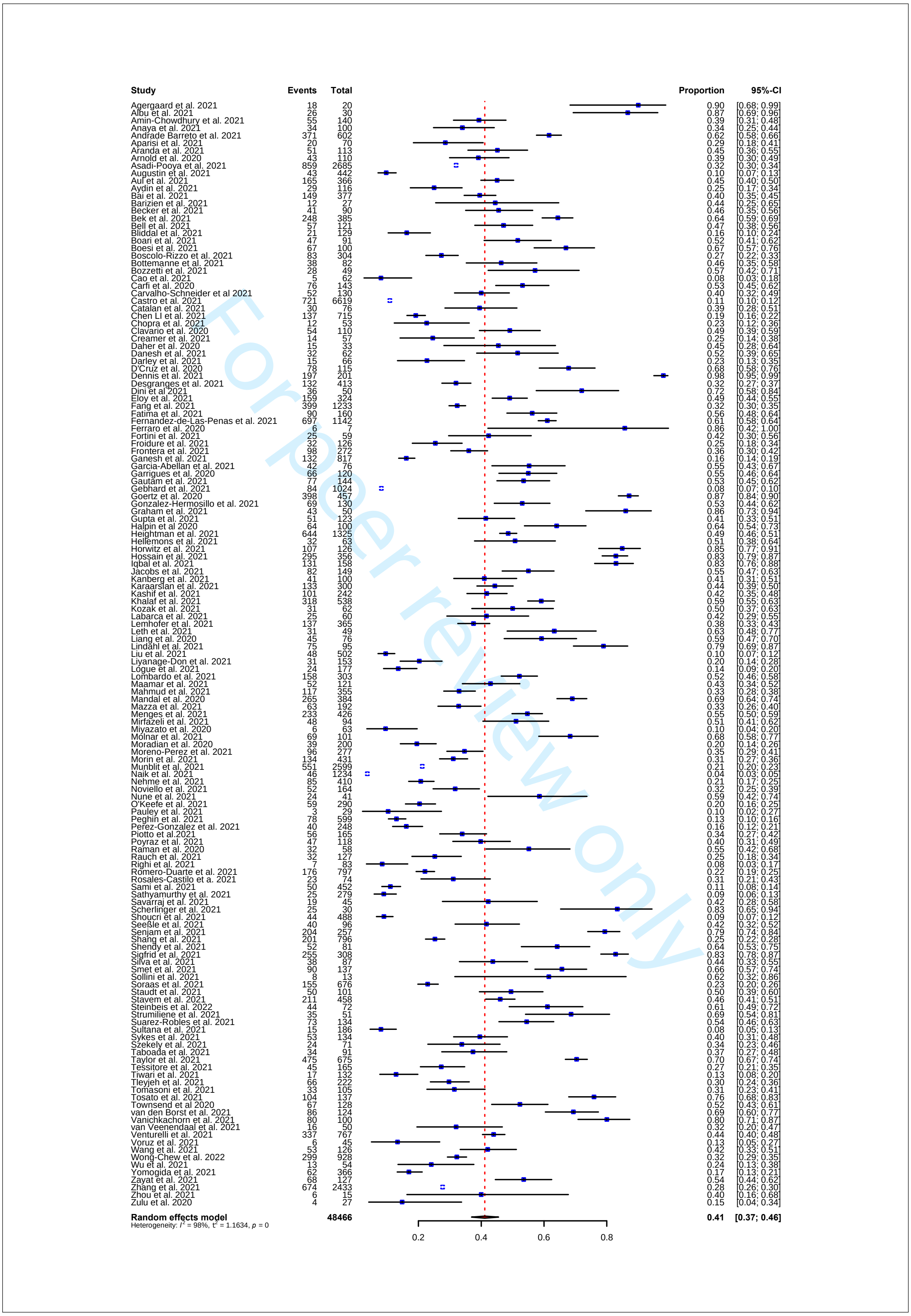
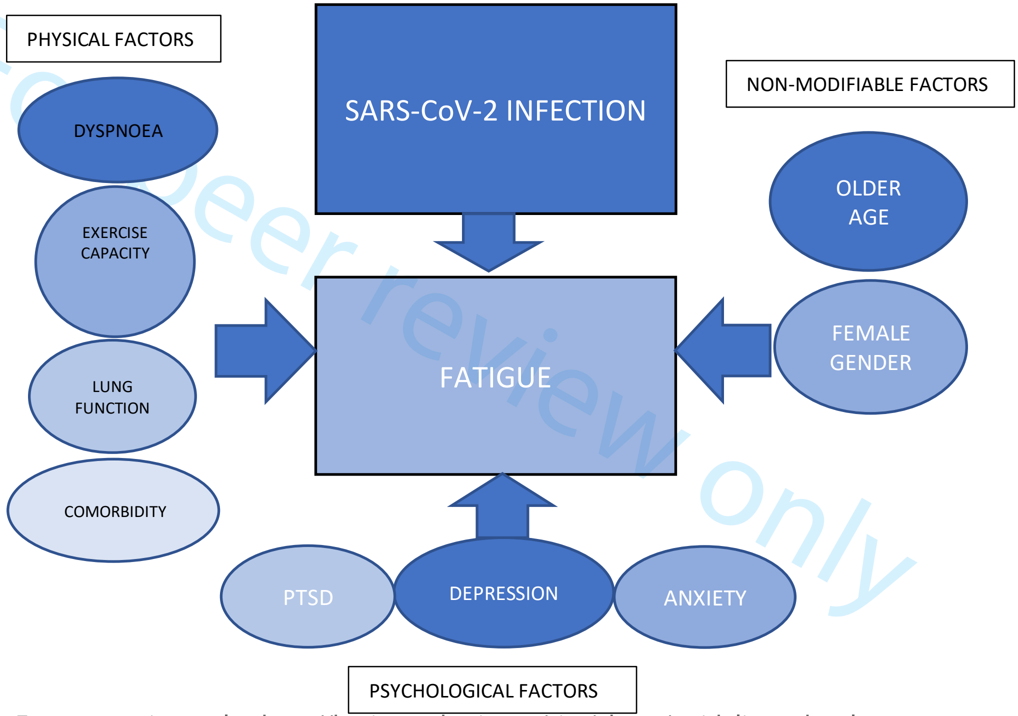


Figure 3. Diagram of fatigue associations



Supplementary File 1. PRISMA-P Protocol

TITLE:	PRISMA-P Protocol for a Systematic Review: Fatigue outcomes following COVID-19: A systematic review and meta-analysis
REGISTRATION:	PROSPERO 2020 CRD42020201247

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	Dr Fiona Gaughran	6th Reviewer
	Professor Trudie Chalder	Senior Reviewer

AMENDMENTS: Protocol amendments will be tracked, dated and numbered. The responsibility for tracking and registering changes to the protocol will be held by the 1st Reviewer with prior agreement and approval from the Senior

Reviewer. Final authorisation for any changes to the protocol will be from the Senior Reviewer.

A summary of changes table (Table 1, Appendix A.) will be utilised to track changes and record authorisations. An explanation and rationale for the amendments will be recorded in Table 2 (Appendix A.)

FUNDING: No specific funding has been obtained for this review.
This protocol was developed and designed in collaboration between all stated authors.

RATIONALE: Fatigue is a commonplace presenting symptom for a number of infectious diseases, including coronaviruses. Studies reporting fatigue in the current COVID-19 epidemic suggest a fatigue prevalence of between 18% in children to 100% in emergency department patients [1] during the acute phase. Fatigue has been implicated in increasing the risk for ICU care in some patients presenting with COVID-19, with a risk ratio of between 1.24 and 1.52. [2] Further, it is an emerging symptom associated with chronic stress among healthy populations during forced lockdown conditions, who reported increased somatic symptomology such as sleepiness, insomnia, headaches, digestive disturbances and fatigue compared to before lockdown conditions. [3]

Apart from acute clinical symptoms, fatigue may continue post-recovery or have a sudden onset following an acute viral infection. The current pandemic has revealed a considerable burden of lasting symptoms with approximately 1 in 4 people experiencing fatigue by one estimate. [4] Studies also indicate fatigue as one of the primary persistent symptoms. Systematic reviews indicate a pooled-prevalence of post-COVID-19 fatigue to vary between 45%, [5] 52% [6] and 64%. [7] For a considerable number of COVID-19 patients, fatigue symptoms extend beyond 3 months and represent the largest burden of post-infection symptomology. [8,9] This accords with evidence for post-viral fatigue in previous coronavirus outbreaks. One study investigating recovered SARS patients, found that 64% suffered continuing fatigue 3 months post-discharge and 60% experienced continuing fatigue at 12 months. [10] Another Hong Kong study reported 40.3% of recovered patients had chronic fatigue 4 years after contracting SARS and around 27% met the criteria for chronic fatigue syndrome.

Factors associated with post-illness fatigue include disease severity at the acute stage, which is more likely to require critical care or hospitalisation. [11–14] Physical factors have also been implicated in some studies. Reduced exercise capacity, for instance, is common in recovered patients even at 6 months post-infection and has been related to lower vitality. This is despite no concurrent impairments in pulmonary functions. [15] Although pulmonary functions are weakly related to fatigue, dyspnoea remains a problem for recovered patients, with studies indicating a positive correlation with fatigue. Other determinants include female gender, [16–19] and older age, particularly over 50 years old [20–22] have been related to worse fatigue following a COVID-19 infection. Psychological factors include anxiety, post-traumatic stress and depressive symptoms, which are frequent in survivors of respiratory viral infections, [23–25] have a consistent relationship with higher fatigue. Depression and PTSD, for instance, were related to fatigue severity in 402 post-Covid patients. [26]

Current systematic reviews and meta-analyses support fatigue as a primary symptom during COVID-19 recovery, which may persist for serval months post-infection. Given the potential to affect recovery, this review will add to the current body of knowledge in both prevalence and associations to potentially aid in developing interventions for fatigue outcomes following the current coronavirus pandemic. The overall aim is to investigate the prevalence of long-term fatigue outcomes in survivors of COVID-19.

This systematic review will comply with the PRISMA-P guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol. [27]

OBJECTIVES: The objective of this review are: (a) to examine the prevalence of continuing/persistent fatigue among recovered patients, (b) to explore potential explanatory variables associated with fatigue outcomes where data is available (e.g. psychological, physical and sociodemographic). The study objectives will utilise a PICO framework (Appendix B.)

METHODS:

Eligibility Criteria

- Original articles available in English;
- Studies with primary data;
- Studies reporting fatigue using a valid fatigue measure (e.g. Chalder Fatigue Questionnaire), the 'vitality' subscale of the SF-36 or SF-12 instruments or studies using a clinical interview, checklist or questionnaire with a fatigue item(s);
- Studies investigating fatigue occurring $\geq$ 30 days after the acute phase/hospitalisation or post-infection as defined in each article. Fatigue defined as 'post-discharge', 'post-hospitalisation', 'post-acute', 'post-illness' or 'post-onset' must have been measured at a median/mean time of $\geq$ 30 days.
- Patient populations with a diagnosis of SARS-CoV-2 (COVID-19) confirmed by RT-PCR, IgM/IgG serology or clinical assessment (e.g. CT scan, chest X-ray);
- Adults $\geq$ 18 years old;
- Letters containing primary data;
- Any study design including cohort, case-control, cross-sectional, randomised control trials, meta-analysis.

Exclusion criteria

- Pandemic fatigue (defined as 'worn out' by pandemic warnings, or by government safety instructions, or with media coverage, or with compliance requirements');
- 'Muscle fatigue', 'leg fatigue' and fatigue data combined with 'malaise' or 'muscle weakness';
- Fatigue associated with physical disorders (e.g. thyroiditis, Parkinson's disease, cancer);
- Pregnant participants; children and adolescents < 18 years old;

- Fatigue measured or reported as a clinical symptom during the 'acute phase' (defined as the period of hospitalisation or fatigue occurring < 30 days post-infection);
- Participants without a confirmed diagnosis of COVID-19 (i.e. participants who self-report a diagnosis), or studies including 'probable' cases;
- Fatigue among healthcare workers, which arising in the context of their work (e.g. burnout, compassion fatigue);
- Newspaper articles, conference papers/abstracts, editorials, opinions, background articles;
- Clinical or treatment procedures or protocols,
- Case reports and qualitative studies;
- COVID-19 vaccination studies, animals;
- Absence of outcome data (i.e. not quantified or reported in text).

Information sources:

PsycINFO, MEDLINE, EMBASE, CINAHL, OpenGrey, Cochrane Database of Systematic Reviews.

Search Strategy:

The search strategy will be piloted and amended where appropriate to select the most appropriate studies. An example of the search strategy is available in Appendix C. The search strategy language will be amended according to each database requirements.

Study Records:

The following data will be extracted and recorded in a spreadsheet: author(s), title, population and participant numbers, follow-up period, control/comparator, location, study inclusion/exclusion criteria, study design, study objectives, outcomes of interest, associations with fatigue, scales/instruments employed, results, effect size and power calculation (Y/N) In addition, the quality of each study (see Risk of Bias) will be indicated. A separate database will be compiled detailing the studies that will be fully-screened but excluded, together with the rationalisation for the exclusion.

Selection Process:

The 1st reviewer will conduct the initial search in the selected databases for relevant studies. The senior reviewer will review a proportion of the identified studies based on the inclusion and exclusion criteria. The senior reviewer will independently audit the selected studies and review the data extraction spreadsheet. Agreement for the final included studies for any meta-analysis and narrative review will be in collaboration. Disagreements will be settled through consensus and agreement. A PRISMA flow chart will be used to record the number of records collected, number of fully-screened records, number of records excluded, studies identified through reference lists and total number of records for inclusion in any meta-analysis.

Data items/collection:

The variables for the data to be recorded will include the following and will be entered into a data extraction spreadsheet:

- citation details
- target population & location (survivors, region/country),
- study eligibility criteria,
- population characteristics (sample size, socio-demographics)
- outcomes under study (fatigue, vitality),
- how the outcomes were measured (Chalder Fatigue Scale), [28] vitality scale of the SF-36/SF-12, including the definition of clinical outcomes for a scale, cut-off points, upper/lower scores, explanation of whether a high or low score is favourable,
- study variables (e.g. PTSD, depressive symptoms, exercise capacity),
- metrics (e.g. changes in fatigue),
- timing of outcome measurements (e.g. assessments at 6-week intervals),
- mean and standard deviations for each group,
- comparator group,
- effect size,
- time (baseline data and follow-up times e.g. 1 month, 3 months),
- study design and setting (e.g. hospital, outpatients, population),

- study methods (single, multicentre, parallel, cluster)

For randomised control trials:

- Intervention or comparator descriptions (e.g. drug type, control group, placebo group),
- Doses, times and frequencies, length of intervention,
- How an intervention was assessed, length of exposure, cumulative exposure,
- Integrity of the intervention (the degree to which the procedures were implemented as stated/planned),
- Post-intervention metrics (e.g. changes in fatigue, pre-post-test),
- Randomisation procedures,
- Adverse effects,

Results

- Number of participants in each stated group (including number of patients lost, withdrawn, lost to follow-up or excluded with reasons),
- Summary data for each group, each outcome and each time point (means and standard deviations for continuous data, OR for dichotomous data),
- Between-group estimates measuring effect of the intervention on the outcome (e.g. OR, RR, mean differences) and their confidence intervals
- Confounders measured.

In the event of incomplete data regarding the exposures or outcomes, effect sizes or other important data, reviewers will request this information from the authors. Where there is no response, the missing data will be calculated according to [29] or the paper will be excluded.

Risk of bias:

Risk of bias (RoB) assessment will be conducted for each included study using the relevant JBI tool. [30] The RoB will be conducted independently by three researchers. The assessments (e.g. good, moderate, poor) will be reported. A selection of reviews will be independently cross-checked by all 3 researchers to establish reliability of the assessments. Methods to summarise the RoB assessments for all the studies and a description of these assessments will be incorporated into the data synthesis (i.e. sensitivity analyses) and their potential influence on the findings will be discussed.

Data synthesis

This systematic review will employ a quantitative approach and provide a summary pooled estimate of the risk for fatigue, combining the results of all the studies where appropriate. Where 3 or more studies can be combined based on the same outcome measure, a meta-analysis will be performed. Where there are less than 3 studies identified for the same outcome, the effect sizes will be described in text. For the meta-analysis, we will compute odds ratios (OR) for binary outcomes to estimate the risk of fatigue relative to the exposure virus and target population (survivors), with 95% confidence intervals as an overall synthesised measure of effect size. For continuous outcomes, standardised mean differences for the combined effect size will be computed. Data from all studies will included in the analysis. Additional statistical tests may be conducted dependent upon data availability (e.g. fatigue outcome relative to gender, socioeconomic status, pre-existing psychiatric conditions etc).

It is expected that there will be considerable heterogeneity in study types and outcome measures, therefore it is expected that a random effects model will be performed for the meta-analysis to provide an estimate of the mean effect size for the included studies. The random effects model is expected to allow for wider heterogeneity and take account of the estimated between-study weight differences. To assess between-study-heterogeneity a Cochran's Q will be performed and the effect of heterogeneity will be quantified using the I^2 statistical-test. A value of 50% or greater for the I^2 will be considered as indicative of greater variability. A value of greater than 75% will be considered as considerable variability. Statistical measures of effect will be extracted from the included studies for calculating pooled effect sizes of the association between an included influenza virus and fatigue outcomes.

Effect sizes, 95% confidence intervals and statistical significance will be presented by quantitative and graphical representations (i.e. forest plots). Statistical significance will be set at $p < 0.05$ (2-tailed) for all analyses. Sensitivity analysis will be conducted utilising the RoB assessments across all the studies. For example, excluding low grade studies, studies with declared conflicts of interest. A funnel plot will be performed to assess publication bias.

Meta-bias(es)

In order to assess publication bias, funnel plots (observed for 10+ studies included in the meta-analysis) with an Egger test [31] to test asymmetry at alpha level 0.1 will be conducted.

Confidence in cumulative evidence

GRADE (Grading of Recommendations, Assessment, Development and Evaluation working group methodology) will be used to assess the quality of evidence for all outcomes. The quality of evidence will be assessed for risk of bias, consistency, directness, precision and publication bias. Quality will be judged as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect)

Reporting standards

The reporting of this systematic review will be in compliance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [32].

References

1 O'Reilly GM, Mitchell RD, Wu J, *et al.* Epidemiology and clinical features of emergency

department patients with suspected COVID-19: Results from the first month of the COVID-19 Emergency Department Quality Improvement Project (COVED-2). *Emerg Med Australas* 2020;:1742-6723.13573. doi:10.1111/1742-6723.13573

2 Zhao J, Gao Y, Huang W, *et al.* Risk factors for the exacerbation of patients with 2019 novel coronavirus: A meta-analysis. *Int J Med Sci* 2020;**17**:1744–50. doi:http://dx.doi.org/10.7150/ijms.47052

3 Majumdar P, Biswas A, Sahu S. COVID-19 pandemic and lockdown: cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. *Chronobiol Int* 2020;**37**:1191–200. doi:10.1080/07420528.2020.1786107

4 Badenoch JB, Rengasamy ER, Watson CJ, *et al.* Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.30.21256413. doi:10.1101/2021.04.30.21256413

5 Hoshijima H, Mihara T, Seki H, *et al.* Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. *medRxiv* 2021;:2021.04.08.21255109. doi:10.1101/2021.04.08.21255109

6 Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, *et al.* Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chron Respir Dis* 2021;**18**:147997312110022. doi:10.1177/14799731211002240

7 Malik P, Patel K, Pinto C, *et al.* Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* Published Online First: 2021. doi:https://dx.doi.org/10.1002/jmv.27309

8 Becker C, Beck K, Zumbrunn S, *et al.* Long COVID 1 year after hospitalisation for COVID-19: a prospective bicentric cohort study. *Swiss Med Wkly* 2021;**151**:w30091. doi:https://dx.doi.org/10.4414/smw.2021.w30091

9 Khalaf M, Bazeed SE, Abdel-Gawad M, *et al.* Prevalence and Predictors of Persistent Symptoms after Clearance of SARS-CoV-2 Infection: A Report from Egypt. *SSRN Electron J* Published Online First: 2020. doi:10.2139/ssrn.3727954

10 Tansey CM, Louie M, Loeb M, *et al.* One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. *Arch Intern Med* 2007;**167**:1312–20. doi:http://dx.doi.org/10.1001/archinte.167.12.1312

11 Rauch B, Kern-Matschilles S, Haschka SJ, *et al.* COVID-19-related symptoms 6 months after the infection - Update on a prospective cohort study in Germany. *medRxiv* 2021;:2021.02.12.21251619. doi:10.1101/2021.02.12.21251619

12 Zhang X, Wang F, Shen Y, *et al.* Symptoms and Health Outcomes among Survivors of COVID-19 Infection 1 Year after Discharge from Hospitals in Wuhan, China. *JAMA Netw Open* 2021;**4**:e2127403. doi:http://dx.doi.org/10.1001/jamanetworkopen.2021.27403

13 Van Den Borst B, Van Hees HWH, Van Helvoort H, *et al.* Comprehensive Health Assessment 3 Months after Recovery from Acute Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis* 2021;**73**:E1089–98. doi:http://dx.doi.org/10.1093/cid/ciaa1750

14 van der Sar - van der Brugge S, Talman S, de Mol M, *et al.* Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respir Med* 2021;**176**:106272. doi:http://dx.doi.org/10.1016/j.rmed.2020.106272

15 Bardakci MI, Ozkarafakili MA, Ozturk EN, *et al.* Evaluation of long-term radiological findings, pulmonary functions, and health-related quality of life in survivors of severe COVID-19. *J Med Virol* 2021;**93**:5574–81. doi:http://dx.doi.org/10.1002/jmv.27101

16 Amin-Chowdhury Z, Harris RJ, Aiano F, *et al.* Characterising post-COVID syndrome more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. *medRxiv* 2021;:2021.03.18.21253633. doi:10.1101/2021.03.18.21253633

17 Bai F, Tomasoni D, Falcinella C, *et al.* Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.cmi.2021.11.002

18 Hellemons ME, Huijts S, Bek L, *et al.* Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for SARS-CoV-2; A Longitudinal Study of Respiratory, Physical and Psychological Outcomes. *Ann Am Thorac Soc* Published Online First: 2021. doi:https://dx.doi.org/10.1513/AnnalsATS.202103-340OC

19 Lombardo MDM, Foppiani A, Peretti GM, *et al.* Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. *Open forum Infect Dis* 2021;**8**:ofab384. doi:https://dx.doi.org/10.1093/ofid/ofab384

20 Daugherty SE, Guo Y, Heath K, *et al.* Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021;**373**:n1098. doi:https://dx.doi.org/10.1136/bmj.n1098

21 Qin ES, Gold LS, Hough CL, *et al.* Patient-Reported Functional Outcomes Thirty Days after Hospitalization for COVID-19. *PM R* Published Online First: 2021. doi:https://dx.doi.org/10.1002/pmrj.12716

22 Yomogida K, Zhu S, Rubino F, *et al.* Post-Acute Sequelae of SARS-CoV-2 Infection Among Adults Aged ≥18 Years — Long Beach, California, April 1–December 10, 2020. *MMWR Morb Mortal Wkly Rep* 2021;**70**:1274–7. doi:10.15585/mmwr.mm7037a2

23 Daher A, Balfanz P, Cornelissen C, *et al.* Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020;**174**:106197. doi:http://dx.doi.org/10.1016/j.rmed.2020.106197

24 D'Cruz RF, Patel A, Perrin F, *et al.* Clinical, radiological, functional and psychological characteristics of severe covid-19 pneumonia survivors: A prospective observational cohort study. *Thorax* 2021;**76**:A34–5. doi:http://dx.doi.org/10.1136/thorax-2020-BTSabstracts.60

25 Liyanage-Don NA, Cornelius T, Sanchez JE, *et al.* Psychological Distress, Persistent Physical Symptoms, and Perceived Recovery After COVID-19 Illness. *J Gen Intern Med* 2021;**36**:2525–7. doi:10.1007/s11606-021-06855-w

26 Mazza MG, Palladini M, De Lorenzo R, *et al.* One-year mental health outcomes in a cohort of COVID-19 survivors. *J Psychiatr Res* 2021;**145**:118–24. doi:https://dx.doi.org/10.1016/j.jpsychires.2021.11.031

27 Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;**349**:g7647–g7647. doi:10.1136/bmj.g7647

28 Chalder T, Berelowitz G, Pawlikowska T, *et al.* Development of a fatigue scale. *J Psychosom Res* 1993;**37**:147–53. doi:10.1016/0022-3999(93)90081-P

29 Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60. doi:10.1136/bmj.327.7414.557

30 Moola S, Munn Z, Tufanaru C, *et al.* Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. *JBI Manual for Evidence Synthesis*. 2020. https://synthesismanual.jbi.global

31 Egger M, Smith GD, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34. doi:10.1136/bmj.315.7109.629

32 Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. 2010;**340**:c869.https://doi.org/10.1136/bmj.c869

Appendix A

Table 1. SUMMARY OF CHANGES TABLE

Document	*Protocol Version Number*	*Date*	*Authorisation*
Amendment No. 1			
Amendment No. 2			
Amendment No. 3			
Amendment No. 4			
Current Protocol	*Final*	*12.12.22*	*TC*
Original	1.01	04.08.20	

Table 2. AMENDMENT RATIONALE

Section Number/Heading	*Description of Amendment*	*Rationale Summary*

Appendix B

PICOS

Patient/Population	Exposure	Comparison	Outcome
Adults	**COVID19 diagnosis**	**Where applicable**	**Fatigue**
Patients Survivors Outpatients Inpatients	SARS-CoV-2 COVID-19 n-CoV-2 2019-nCoV2 Coronavirus Socio-demographics COVID-19 severity ICU admission Ventilation status Anxiety symptoms Depressive symptoms PTSD symptoms Stress/distress Sleep Quality of life Physical functioning BMI Clinical factors (lung function, serology, CT scans) Comorbidities	Healthy controls Non-treatment Treatment as usual	Fatigue Vitality Low energy Chronic fatigue Tiredness Exhaustion Asthenia General fatigue Lethargy

Appendix C

Example Search Strategy

	Database	Search
	PSYCINFO	
1		("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").mp
2		exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp.
3		(COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp.
4		(covid19 or covid-19 or covid*).mp.
5		1 OR 2 OR 3 OR 4
6		chronic fatigue*. mp
7		(fatigue or tired*).mp [mesh word]. or exhaust*.tw.
8		((((quality adj2 life) or QoL or health related quality) adj2 life) or HRQoL).tw.
9		6 OR 7 OR 8
10		(5 and 9) not cancer not child* not adolescent* not vaccin* not burnout not HIV Limit 10 to up="20190101-2021"

Supplementary File 2. Full search protocols

APA PSYCINFO

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").mp.659
2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 9867
3 "chronic fatigue*".mp. 3079
4 (fatigue or tired*).mp [mesh word]. or exhaust*.tw. 47997
5 ((((quality adj2 life) or QoL or health related quality) adj2 life) or HRQoL).tw. 80465
6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 14627
7 (covid19 or covid-19 or covid*).mp. 14685
8 1 or 2 or 6 or 7 15226
9 3 or 4 or 5 124345
10 (8 and 9) not cancer not child* not adolescent* not vaccin* not burnout not HIV 386
11 limit 10 to up="20190101-20211231" 314

MEDLINE(R) ALL

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").ab. 28273
2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 133179
3 "chronic fatigue*".mp. 7798
4 (fatigue or tired*).mp. 128687
5 ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).ab. 53118
6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 237888
7 (covid19 or covid-19 or covid*).mp. 230830
8 1 or 2 or 6 or 7 252264
9 3 or 4 or ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).mp. 182154
10 (8 and 9) not cancer not vaccin* not child* not adolescent* not burnout not HIV.mp. 4117
11 limit 10 to yr="2019-2021" 3304

EMBASE CLASSIC+EMBASE

1	("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").ab.	28257
2	exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp.	83683
3	"chronic fatigue*".mp.	13417
4	(fatigue or tired*).mp.	317550
5	((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).ab.	78429
6	(COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp.	242298
7	(covid19 or covid-19 or covid*).mp.	233333
8	1 or 2 or 6 or 7	269814
9	3 or 4 or ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).mp.	394392
10	(8 and 9) not cancer not vaccin* not child* not adolescent* not burnout not HIV.mp.	7449
11	limit 10 to yr="2019-2021"	6372

CINAHL

1	MH coronavirus infections or corona virus or corona*	10,982
2	AB severe acute respiratory syndrome coronavirus	3,719
3	MH severe acute respiratory syndrome	556
4	MH covid-19 or Covid19 or SARS-CoV* or SARS-CoV-2 or SARSCoV2 or SARSCOV-2 or covid19 or covid*	50,545
5	AB ncov-2019 or nCoV-2 or 2019-nCoV* or nCoV2	8,774
6	AB nCov-2019 or nCoV-2 or 2019-nCov* or ncov2	8,570
7	MH fatigue or AB (fatigue or exhaustion or tiredness) or AB (health related quality of life or hrqol)	17,446
8	1 or 2 or 3 or 4 or 5 or 6 not HIV not child* not adolescent* not vaccin* not burnout	64,543
9	7 and 8 Limiters – published date: 20190101-20211231, English language	620

MEDRXIV & BIORXIV

For term "COVID-19 or SARS-CoV-2 or coronavirus AND fatigue or tired" and posted between "01 Jan, 2019 and 21 Dec, 2021"

Returned 2,172 results

COCHRANE LIBRARY

Title abstract keyword COVID-19 or covid19 or or covid-19 or covid* or "corona virus" or "coronavirus infection" or "SARS CoV-2" or "SARS-CoV-2" or "SARS-CoV*" or "SARSCOV2" or "SARSCOV-2" or "nCoV-2" or "2019-nCoV*" or nCoV2" or *keyword* "severe acute respiratory syndrome coronavirus" AND fatigue or "chronic fatigue" or tired* or exhaust* or "health related quality adj1 life" or HRQoL

Selected Facets: 2019-2021 (Publication date)

Returned 89 Cochrane Reviews

OPEN GREY

"COVID-19"

Returned 1,391 results

Supplementary file 3. Summary of systematic reviews

Author	Title	Study Design	Included Articles N.	Follow-up Time	Fatigue Prevalence & Associations	*p*
Aiyegbusi et al. (2021)	Symptoms, complications and management of long COVID: a review	Systematic review & Meta-analysis	24	1 month	47% (CI 31–63) 16 studies	
Badenoch et al. (2021)	Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis	Systematic review & Meta-analysis	51	Mean 77 days (Range 14-182)	24·4% (CI 17·5-32.9)	
Cabera Martimbianco et al. (2021)	Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review	Narrative systematic review	25	Post-infection or discharge	-	
Cares-Marambio et al. (2021)	Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review	Systematic review & Meta-analysis	9	Post-discharge	52% (CI 0.38–0.66)	
Cha & Baek et al. (2021)	Symptoms and management of long COVID: A scoping review	Scoping review	34	> 4 weeks	-	
Chen et al. (2021)	Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review	Systematic review & Meta-analysis	40	> 28 days	**Total (22 studies)** 23 (CI 0.13-0.38) **Hospitalised (8 studies)** 26 (CI 0.17-0.38)	
Domingo et al. (2021)	Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review	Living systematic review & Meta-analysis	36	4-12 weeks ≥ 12 weeks	**4-12 weeks** 51%, (CI: 39-64) **≥ 12 weeks** 47%, (CI: 27-68)	
Falk et al. (2021)	Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review	Narrative systematic review	339	1-4 months post-discharge	-	
Fernandez-de-Las-Penas et al. (2021)	Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis	Systematic review & Meta-analysis	33	30, 60, 90 days post-virus	**30 days** 11.7% (CI 3.1-35.3) **60 days** 56.2% (CI 28.3-80.7) **≥ 90 days** 35.3% (CI 25.3-46.8)	
Garg et al. (2021)	The Conundrum of 'Long-COVID-19': A Narrative Review	Systematic Review	212	-	-	
Gavriatopoulou et al. (2021)	Epidemiology and organ specific sequelae of post-acute COVID 19: A narrative review	Narrative Systematic review	12	> 4 weeks	-	

Author	Title	Study Design	Included Articles N.	Follow-up Time	Fatigue Prevalence & Associations	*p*
Hoshijima et al. (2021)	Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis	Systematic review & Meta-analysis (RAPID)	35	1 month	45% (32-59%)	
Jennings et al. (2021)	A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: Ongoing symptomatic phase vs. post-COVID-19 syndrome	Systematic review & Meta-analysis	39	> 4 weeks	**Symptoms (16 studies)** 44% (CI 10-71) **Ongoing Symptoms (19 studies** 43% (CI 5-83)	
Long et al. (2021)	Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis	Systematic review & Meta-analysis	16	> 1 month Post-discharge	47%	
Malik et al. (2021)	Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis	Systematic review & Meta-analysis	22	Post-Covid	**Pooled Total** 64% **Quality of life** OR 1.06	.001
Nasserie et al. (2021)	Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review	Systematic review	45	2 months	Median 39.8% (IQR, 31.4-59.0%) 25 studies	
Poudel et al. (2021)	Impact of Covid-19 on health-related quality of life of patients: A structured review	Rapid review	12	> 4 weeks post-discharge	-	
Rao et al. (2021)	Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; a systematic review and meta-analysis	Systematic review & Meta-analysis	41	1-6 months Post-infection	**1-2 months** 52.7% ER 0.517 **2-3 months** 47.8% ER 0.527 **Female Gender** OR 1.782	
Rogers et al. (2020)	Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: A systematic review and meta-analysis with comparison to the COVID-19 pandemic	Meta-analysis	4	Post-illness	61 (19.3%)	
Sanchez-Ramirez et al. (2021)	Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis	Systematic review & Meta-analysis	24	4 months	38% 15 articles	
Shanbehzadeh et al. (2021)	Physical and mental health complications post-Covid-19: Scoping review	Scoping Systematic Review	34	3 months	-	

Author	Title	Study Design	Included Articles N.	Follow-up Time	Fatigue Prevalence & Associations	*p*
Wong et al. (2021)	Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology	Narrative systematic review	21	> 1 month	-	

Supplementary file 4. Quality Assessments for all included studies

Cohort

Study	*Were the groups similar & recruited from the same population?*	*Were the exposures measured similarly to assign people to exposed & unexposed groups?*	*Was the exposure measured in a valid & reliable way?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?*	*Were the outcomes measured in a valid & reliable way?*	*Was the follow up time reported & sufficient to be long enough for outcomes to occur?*	*Was follow up complete, & if not, were the reasons to loss to follow up described & explored?*	*Were strategies to address incomplete follow up utilized?*	*Was appropriate statistical analysis used?*	*Overall appraisal*
Amin-Chowdhury et al. 2021	Y	Y	Y	Y	Y	N	N	Y	?	N	Y	Low
Aparisi et al. 2021	Y	Y	Y	N	N	N	N	Y	Y	NA	Y	Moderate
Aranda et al. 2021	Y	-	Y	Y	Y	?	N	Y	?	?	Y	Moderate
Arnold et al. 2020	Y	Y	Y	N	N	N	Y	Y	N	N	Y	Moderate
Asadi-Pooya et al. 2021	Y	-	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Augustin et al. 2021	Y	Y	Y	Y	?	N	N	Y	Y	Y	Y	Moderate
Aul et al. 2021	Y	Y	Y	?	Y	?	N	Y	N	N	Y	Moderate
Aydin et al. 2021	-	-	Y	Y	Y	?	Y	Y	N	N	Y	Moderate
Bai et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Moderate
Bardakci et al. 2021	Y	Y	Y	N	N	?	Y	Y	N	N	Y	Moderate
Barizien et al. 2021	Y	Y	Y	N	N	N	N	Y	N	N	Y	Low
Becker et al. 2021	Y	Y	?	Y	Y	?	N	Y	Y	N	Y	Low
Bek et al. 2021	Y	Y	Y	?	?	N	Y	Y	Y	?	Y	Moderate
Bell et al. 2021	Y	Y	Y	?	N	N	N	Y	Y	Y	Y	Moderate
Bliddal et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Boari et al. 2021	Y	Y	Y	?	Y	N	N	Y	Y	Y	Y	Moderate
Boscolo-Rizzo et al. 2021	Y	-	Y	N	Y	?	N	Y	?	N	Y	Moderate
Bottemane et al. 2021	Y	?	Y	Y	Y	N	N	Y	Y	Y	Y	Moderate
Bozzetti et al. 2021	Y	Y	Y	N	N	?	N	Y	N	N	Y	Low
Cao et al. 2021	?	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	High
Carfi et al. 2020	Y	?	Y	Y	N	N	N	Y	?	N	Y	Low
Carvalho-Schneider et al. 2021	Y	Y	Y	?	Y	N	N	Y	Y	Y	Y	Moderate
Catalan et al. 2021	Y	Y	Y	Y	?	N	?	Y	?	?	Y	Low
Chen et al. 2021	Y	-	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Chopra et al. 2021	Y	Y	Y	Y	Y	N	N	Y	-	-	Y	Moderate
Clavario et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Creamer et al. 2021	Y	Y	Y	N	N	?	N	Y	?	?	Y	Low
Daher et al. 2021	Y	-	Y	N	N	?	N	Y	Y	?	Y	Moderate
Dalbosco-Salas et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	?	Y	Moderate
Darley et al. 2021	Y	?	Y	Y	Y	N	Y	Y	Y	Y	Y	High
Daugherty et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	-	-	Y	High
Daynes et al. 2021	Y	?	?	?	?	N	Y	Y	Y	?	Y	Low
D'Cruz et al. 2021	Y	Y	Y	Y	Y	N	Y	Y	-	-	Y	Moderate
Dennis et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	High
Desgranges et al. 2021	Y	Y	Y	Y	Y	?	N	Y	-	-	Y	Moderate
Donaghy et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Eloy et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Moderate
Evans et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Fang et al. 2021	Y	Y	Y	Y	Y	?	?	Y	Y	Y	Y	Moderate
Fatima et al. 2021	Y	Y	Y	N	N	N	N	Y	?	N	Y	Low
Fernandez-de-las-Penas et al. 2021	Y	Y	Y	N	Y	N	Y	Y	-	-	Y	Moderate
Fortini et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate

Study	*Were the groups similar & recruited from the same population?*	*Were the exposures measured similarly to assign people to exposed & unexposed groups?*	*Was the exposure measured in a valid & reliable way?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?*	*Were the outcomes measured in a valid & reliable way?*	*Was the follow up time reported & sufficient to be long enough for outcomes to occur?*	*Was follow up complete, & if not, were the reasons to loss to follow up described & explored?*	*Were strategies to address incomplete follow up utilized?*	*Was appropriate statistical analysis used?*	*Overall appraisal*
Froidure et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Frontera et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Gamberini et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	N	N	Y	Moderate
Garcia-Abellan et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Garrigues et al. 2020	Y	Y	Y	N	N	N	N	Y	Y	N	Y	Low
Gebhard et al. 2021	-	Y	Y	?	Y	?	N	Y	-	-	Y	Moderate
Goertz et al. 2021	N	Y	Y	Y	Y	?	N	Y	-	-	Y	Moderate
Gonzalez-Hermosillo et al. 2021	Y	Y	Y	?	Y	N	Y	Y	N	?	Y	Moderate
Graham et al. 2021	Y	Y	Y	?	Y	?	Y	Y	?	?	Y	Moderate
Guo Lin et al. 2020	Y	?	Y	Y	Y	?	Y	Y	?	?	Y	Moderate
Gupta et al. 2021	Y	?	Y	N	N	?	N	Y	N	N	Y	Moderate
Heightman et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Hellemons et al. 2021	N	N	Y	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Henneghan et al. 2021	Y	-	Y	Y	Y	N	Y	Y	N	N	y	Moderate
Horwitz et al. 2021	Y	-	Y	N	N	?	Y	Y	Y	N	Y	Low
Hossain et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Jacobs et al. 2021	Y	Y	Y	?	Y	N	Y	Y	Y	N	Y	Moderate
Kanberg et al. 2021	Y	Y	Y	?	Y	?	Y	Y	N	N	Y	Moderate
Karaarslan et al. 2021	Y	Y	Y	Y	Y	?	N	Y	?	?	Y	Moderate
Kayaaslan et al. 2021	Y	?	Y	N	N	?	N	Y	N	N	Y	Moderate
Kedor et al. 2021	Y	?	Y	N	N	Y	Y	Y	N	N	Y	Moderate
Khalaf et al. 2021	Y	Y	Y	N	Y	N	N	Y	Y	?	Y	Moderate
Kozak et al. 2021	Y	Y	Y	Y	N	N	N	Y	-	-	Y	Moderate
Latronico et al. 2021	?	Y	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Leth et al. 2021	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Moderate
Liang et al. 2021	Y	Y	Y	Y	N	?	N	Y	Y	N	Y	Moderate
Lindahl et al. 2021	Y	Y	Y	Y	Y	N	Y	Y	Y	-	Y	Moderate
Liu et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	?	Y	Moderate
Logue et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Lombardo et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Mahmud et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	?	Y	Moderate
Mancini et al. 2021	Y	Y	Y	N	N	?	Y	Y	N	N	Y	Moderate
Mantovani et al. 2021	-	Y	Y	N	N	Y	Y	Y	?	?	Y	Low
Mazza et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Menges et al. 2021	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	High
Mirfazeli et al. 2021	Y	Y	Y	N	Y	?	Y	Y	Y	?	Y	Low
Miyazato et al. 2020	Y	?	Y	N	N	N	N	Y	N	N	Y	Low
Molnar et al. 2021	Y	Y	Y	N	Y	?	Y	Y	Y	N	Y	Moderate
Moreno-Perez et al. 2021	Y	-	Y	Y	Y	?	N	Y	Y	?	Y	Moderate
Morin et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	Y	Y	Moderate
Munblit et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	Y	Y	Moderate
Naik et al. 2021	Y	Y	Y	N	Y	?	N	Y	Y	N	Y	Moderate
Nehme et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Moderate
Novak et al. 2021	Y	Y	Y	Y	N	N	Y	?	?	?	Y	Low
Nune et al. 2021	Y	?	Y	Y	Y	?	N	Y	N	?	Y	Moderate

Study	*Were the groups similar & recruited from the same population?*	*Were the exposures measured similarly to assign people to exposed & unexposed groups?*	*Was the exposure measured in a valid & reliable way?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?*	*Were the outcomes measured in a valid & reliable way?*	*Was the follow up time reported & sufficient to be long enough for outcomes to occur?*	*Was follow up complete, & if not, were the reasons to loss to follow up described & explored?*	*Were strategies to address incomplete follow up utilized?*	*Was appropriate statistical analysis used?*	*Overall appraisal*
Pauley et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	N	Y	Moderate
Peghin et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Pérez-González et al. 2021	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Moderate
Pilotto et al. 2021	Y	Y	Y	Y	Y	?	N	Y	N	N	Y	Low
Raman et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	N	?	Y	Moderate
Rass et al. 2021	Y	Y	y	N	Y	?	Y	Y	Y	N	Y	Moderate
Rauch et al. 2021	Y	Y	Y	N	N	?	N	Y	Y	Y	Y	Moderate
Righi et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Romero-Duarte et al. 2021	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Moderate
Rosales- Castillo et al. 2021	-	-	Y	N	N	N	?	Y	?	?	Y	Low
Sami et al. 2020	Y	Y	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Sathyamurthy et al. 2021	Y	Y	Y	N	N	?	N	Y	Y	N	Y	Low
Savarraj et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	N	Y	Low
Schandl et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Moderate
Scherlinger et al. 2021	Y	Y	Y	N	Y	N	Y	Y	Y	?	Y	Moderate
Seeßle et al. 2021	Y	?	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Shang et al. 2021	Y	Y	Y	N	Y	?	N	Y	N	N	Y	Low
Sigfrid et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	N	Y	Moderate
Soraas et al. 2021	Y	Y	Y	N	Y	?	Y	Y	N	N	Y	Moderate
Staudt et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Steinbeis et al. 2021	Y	?	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Strumiliene et al. 2021	Y	Y	Y	Y	Y	N	Y	Y	Y	?	Y	Moderate
Sykes et al. 2021	Y	Y	Y	N	Y	N	N	Y	Y	N	Y	Moderate
Szekely et al. 2021	Y	Y	Y	?	Y	?	?	Y	Y	Y	Y	Moderate
Taboada et al. 2021	Y	?	Y	:	Y	?	N	Y	?	?	Y	Low
Taylor et al. 2021	Y	Y	Y	N	N	?	Y	Y	-	-	Y	Moderate
Tessitore et la. 2021	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Moderate
Tleyjeh et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	N	N	Y	Moderate
Valent et al. 2020	?	Y	Y	N	?	?	Y	Y	N	N	Y	Moderate
Van den Borst et al. 2021	Y	Y	Y	N	N	?	N	N	Y	?	Y	Moderate
van der Sar- van der Brugge et al.2021	Y	Y	Y	N	N	?	Y	N	Y	?	Y	Moderate
van Veenendaal et al. 2021	Y	N	Y	N	N	?	N	Y	Y	-	Y	Moderate
Venturelli et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	-	Y	Moderate
Voruz et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	-	Y	Moderate
Wang et al. 2021	Y	?	Y	N	N	?	?	Y	?	N	Y	Low
Weerahandi et al. 2020	Y	?	Y	N	N	?	N	Y	Y	Y	Y	Low
Wong-Chew et al. 2022	Y	Y	Y	Y	Y	?	N	Y	N	?	Y	Moderate
Wu et al. 2021	Y	Y	Y	N	N	?	N	Y	Y	-	Y	Moderate
Yildirim et al. 2021	Y	Y	Y	N	N	?	Y	Y	N	N	Y	Moderate
Yomogida et al. 2021	Y	?	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Zayat et al. 2021	Y	Y	Y	N	N	N	N	Y	Y	?	Y	Low
Zhang et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	Y	Y	Moderate
Zhao Yang et al. 2021	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Moderate
Zulu et al. 2020	Y	?	Y	N	N	?	Y	N	?	N	Y	Low

Cross-sectional

Study	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects & the setting described in detail?	Was the exposure measured in a valid & reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid & reliable way?	Was appropriate statistical analysis used?	*Overall appraisal*
Albu et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Low
Andrade Barreto et al. 2021	Y	Y	Y	Y	N	?	N	Y	Moderate
Boesl et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Danesh et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Dini et al. 2021	Y	Y	Y	Y	N	Y	N	Y	Moderate
Ganesh et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Halpin et al. 2020	Y	Y	Y	Y	N	N	Y	Y	Moderate
Iqbal et al. 2021	Y	Y	Y	Y	N	N	N	Y	Moderate
Kashif et al. 2021	Y	Y	Y	Y	N	N	N	Y	Low
Labarca et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Lemhofer et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Liyanage-Don et al. 2021	Y	Y	?	?	Y	Y	N	Y	Low
Maamar et al. 2021	N	Y	Y	Y	?	Y	N	Y	Moderate
Mandal et al. 2020	Y	Y	Y	Y	N	N	N	Y	Moderate
Moradian et al. 2020	Y	Y	Y	Y	N	Y	N	Y	Moderate
O'Keefe et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Moderate
Poyraz et al. 2021	Y	Y	Y	Y	N	Y	N	Y	Moderate
Qin et al. 2021	Y	Y	Y	Y	?	?	Y	Y	Moderate
Senjam et al. 2021	Y	Y	Y	Y	?	Y	N	Y	Low
Shendy et al. 2020	Y	Y	Y	Y	N	N	Y	Y	Moderate
Silva et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Smet et al. 2021	N	N	Y	Y	Y	N	N	Y	Low
Stavem et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Suarez-Robles et al. 2021	Y	Y	Y	Y	N	N	N	Y	Moderate
Sultana et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Moderate
Tiwari et al. 2021	Y	Y	Y	Y	N	N	N	Y	Moderate
Tomasoni et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Moderate
Tosato et al. 2021	Y	Y	Y	Y	N	Y	N	Y	Moderate
Townsend et al. 2020	Y	Y	Y	Y	?	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

Case series

Study	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	*Overall appraisal*
Anaya et al. 2021	Y	N	Y	Y	N	N	Y	Y	N	Y	Low
Ferraro et al. 2020	Y	Y	Y	Y	N	Y	Y	Y	?	Y	Low
Gautam et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Study	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	*Overall appraisal*
Shoucri et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Vanichkachorn et al. 2021	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

Case-control studies

Study	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Were cases & controls matched appropriately?	Were the same criteria used for identification of cases & controls?	Was exposure measured in a standard, valid & reliable way?	Was exposure measured in the same way for cases & controls?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were outcomes assessed in a standard, valid & reliable way for cases & controls?	Was the exposure period of interest long enough to be meaningful?	Was appropriate statistical analysis used?	Overall appraisal
Agergaard et al. 2021	Y	Y	Y	Y	Y	Y	N	?	Y	Y	Moderate
Castro et al. 2021	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	High
Elanwar et al. 2021	Y	?	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Elkan et al. 2021	Y	Y	Y	Y	N	N	N	Y	Y	Y	Moderate
Noviello et al. 2021	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Moderate
Ortelli et al. 2021	Y	Y	?	Y	Y	?	?	Y	Y	Y	Moderate
Sollini et al. 2021	Y	Y	Y	Y	?	Y	N	N	Y	Y	Moderate
Zhou et al. 2021	Y	Y	?	Y	Y	N	N	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

Randomised Controlled Trials

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Overall appraisal
Chen, Liu et al. 2021	Y	Y	Y	-	Y	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Chudzik et al. 2021	N	?	Y	Y	N	?	Y	?	Y	Y	Y	Y	?	Low
Liu et al. 2020	Y	?	Y	?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

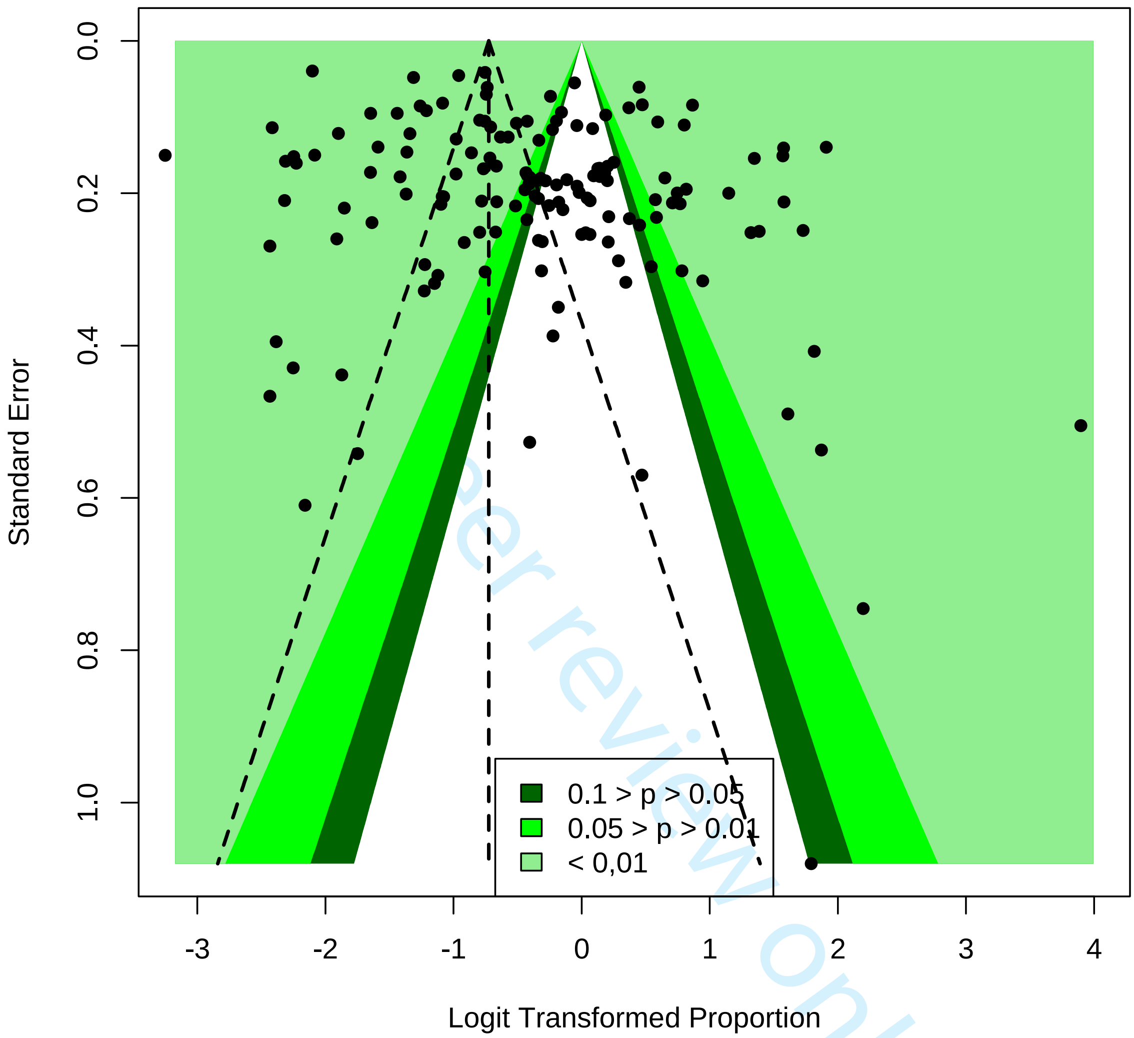
Randomised controlled trials JBI items

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomized?

10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

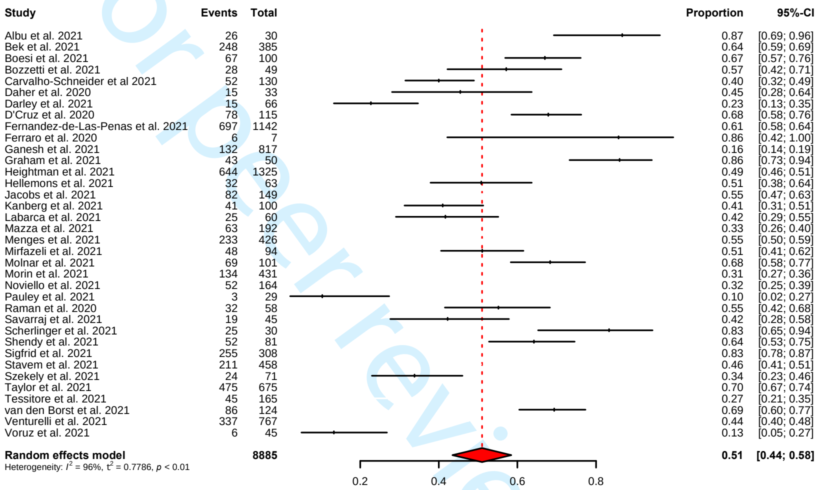
Supplementary file 5.

Funnel plot for total fatigue proportions



Supplementary file 6.

Forest plot for fatigue proportions using a valid scale

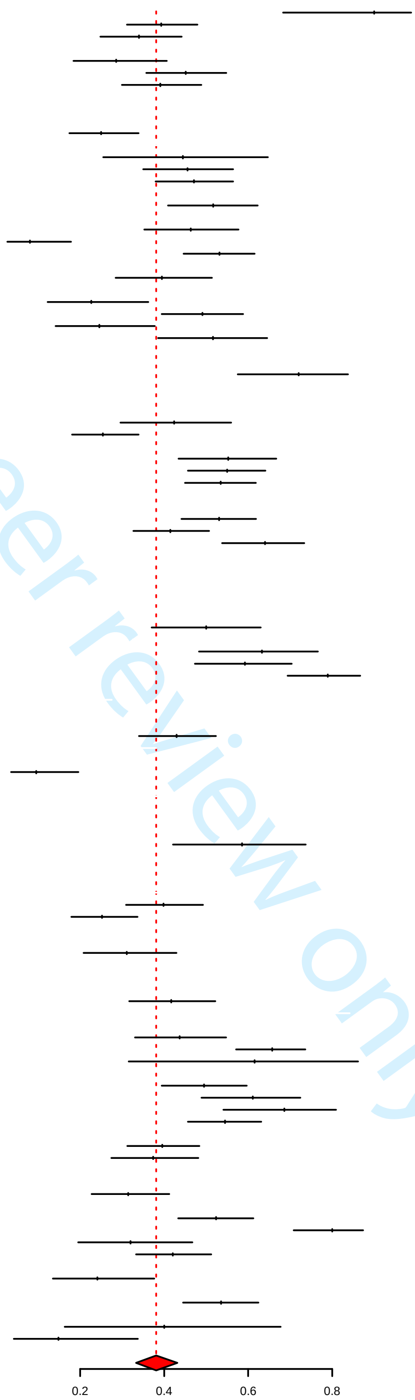


Supplementary file 7.

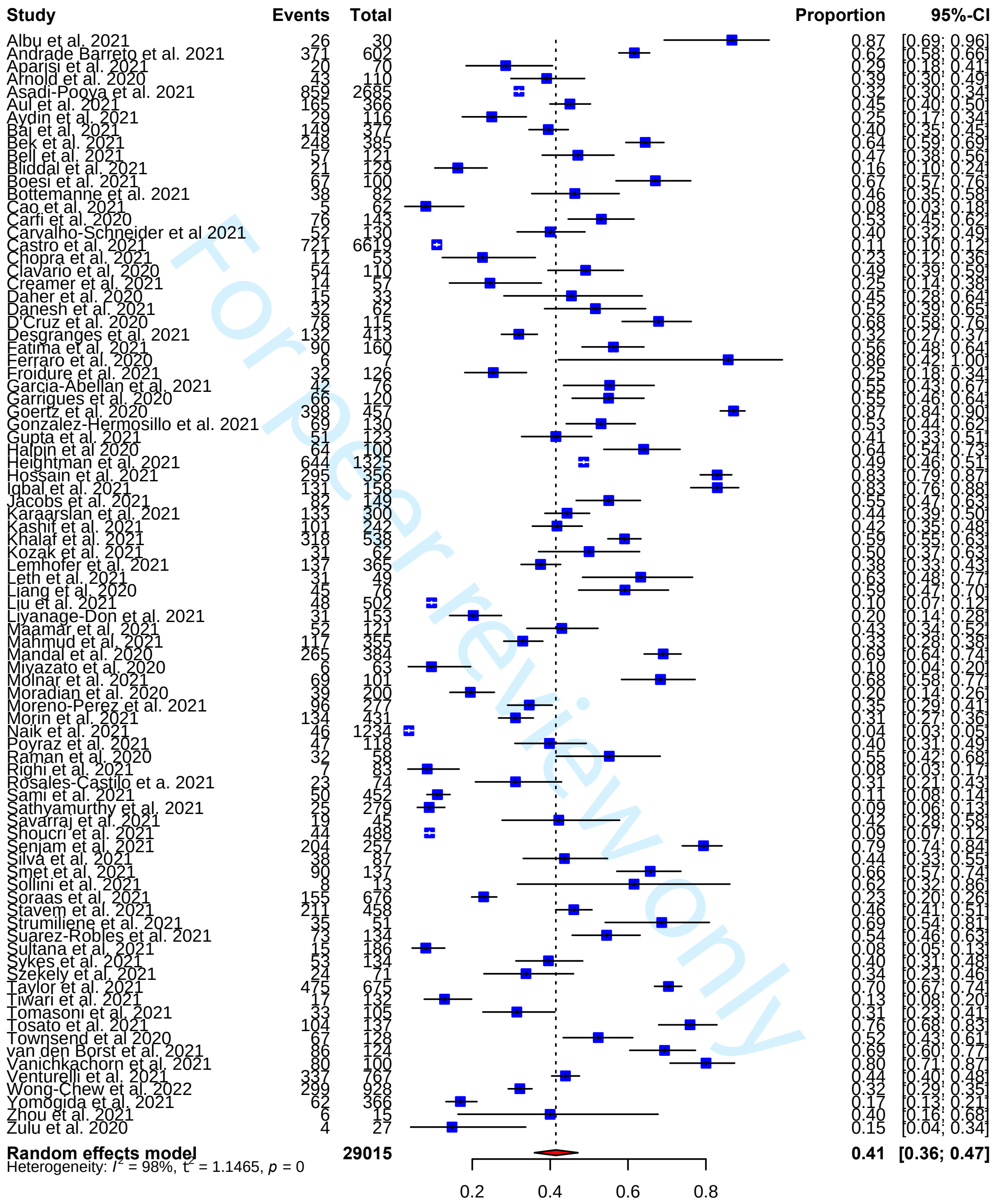
Forest plot for fatigue proportions without a valid scale

Study	Events	Total	Proportion	95%-CI
Agergaard et al. 2021	18	20	0.90	[0.68; 0.99]
Amin-Chowdhury et al. 2021	55	140	0.39	[0.31; 0.48]
Anaya et al. 2021	34	100	0.34	[0.25; 0.44]
Andrade Barreto et al. 2021	371	602	0.62	[0.58; 0.66]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Aranda et al. 2021	51	113	0.45	[0.36; 0.55]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi-Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Augustin et al. 2021	43	442	0.10	[0.07; 0.13]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Barizien et al. 2021	12	27	0.44	[0.25; 0.65]
Becker et al. 2021	41	90	0.46	[0.35; 0.56]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boari et al. 2021	47	91	0.52	[0.41; 0.62]
Boscolo-Rizzo et al. 2021	83	304	0.27	[0.22; 0.33]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carfi et al. 2020	76	143	0.53	[0.45; 0.62]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Catalan et al. 2021	30	76	0.39	[0.28; 0.51]
Chen LI et al. 2021	137	715	0.19	[0.16; 0.22]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Creamer et al. 2021	14	57	0.25	[0.14; 0.38]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
Dennis et al. 2021	197	201	0.98	[0.95; 0.99]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Dini et al 2021	36	50	0.72	[0.58; 0.84]
Eloy et al. 2021	159	324	0.49	[0.44; 0.55]
Fang et al. 2021	399	1233	0.32	[0.30; 0.35]
Fatima et al. 2021	90	160	0.56	[0.48; 0.64]
Fortini et al. 2021	25	59	0.42	[0.30; 0.56]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Frontera et al. 2021	98	272	0.36	[0.30; 0.42]
Garcia-Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Garrigues et al. 2020	66	120	0.55	[0.46; 0.64]
Gautam et al. 2021	77	144	0.53	[0.45; 0.62]
Gebhard et al. 2021	84	1024	0.08	[0.07; 0.10]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez-Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Horwitz et al. 2021	107	126	0.85	[0.77; 0.91]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Karaarslan et al. 2021	133	300	0.44	[0.39; 0.50]
Kashif et al. 2021	101	242	0.42	[0.35; 0.48]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Lindahl et al. 2021	75	95	0.79	[0.69; 0.87]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Liyanage-Don et al. 2021	31	153	0.20	[0.14; 0.28]
Logue et al. 2021	24	177	0.14	[0.09; 0.20]
Lombardo et al. 2021	158	303	0.52	[0.46; 0.58]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Miyazato et al. 2020	6	63	0.10	[0.04; 0.20]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno-Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Munblit et al. 2021	551	2599	0.21	[0.20; 0.23]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Nehme et al. 2021	85	410	0.21	[0.17; 0.25]
Nune et al. 2021	24	41	0.59	[0.42; 0.74]
O'Keefe et al. 2021	59	290	0.20	[0.16; 0.25]
Peghin et al. 2021	78	599	0.13	[0.10; 0.16]
Perez-Gonzalez et al. 2021	40	248	0.16	[0.12; 0.21]
Piotto et al.2021	56	165	0.34	[0.27; 0.42]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Rauch et al. 2021	32	127	0.25	[0.18; 0.34]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Romero-Duarte et al. 2021	176	797	0.22	[0.19; 0.25]
Rosales-Castilo et a. 2021	23	74	0.31	[0.21; 0.43]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Sathyamurthy et al. 2021	25	279	0.09	[0.06; 0.13]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Seeßle et al. 2021	40	96	0.42	[0.32; 0.52]
Senjam et al. 2021	204	257	0.79	[0.74; 0.84]
Shang et al. 2021	201	796	0.25	[0.22; 0.28]
Silva et al. 2021	38	87	0.44	[0.33; 0.55]
Smet et al. 2021	90	137	0.66	[0.57; 0.74]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Staudt et al. 2021	50	101	0.50	[0.39; 0.60]
Steinbeis et al. 2022	44	72	0.61	[0.49; 0.72]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez-Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Taboada et al. 2021	34	91	0.37	[0.27; 0.48]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tleyjeh et al. 2021	66	222	0.30	[0.24; 0.36]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
Vanichkachorn et al. 2021	80	100	0.80	[0.71; 0.87]
van Veenendaal et al. 2021	16	50	0.32	[0.20; 0.47]
Wang et al. 2021	53	126	0.42	[0.33; 0.51]
Wong-Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Wu et al. 2021	13	54	0.24	[0.13; 0.38]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zayat et al. 2021	68	127	0.54	[0.44; 0.62]
Zhang et al. 2021	674	2433	0.28	[0.26; 0.30]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Zulu et al. 2020	4	27	0.15	[0.04; 0.34]
Random effects model		**39581**	**0.38**	**[0.33; 0.43]**

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.2087$, $p = 0$



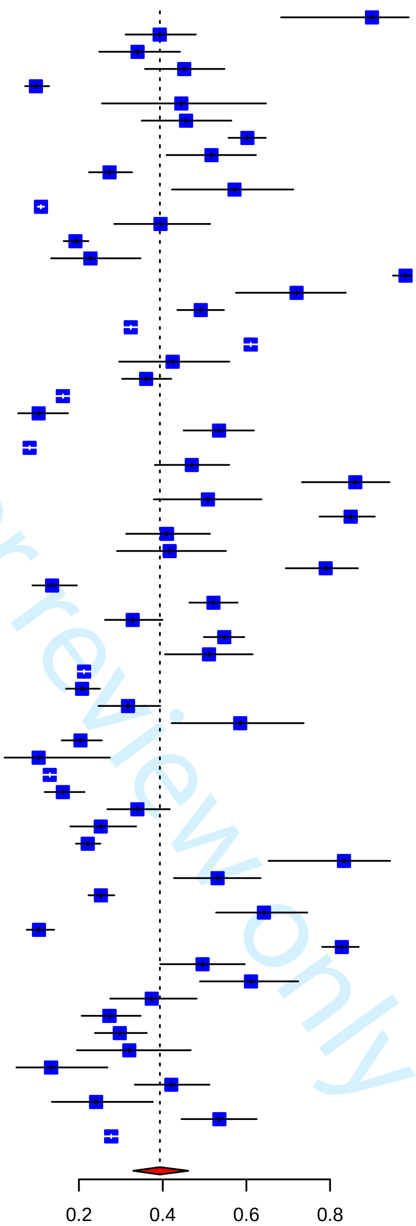
Supplementary file 8. Forest plot for fatigue proportions at 1-3 months



Supplementary file 9. Forest plot for fatigue proportions >3 months

Study	Events	Total	Proportion	95%-CI
Agergaard et al. 2021	18	20	0.90	[0.68; 0.99]
Amin-Chowdhury et al. 2021	55	140	0.39	[0.31; 0.48]
Anaya et al. 2021	34	100	0.34	[0.25; 0.44]
Aranda et al. 2021	51	113	0.45	[0.36; 0.55]
Augustin et al. 2021	43	442	0.10	[0.07; 0.13]
Barizien et al. 2021	12	27	0.44	[0.25; 0.65]
Becker et al. 2021	41	90	0.46	[0.35; 0.56]
Bek et al. 2021	291	483	0.60	[0.56; 0.65]
Boari et al. 2021	47	91	0.52	[0.41; 0.62]
Boscolo-Rizzo et al. 2021	83	304	0.27	[0.22; 0.33]
Bozzetti et al. 2021	28	49	0.57	[0.42; 0.71]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Catalan et al. 2021	30	76	0.39	[0.28; 0.51]
Chen LI et al. 2021	137	715	0.19	[0.16; 0.22]
Darley et al. 2021	15	66	0.23	[0.13; 0.35]
Dennis et al. 2021	197	201	0.98	[0.95; 0.99]
Dini et al 2021	36	50	0.72	[0.58; 0.84]
Eloy et al. 2021	159	324	0.49	[0.44; 0.55]
Fang et al. 2021	399	1233	0.32	[0.30; 0.35]
Fernandez-de-Las-Penas et al. 2021	697	1142	0.61	[0.58; 0.64]
Fortini et al. 2021	25	59	0.42	[0.30; 0.56]
Frontera et al. 2021	98	272	0.36	[0.30; 0.42]
Ganesh et al. 2021	132	817	0.16	[0.14; 0.19]
Garcia-Abellan et al. 2021	12	116	0.10	[0.05; 0.17]
Gautam et al. 2021	77	144	0.53	[0.45; 0.62]
Gebhard et al. 2021	84	1024	0.08	[0.07; 0.10]
Gonzalez-Hermosillo et al. 2021	61	130	0.47	[0.38; 0.56]
Graham et al. 2021	43	50	0.86	[0.73; 0.94]
Hellemons et al. 2021	32	63	0.51	[0.38; 0.64]
Horwitz et al. 2021	107	126	0.85	[0.77; 0.91]
Kanberg et al. 2021	41	100	0.41	[0.31; 0.51]
Labarca et al. 2021	25	60	0.42	[0.29; 0.55]
Lindahl et al. 2021	75	95	0.79	[0.69; 0.87]
Logue et al. 2021	24	177	0.14	[0.09; 0.20]
Lombardo et al. 2021	158	303	0.52	[0.46; 0.58]
Mazza et al. 2021	63	192	0.33	[0.26; 0.40]
Menges et al. 2021	233	426	0.55	[0.50; 0.59]
Mirfazeli et al. 2021	48	94	0.51	[0.41; 0.62]
Munblit et al. 2021	551	2599	0.21	[0.20; 0.23]
Nehme et al. 2021	85	410	0.21	[0.17; 0.25]
Noviello et al. 2021	52	164	0.32	[0.25; 0.39]
Nune et al. 2021	24	41	0.59	[0.42; 0.74]
O'Keefe et al. 2021	59	290	0.20	[0.16; 0.25]
Pauley et al. 2021	3	29	0.10	[0.02; 0.27]
Peghin et al. 2021	78	599	0.13	[0.10; 0.16]
Perez-Gonzalez et al. 2021	40	248	0.16	[0.12; 0.21]
Pilotto et al.2021	56	165	0.34	[0.27; 0.42]
Rauch et al. 2021	32	127	0.25	[0.18; 0.34]
Romero-Duarte et al. 2021	176	797	0.22	[0.19; 0.25]
Scherlinger et al. 2021	25	30	0.83	[0.65; 0.94]
Seeßle et al. 2021	51	96	0.53	[0.43; 0.63]
Shang et al. 2021	201	796	0.25	[0.22; 0.28]
Shendy et al. 2021	52	81	0.64	[0.53; 0.75]
Shoucri et al. 2021	38	364	0.10	[0.07; 0.14]
Sigfrid et al. 2021	255	308	0.83	[0.78; 0.87]
Staudt et al. 2021	50	101	0.50	[0.39; 0.60]
Steinbeis et al. 2022	44	72	0.61	[0.49; 0.72]
Taboada et al. 2021	34	91	0.37	[0.27; 0.48]
Tessitore et al. 2021	45	165	0.27	[0.21; 0.35]
Tleyjeh et al. 2021	66	222	0.30	[0.24; 0.36]
van Veenendaal et al. 2021	16	50	0.32	[0.20; 0.47]
Voruz et al. 2021	6	45	0.13	[0.05; 0.27]
Wang et al. 2021	53	126	0.42	[0.33; 0.51]
Wu et al. 2021	13	54	0.24	[0.13; 0.38]
Zayat et al. 2021	68	127	0.54	[0.44; 0.62]
Zhang et al. 2021	674	2433	0.28	[0.26; 0.30]
Random effects model		**27163**	**0.39**	**[0.33; 0.46]**

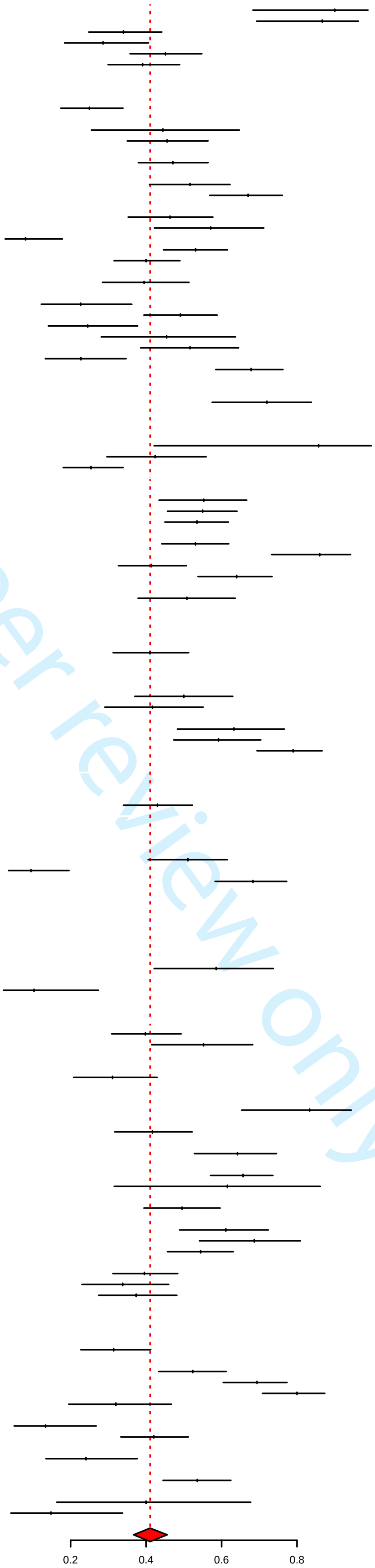
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.2522$, $p = 0$



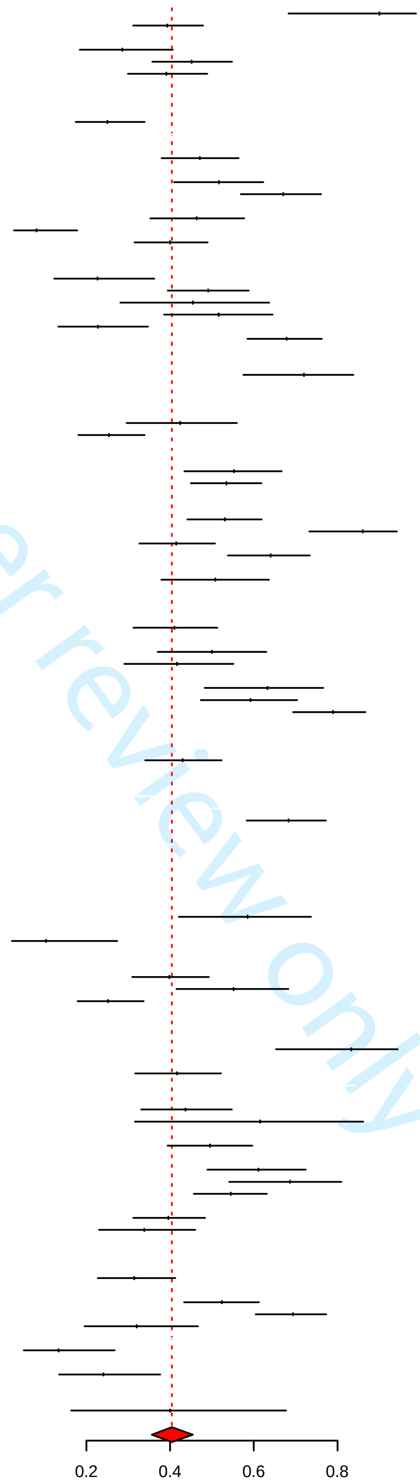
Supplementary file 10. Forest plot excluding unpublished articles

Study	Events	Total	Proportion	95%-CI
Agergaard et al. 2021	18	20	0.90	[0.68; 0.99]
Albu et al. 2021	26	30	0.87	[0.69; 0.96]
Anaya et al. 2021	34	100	0.34	[0.25; 0.44]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Aranda et al. 2021	51	113	0.45	[0.36; 0.55]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi-Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Augustin et al. 2021	43	442	0.10	[0.07; 0.13]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Barizien et al. 2021	12	27	0.44	[0.25; 0.65]
Becker et al. 2021	41	90	0.46	[0.35; 0.56]
Bek et al. 2021	248	385	0.64	[0.59; 0.69]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boari et al. 2021	47	91	0.52	[0.41; 0.62]
Boesi et al. 2021	67	100	0.67	[0.57; 0.76]
Boscolo-Rizzo et al. 2021	83	304	0.27	[0.22; 0.33]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Bozzetti et al. 2021	28	49	0.57	[0.42; 0.71]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carfi et al. 2020	76	143	0.53	[0.45; 0.62]
Carvalho-Schneider et al 2021	52	130	0.40	[0.32; 0.49]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Catalan et al. 2021	30	76	0.39	[0.28; 0.51]
Chen LI et al. 2021	137	715	0.19	[0.16; 0.22]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Creamer et al. 2021	14	57	0.25	[0.14; 0.38]
Daher et al. 2020	15	33	0.45	[0.28; 0.64]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
Darley et al. 2021	15	66	0.23	[0.13; 0.35]
D'Cruz et al. 2020	78	115	0.68	[0.58; 0.76]
Dennis et al. 2021	197	201	0.98	[0.95; 0.99]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Dini et al 2021	36	50	0.72	[0.58; 0.84]
Eloy et al. 2021	159	324	0.49	[0.44; 0.55]
Fang et al. 2021	399	1233	0.32	[0.30; 0.35]
Fernandez-de-Las-Penas et al. 2021	697	1142	0.61	[0.58; 0.64]
Ferraro et al. 2020	6	7	0.86	[0.42; 1.00]
Fortini et al. 2021	25	59	0.42	[0.30; 0.56]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Frontera et al. 2021	98	272	0.36	[0.30; 0.42]
Ganesh et al. 2021	132	817	0.16	[0.14; 0.19]
Garcia-Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Garrigues et al. 2020	66	120	0.55	[0.46; 0.64]
Gautam et al. 2021	77	144	0.53	[0.45; 0.62]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez-Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Graham et al. 2021	43	50	0.86	[0.73; 0.94]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Heightman et al. 2021	644	1325	0.49	[0.46; 0.51]
Hellemons et al. 2021	32	63	0.51	[0.38; 0.64]
Horwitz et al. 2021	107	126	0.85	[0.77; 0.91]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Jacobs et al. 2021	82	149	0.55	[0.47; 0.63]
Kanberg et al. 2021	41	100	0.41	[0.31; 0.51]
Karaarslan et al. 2021	133	300	0.44	[0.39; 0.50]
Kashif et al. 2021	101	242	0.42	[0.35; 0.48]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Labarca et al. 2021	25	60	0.42	[0.29; 0.55]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Lindahl et al. 2021	75	95	0.79	[0.69; 0.87]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Liyanage-Don et al. 2021	31	153	0.20	[0.14; 0.28]
Logue et al. 2021	24	177	0.14	[0.09; 0.20]
Lombardo et al. 2021	158	303	0.52	[0.46; 0.58]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Mazza et al. 2021	63	192	0.33	[0.26; 0.40]
Menges et al. 2021	233	426	0.55	[0.50; 0.59]
Mirfazeli et al. 2021	48	94	0.51	[0.41; 0.62]
Miyazato et al. 2020	6	63	0.10	[0.04; 0.20]
Molnar et al. 2021	69	101	0.68	[0.58; 0.77]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno-Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Morin et al. 2021	134	431	0.31	[0.27; 0.36]
Munblit et al. 2021	551	2599	0.21	[0.20; 0.23]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Nehme et al. 2021	85	410	0.21	[0.17; 0.25]
Noviello et al. 2021	52	164	0.32	[0.25; 0.39]
Nune et al. 2021	24	41	0.59	[0.42; 0.74]
O'Keefe et al. 2021	59	290	0.20	[0.16; 0.25]
Pauley et al. 2021	3	29	0.10	[0.02; 0.27]
Peghin et al. 2021	78	599	0.13	[0.10; 0.16]
Perez-Gonzalez et al. 2021	40	248	0.16	[0.12; 0.21]
Piotto et al.2021	56	165	0.34	[0.27; 0.42]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Raman et al. 2020	32	58	0.55	[0.42; 0.68]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Romero-Duarte et al. 2021	176	797	0.22	[0.19; 0.25]
Rosales-Castilo et a. 2021	23	74	0.31	[0.21; 0.43]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Sathyamurthy et al. 2021	25	279	0.09	[0.06; 0.13]
Scherlinger et al. 2021	25	30	0.83	[0.65; 0.94]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Seeßle et al. 2021	40	96	0.42	[0.32; 0.52]
Shang et al. 2021	201	796	0.25	[0.22; 0.28]
Shendy et al. 2021	52	81	0.64	[0.53; 0.75]
Sigfrid et al. 2021	255	308	0.83	[0.78; 0.87]
Smet et al. 2021	90	137	0.66	[0.57; 0.74]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Staudt et al. 2021	50	101	0.50	[0.39; 0.60]
Stavem et al. 2021	211	458	0.46	[0.41; 0.51]
Steinbeis et al. 2022	44	72	0.61	[0.49; 0.72]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez-Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Szekely et al. 2021	24	71	0.34	[0.23; 0.46]
Taboada et al. 2021	34	91	0.37	[0.27; 0.48]
Taylor et al. 2021	475	675	0.70	[0.67; 0.74]
Tessitore et al. 2021	45	165	0.27	[0.21; 0.35]
Tleyjeh et al. 2021	66	222	0.30	[0.24; 0.36]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
van den Borst et al. 2021	86	124	0.69	[0.60; 0.77]
Vanichkachorn et al. 2021	80	100	0.80	[0.71; 0.87]
van Veenendaal et al. 2021	16	50	0.32	[0.20; 0.47]
Venturelli et al. 2021	337	767	0.44	[0.40; 0.48]
Voruz et al. 2021	6	45	0.13	[0.05; 0.27]
Wang et al. 2021	53	126	0.42	[0.33; 0.51]
Wong-Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Wu et al. 2021	13	54	0.24	[0.13; 0.38]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zayat et al. 2021	68	127	0.54	[0.44; 0.62]
Zhang et al. 2021	674	2433	0.28	[0.26; 0.30]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Zulu et al. 2020	4	27	0.15	[0.04; 0.34]
Random effects model		**46024**	**0.41**	**[0.37; 0.46]**

Heterogeneity: I^2 = 98%, τ^2 = 1.1674, p = 0



Supplementary file. 11 Forest plot for fatigue proportions with low grade studies removed

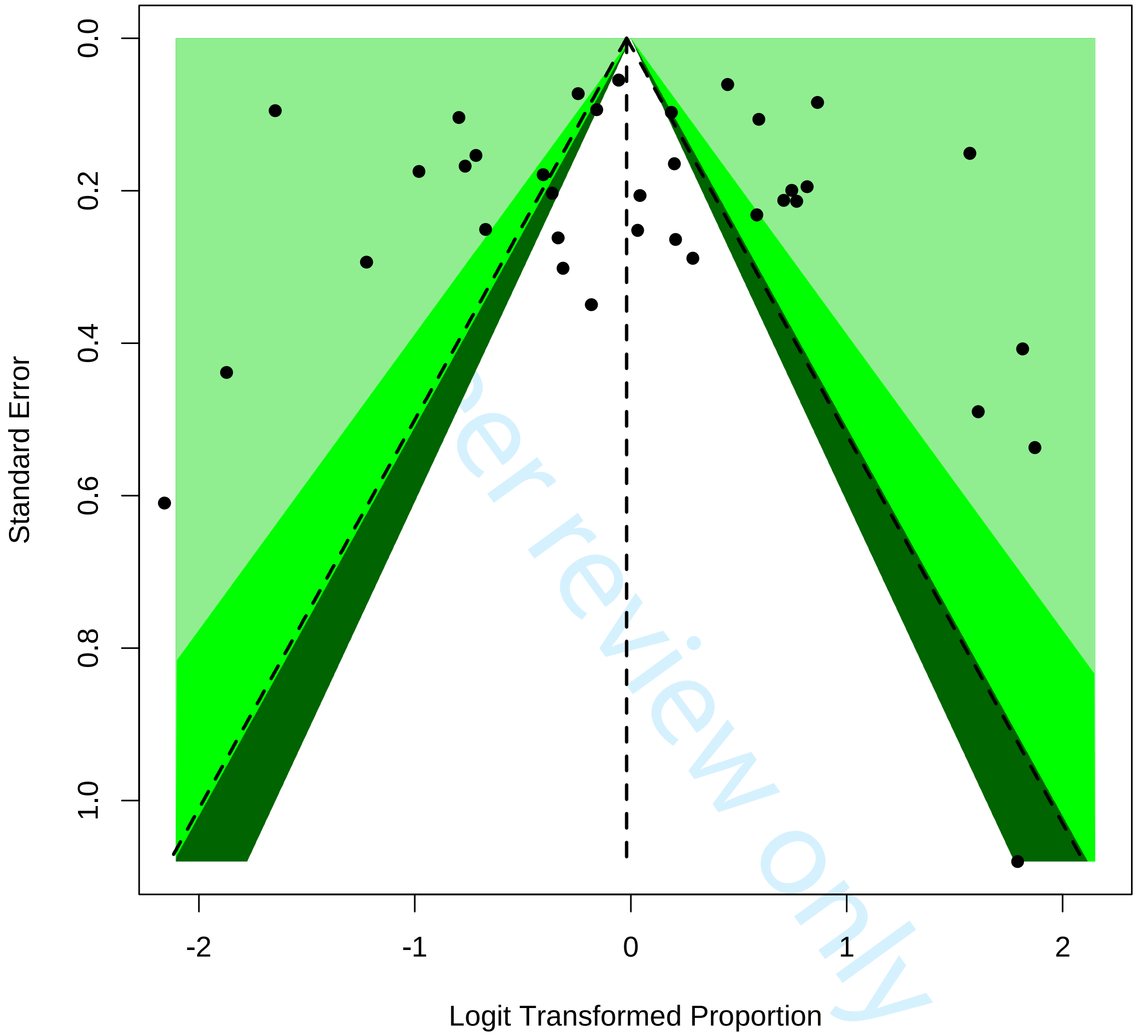


Study	Events	Total	Proportion	95%-CI
Agergaard et al. 2021	18	20	0.90	[0.68; 0.99]
Amin-Chowdhury et al. 2021	55	140	0.39	[0.31; 0.48]
Andrade Barreto et al. 2021	371	602	0.62	[0.58; 0.66]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Aranda et al. 2021	51	113	0.45	[0.36; 0.55]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi-Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Augustin et al. 2021	43	442	0.10	[0.07; 0.13]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Bek et al. 2021	248	385	0.64	[0.59; 0.69]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boari et al. 2021	47	91	0.52	[0.41; 0.62]
Boesi et al. 2021	67	100	0.67	[0.57; 0.76]
Boscolo-Rizzo et al. 2021	83	304	0.27	[0.22; 0.33]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carvalho-Schneider et al 2021	52	130	0.40	[0.32; 0.49]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Chen LI et al. 2021	137	715	0.19	[0.16; 0.22]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Daher et al. 2020	15	33	0.45	[0.28; 0.64]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
Darley et al. 2021	15	66	0.23	[0.13; 0.35]
D'Cruz et al. 2020	78	115	0.68	[0.58; 0.76]
Dennis et al. 2021	197	201	0.98	[0.95; 0.99]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Dini et al 2021	36	50	0.72	[0.58; 0.84]
Eloy et al. 2021	159	324	0.49	[0.44; 0.55]
Fang et al. 2021	399	1233	0.32	[0.30; 0.35]
Fernandez-de-Las-Penas et al. 2021	697	1142	0.61	[0.58; 0.64]
Fortini et al. 2021	25	59	0.42	[0.30; 0.56]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Frontera et al. 2021	98	272	0.36	[0.30; 0.42]
Ganesh et al. 2021	132	817	0.16	[0.14; 0.19]
Garcia-Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Gautam et al. 2021	77	144	0.53	[0.45; 0.62]
Gebhard et al. 2021	84	1024	0.08	[0.07; 0.10]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez-Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Graham et al. 2021	43	50	0.86	[0.73; 0.94]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Heightman et al. 2021	644	1325	0.49	[0.46; 0.51]
Hellemons et al. 2021	32	63	0.51	[0.38; 0.64]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Jacobs et al. 2021	82	149	0.55	[0.47; 0.63]
Kanberg et al. 2021	41	100	0.41	[0.31; 0.51]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Labarca et al. 2021	25	60	0.42	[0.29; 0.55]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Lindahl et al. 2021	75	95	0.79	[0.69; 0.87]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Logue et al. 2021	24	177	0.14	[0.09; 0.20]
Lombardo et al. 2021	158	303	0.52	[0.46; 0.58]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Mazza et al. 2021	63	192	0.33	[0.26; 0.40]
Menges et al. 2021	233	426	0.55	[0.50; 0.59]
Molnar et al. 2021	69	101	0.68	[0.58; 0.77]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno-Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Morin et al. 2021	134	431	0.31	[0.27; 0.36]
Munblit et al. 2021	551	2599	0.21	[0.20; 0.23]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Nehme et al. 2021	85	410	0.21	[0.17; 0.25]
Noviello et al. 2021	52	164	0.32	[0.25; 0.39]
Nune et al. 2021	24	41	0.59	[0.42; 0.74]
O'Keefe et al. 2021	59	290	0.20	[0.16; 0.25]
Pauley et al. 2021	3	29	0.10	[0.02; 0.27]
Peghin et al. 2021	78	599	0.13	[0.10; 0.16]
Perez-Gonzalez et al. 2021	40	248	0.16	[0.12; 0.21]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Raman et al. 2020	32	58	0.55	[0.42; 0.68]
Rauch et al. 2021	32	127	0.25	[0.18; 0.34]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Romero-Duarte et al. 2021	176	797	0.22	[0.19; 0.25]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Scherlinger et al. 2021	25	30	0.83	[0.65; 0.94]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Seeßle et al. 2021	40	96	0.42	[0.32; 0.52]
Senjam et al. 2021	204	257	0.79	[0.74; 0.84]
Sigfrid et al. 2021	255	308	0.83	[0.78; 0.87]
Silva et al. 2021	38	87	0.44	[0.33; 0.55]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Staudt et al. 2021	50	101	0.50	[0.39; 0.60]
Stavem et al. 2021	211	458	0.46	[0.41; 0.51]
Steinbeis et al. 2022	44	72	0.61	[0.49; 0.72]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez-Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Szekely et al. 2021	24	71	0.34	[0.23; 0.46]
Taylor et al. 2021	475	675	0.70	[0.67; 0.74]
Tessitore et al. 2021	45	165	0.27	[0.21; 0.35]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
van den Borst et al. 2021	86	124	0.69	[0.60; 0.77]
van Veenendaal et al. 2021	16	50	0.32	[0.20; 0.47]
Venturelli et al. 2021	337	767	0.44	[0.40; 0.48]
Voruz et al. 2021	6	45	0.13	[0.05; 0.27]
Wong-Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Wu et al. 2021	13	54	0.24	[0.13; 0.38]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zhang et al. 2021	674	2433	0.28	[0.26; 0.30]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Random effects model		**44359**	**0.40**	**[0.36; 0.45]**

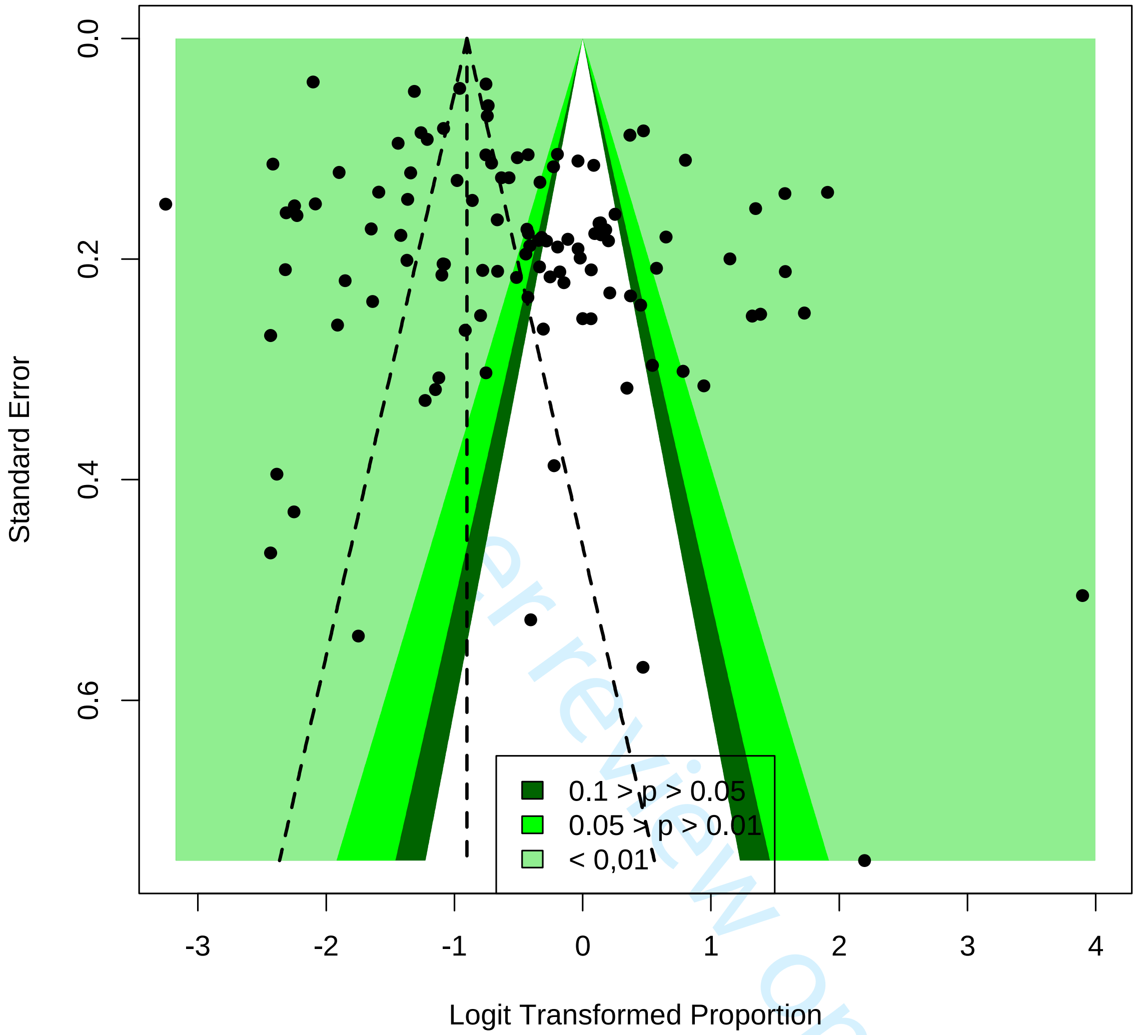
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.2259$, $p = 0$

Supplementary file. 12 Funnel plots for fatigue proportions using a scale or no scale

Funnel plot for studies using a valid scale

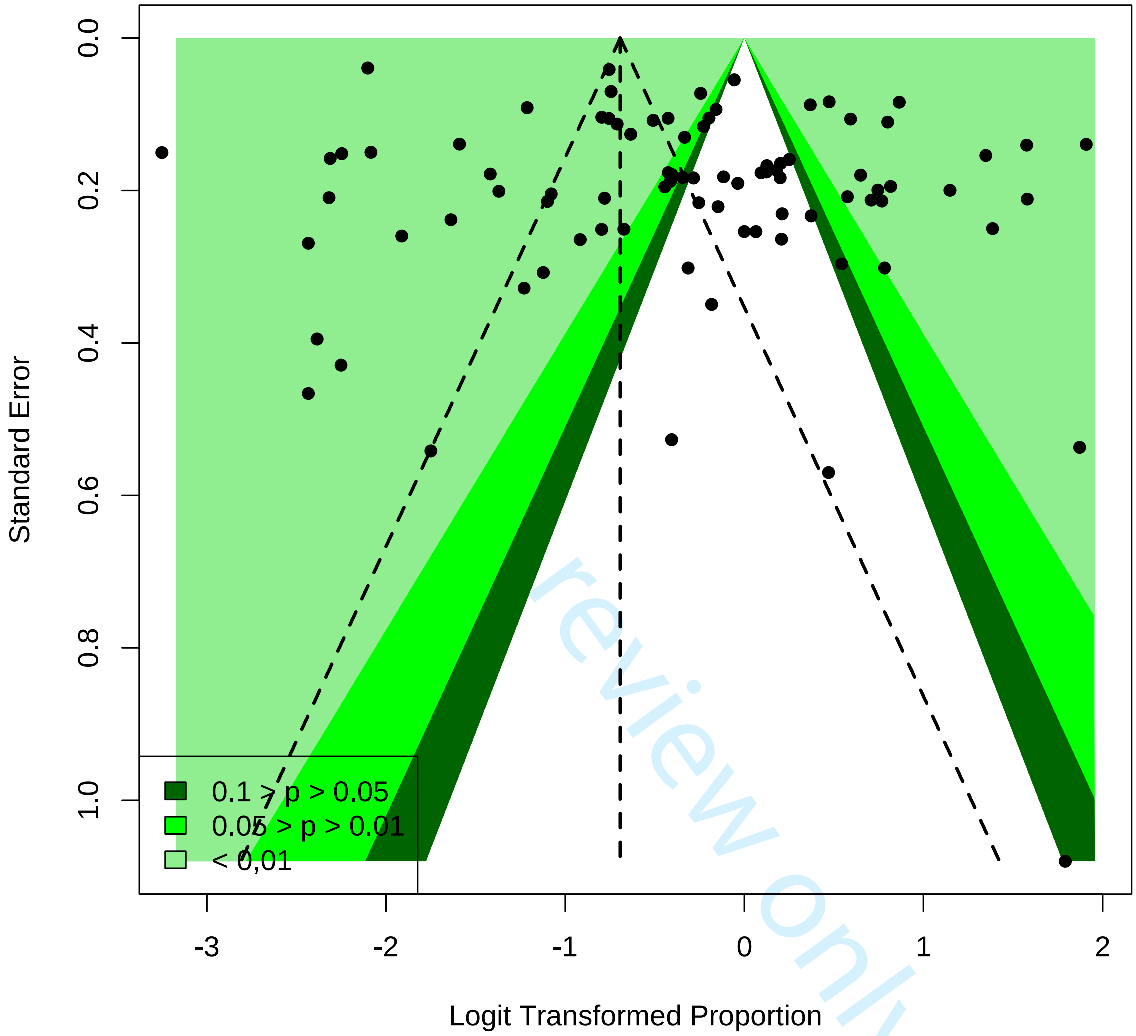


Funnel plot for studies not using a valid scale

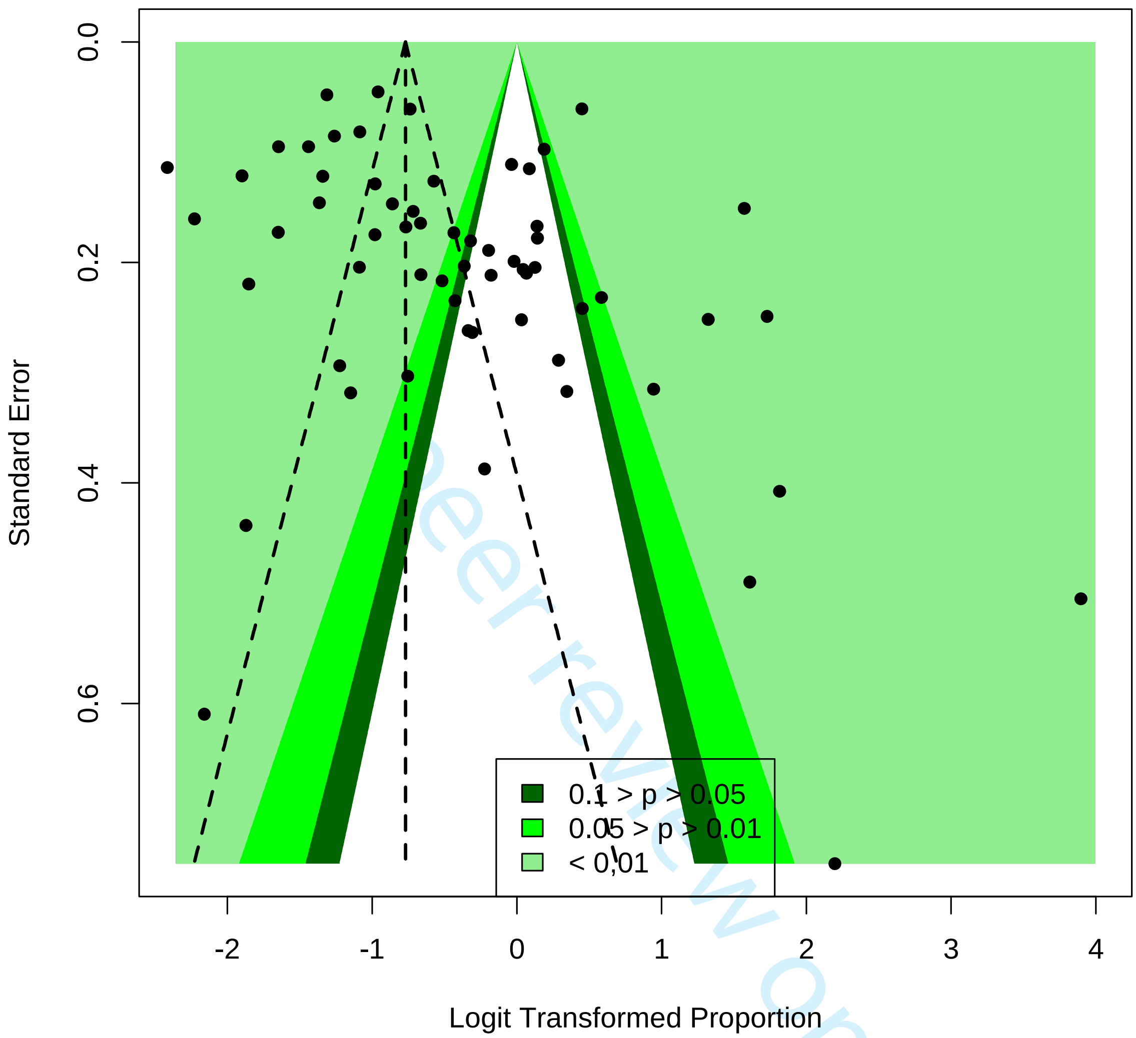


Supplementary file 13. Funnel plots for fatigue proportions 1-3 months & >3 months

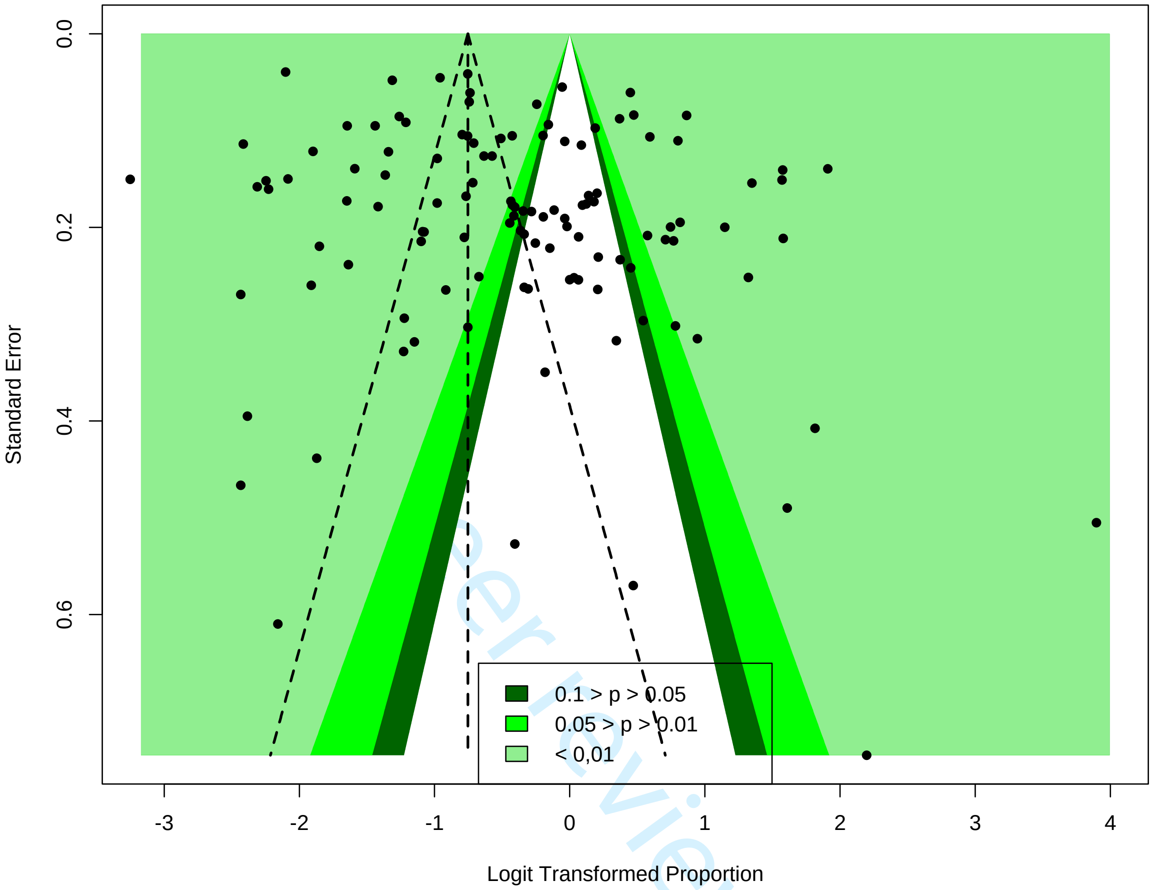
Funnel plot for 1-3 months



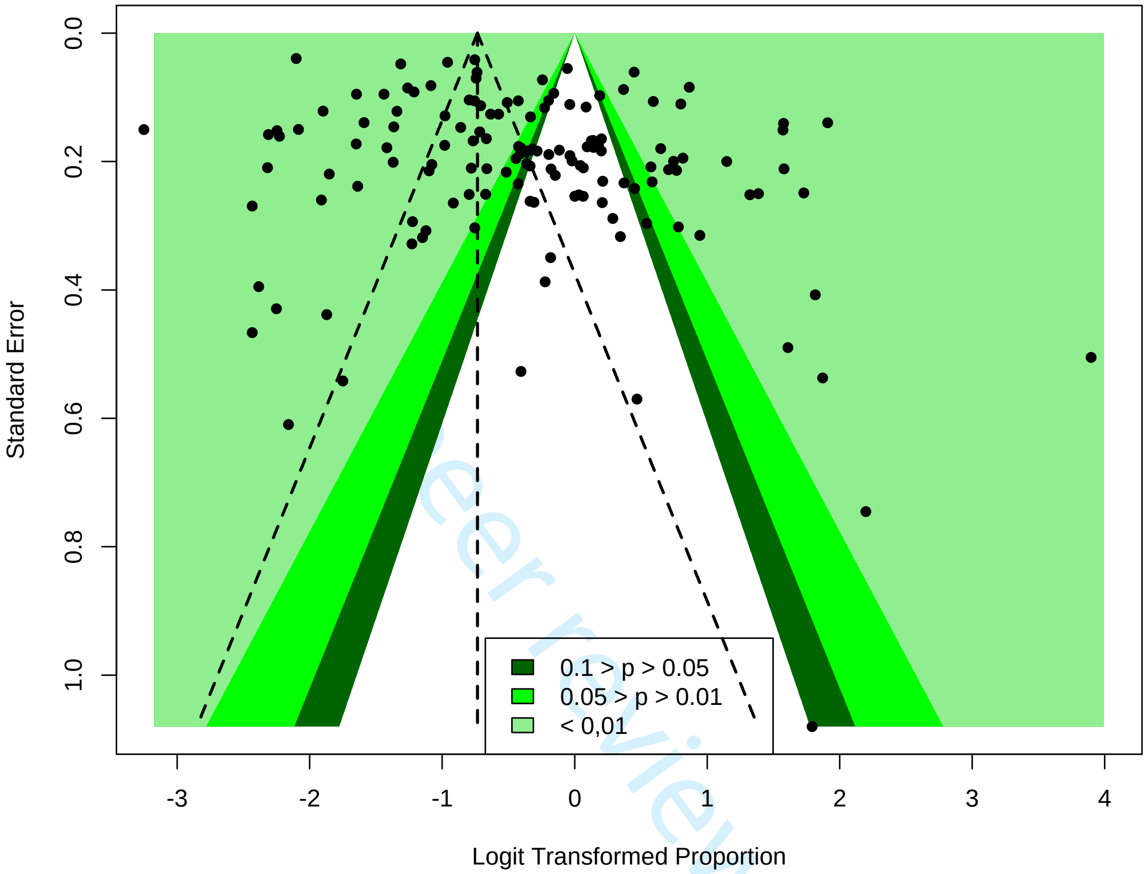
Funnel plot for >3 months



Supplementary file 14. Funnel plot for fatigue proportions excluding 'low grade' quality assessments



Supplementary file. 15 Funnel plot for fatigue proportions excluding unpublished articles



Supplementary File 16. Table of reported risk factors for fatigue

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Agergaard et al. (2021) Denmark	Outpatients	Case-control	20	77-255 days	Questionnaire	Myopathy	11 (100)	
						No myopathy	3 (33)	< .05
							RR 3.27	
Albu et al. (2021) Spain	Outpatients	Cross-sectional	30	$\geq$ 3 months	MFIS	**ICU**		
						Overall Fatigue	13 (81.2)	
						Physical activities	80.55	*0.28*
						Cognitive activities	72.5	*0.28*
						Psychosocial activities	20	*0.40*
						No ICU		
						Overall Fatigue	13 (92.8)	
						Physical activities	81.9	
						Cognitive activities	73.75	
						Psychosocial activities	35	
						Depression		
						Physical fatigue	r = .490	*<.001*
						Cognitive fatigue	r = .490	*<.001*
						Social fatigue	r = .540	*<.001*
						Anxiety		
						Physical fatigue	r = .270	*NS*
						Cognitive fatigue	r = .270	*NS*
						Social fatigue	r = .340	*NS*
						Sleep quality		
						Physical fatigue	r = .640	*<.001*
						Cognitive fatigue	r = .640	*<.001*
						Social fatigue	r = .620	*<.001*
Amin-Chowdhury et al. (2021) UK	Survey	Prospective cohort	1,671	7 months	ADQ	**Gender (F)**	OR = 2.22	*<.001*
						Comorbidities	OR = 1.98	*<.001*
Anaya et al. (2021) Colombia	Survey	Case series	100	219 days	Questionnaire	**Disease severity**		
						Ambulatory	9 (25.7)	0.407
						Severe	15 (36.6)	
						Critical	10 (41.7)	
Andrade Barreto et al. (2021) Brazil	Outpatients	Cross-sectional	602	> 1 month	Questionnaire	**Mild disease**		
						Female	133 (73.5)	
						Male	33 (55.9)	*.011*
						Moderate disease		
						Female	59 (62.1)	
						Male	30 (41.1)	*.007*
						Severe disease		
						Female	53 (67.1)	*.086*
						Male	63 (54.8)	
						Quality of life (Total)	β = -8.28	*<.001*
Aparisi et al. (2021) Italy	Outpatients	Prospective cohort	70	3 months	Clinical assessment for symptom burden	**Persistent dyspnoea**	17 (41.5)	*0.005*
						Residual dyspnoea	3 (10.3)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Arnold et al. (2020) UK	Outpatients	Prospective cohort	110	8-12 weeks	ADQ	**Disease severity & excessive Fatigue**		
						Mild	7/27 (26%)	*NR*
						Moderate	26/65 (40%)	
						Severe	10/18 (56%)	
						Disease severity & vitality	**M (SD)**	
						Mild	43 (20)	
						Moderate	49 (22)	
						Severe	36 (24)	
Aul et al. (2021) UK	Survey	Cross-sectional	387	6 weeks	Questionnaire	**Age**		
						Fatigue	61 (49-72)	*0.12*
						No fatigue	64 (50-76)	
						Gender (M)		
						Fatigue	89 (42.8)	*0.40*
						No fatigue	119 (57.2)	
						BMI		
						Fatigue	26.5 (23.5-30)	*.035*
						No fatigue	28.9 (23.9-32.7)	
						ICU		
						Fatigue	49 (59)	*.003*
						No fatigue	34 (41)	
						Intubated		
						Fatigue	40 (67.8)	*<.001*
						No fatigue	19 (32.2)	
						Days intubated		
						Fatigue	22 (11-45)	*.097*
						No fatigue	17 (7-26)	
						Lymphocytes (10^9/L)		
						Fatigue	0.7 (0.5-1.0)	*0.64*
						No fatigue	0.7 (0.5-1.0)	
						Peak WBC (10^9/L)		
						Fatigue	10.1 (7.1-15.6)	*0.37*
						No fatigue	9.8 (7.2-13.7)	
						Peak CRP (mg/L)		
						Fatigue	147 (81-276)	*.081*
						No fatigue	133 (73-212)	
						Peak ferritin (µg/L)		
						Fatigue	999 (562-2053.5)	*.68*
						No fatigue	961.5 (559-1625)	
						Peak D-dimer (ng/ml)		
						Fatigue	1122 (326-3821)	*.138*
						No fatigue	657.5 (328-2473)	
						High risk inpatient CXR		
						Fatigue	83 (55.7)	*NS*
						No fatigue	78 (47.9)	
							OR 7.04	
						Post-COVID fibrosis		*.167*
						Ethnicity	-	*NS*
								.001
Augustin et al. (2021)	Outpatients	Prospective	958	4, 7 months	ADQ	**IgG Levels**		

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Germany		cohort				Low ≤ 1.1 Medium 1.2-4 High > 4 **Gender** Male Female	NR NR NR 13/353 (8.6%) 37/353 (18.3%)	*NR* *NR* *NR* *NR*
Aydin et al. (2021) Turkey	Outpatients	Cohort	116	44 days	ADQ	**Gender (F)**	OR = 1.8	*.008*
Bai et al. (2021) Italy	Outpatients	Prospective cohort	377	102 days	Clinical interview	**Gender** Females Males **Long-Covid** No Yes	 75/137 (54.7) 74/240 (30.8) 20/117 (17.1) 39/260 (15)	 .001 .732
Barizien et al. (2021) France	Outpatients	Prospective cohort	39	7 months	Clinician assessment	**Fatigued v Not fatigued** Age Gender (F) Physical comorbidities Loss of taste & smell Weight (before & current) Height BMI (before & current) Loss of weight Heart rate (BPM) Blood pressure NJIMEGEN Score PTSD Score 30 s of up & down test O^2 saturation (%) Months since diagnosis Systolic & diastolic BP		 *.085* *.059* *NS* *.951* *NS* *.499* *NS* *.632* *.708* *NS* *.002* *.001* *.192* *.663* *.157* *NS*
Becker et al. (2021) Switzerland	Outpatients	Prospective cohort	90	12 months	ADQ VAS	Psychological distress No psychological distress	**9 (23.1)** **30 (76.9)**	**.288**
Bek et al. (2021) Netherlands	Outpatients	Prospective cohort	492	3, 6, 12 months	FAS	Gender Comorbidity (Y) Employment (N) Employment Retired	**OR 2.76** **OR 2.19** **OR 0.57** **OR** 0.38	**<.001** **.007** **.009** **<.001**
Bell et al. (2021) USA	Survey	Prospective cohort	303	> 30 days	ADQ	**Follow-up** ≥ 30 days 30-59 days ≥ 60 days	 78 (37.5) 21 (24.1) 57 (47.1)	 -
Boesl et al. (2021) Italy	Outpatients	Cross-sectional	100	≥ 12 weeks	FSS	 **No impairment due to fatigue (1-3 on FSS)** Total Female Male	**N (%)** 18 (19.8) 13 (20.3) 5 (18.5)	 *NR*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Impairment due to fatigue (4-7 on FSS) Total Female Male	 73 (80.2) 51 (79.7) 22 (81.5)	 *NR*
Bottemanne et al. 2021 France	Outpatients Telephone	Prospective cohort	84	1, 3 months	Clinical interview	**3-month outcomes** Anxiety @ 1 month Physical symptoms @ 1 month Depression	- aOR 0.81 aOR 4.00 aOR 0.84	 .250 .236 .307
Bozzetti et al. (2021) Italy	Outpatients	Prospective cohort	49	6 months	Questionnaire	**≥ 50% reduction of serum NfL levels** **< 50% reduction of serum NfL level**	4/14 (33) 4/15 (27)	 *.999*
Carvalho-Schneider et al. (2021) France	Survey	Prospective cohort	150	30-60 days	WHO Performance Status Classification	**Severe asthenia** Day 30 Day 60	 11 (7) 4 (3.1)	-
Castro et al. (2021) USA	EHR	Retrospective case-control	6,619	31-90 days 91-150 days	Reported symptoms	**Positive test v Negative test**	aOR = 0.98	*.761*
Catalan et al. (2021) Spain	Survey	Cohort	76	12 months	Questionnaire SF-36	**No Steroids** Asthenia Vitality **Steroids** Asthenia Vitality	 19 (43.2) 62.5 (IQR 40–85) 11 (34.4) 80 (56.2–85)	 *.440* *.120*
Chen, Li et al. (2021) China	Telephone	Longitudinal cohort	715	Median 225 days	Questionnaire	Mechanical ventilation (ICU) Re-admission after discharge Hypertension	OR 5.52 OR 3.41 OR 1.65	.001 .001 .0016
Chudzik et al. (2021) Poland	Outpatients	RCT	50	4 weeks	FAS	**Phase 0** 1-MNA supplementation No supplement **Phase 1** 1-MNA supplementation No supplement	**M (SD)** 4.23 4.53 4.42 4.94	 *.008*
Clavario et al. (2020) Italy	Outpatients	Prospective cohort	110	3 months	Questionnaire	**% predicted VO2 below 85%** **% predicted VO2 above 85%**	21/38 (55.3) 33/72 (45.8)	.459
Daugherty et al. (2021) USA	EHR	Retrospective cohort	27,074	1-6 months	ICD10	**Fatigue** **Age > 50**	HR = 2.20 -	 *<.001*
D'Cruz et al. (2020) UK	Outpatients	Prospective cohort	119	61 days	NRM	**Breathlessness** **Post-COVID-19 function** **Positive mental health** **Psychological impairment** **Age** **Pre-existing comorbidities**	OR = 3.19 OR = 4.66 OR = 3.58 NR NR NR	*.002* *.000* *.012* *NS* *NS* *NS*
Dennis et al. (2021 UK	Outpatients	Prospective cohort	201	Median 141 days	NR	**Not hospitalised** **Hospitalised**	**159/163 (97.5)** **37 (100)**	 *1.0*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Moderate PCS **Severe PCS**	**73/77 (96.1)** **115/116 (99.1)**	 *.302*
Desgranges et al. (2021) Switzerland	Survey	Cohort	418	3-10 months	Questionnaire	 **Overweight/Obese** **Female** **Age** **Smoker** **Physical comorbidities** **Time of phone survey**	- OR = 1.70 OR = 1.61 OR = 1.08 OR = 1.79 - -	*.006* *.001* *.001* *NS* *NS* *NS* *NS*
Dini et al. (2021) Italy	Outpatients	Cross-sectional	50	5 months	Questionnaire	**Fatigue** None Minimal Moderate Severe Very Severe **Lower resilience**	 14 (28) 16 (32) 13 (26) 6 (12) 1 (2) -2.51	 *.015*
Fang et al. 2021 China	Telephone	Prospective cohort	1233	12 months	Physician interview	Severe disease Non-severe disease	166/438 (37.9) 234/795 (29.4)	.002
Fatima et al. (2021) India	Survey	Cohort	160	40 days	ADQ	Fatigue on 'daily routine'	33 (20.6)	-
Fernandez-de-Las-Penas et al. (2021) Spain	Survey	Cohort	1142	7 months	FIC ADQ	**Gender** Male Female **Persistent fatigue (F)** **ICU Admission** **Medical comorbidity**	 329 (54.7) 367 (67.8) OR 1.80 OR 0.98 NR	 *.05* *.001* *.963* *NS*
Froidure et al. (2021) Italy	Outpatients	Cohort	126	3 months	Questionnaire	**Pulmonary functions** **Age** **Sex** **Dyspnoea**	NR NR NR NR	*NS* *NS* *NS* *NS*
Frontera et al. (2021) USA	Survey	Prospective cohort	272	6 months	ADQ	 **Neurologic COVID v controls** **Return to work**	**Median (IQR)** 45.6 (38.2–54.4) r = .118	 *.760* *.160*
Garrigues et al. (2020) France	Outpatients	Cross-sectional	120	110.9 days	Questionnaire	**Ward Group** Fatigue **ICU Group** Fatigue	 52(54.2) 14(58.3)	 *NS*
Gebhard et al. (2021) Switzerland	Survey	Cohort	1024	6.5 months	ADQ	**Gender** Women Men	 44 (8) 40 (8)	 -
Gonzalez-Hermosillo et al. (2021) Mexico	Survey	Prospective cohort	130	3 months 6 months	Questionnaire	**CFS** **Female** **Age >40** **Anxiety** Fatigued Not fatigued **Depression**	17 (17.2) OR = 1.95 OR = 2.5 39 (56.3) 15 (24.6)	*.07* *.03* *.001* *.004*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Fatigued	31 (44.9)	*.05*
						Not fatigued	13 (21.3)	
						Fatigue (3 mths v. 6 mths)		*.01*
						Dyspnoea on effort	-	*.53*
						Resting dyspnoea	-	*.05*
						Gastrointestinal symptoms	-	*.05*
						Neurocognitive symptoms	-	*.05*
						Sleep	-	*.05*
						Autonomic dysregulation	-	
						Pain	-	
Graham et al. (2021) USA	Survey	Cohort	100	7 months	PROMIS	**Processing speed**	r = .450	.02
						Executive function	r = .430	.02
						Working memory	r = .440	.02
						Attention		
						SARS-CoV+	r = −.070	.79
						SARS-CoV-	r = −.760	.02
Halpin et al. (2020) UK	Outpatients	Cross-sectional	100	4-8 weeks	Fatigue	**New fatigue**		
						Ward	41 (60.3)	*NR*
						ICU	23 (72)	
						Fatigue Severity Severe		
						Ward	10 (14.7)	*NR*
						ICU	4 (12.5)	
						Fatigue severity moderate		
						Ward	14 (20.6)	*NR*
						ICU	13 (40.6)	
						Fatigue Severity mild		
						Ward	17 (25)	*NR*
						ICU	6 (18.8)	
						Gender		
						Moderate/Severe fatigue		
						Women	46 (61)	*NR*
						Men	54 (26.6)	
						PTSD		
						Severe fatigue	(43.9)	*NR*
						No fatigue	(18.6)	
						Cognitive problems		
						Moderate/Severe fatigue	(41.4)	*NR*
						Less severe fatigue	(18.6)	
						Breathlessness		
						Moderate/Severe fatigue	(65.9)	*NR*
						Less severe fatigue	(39)	
						Age	NR	*NS*
						Ethnicity (severe v. non severe fatigue)	NR	*NS*
						BMI (severe v. non severe fatigue)	NR	*NS*
Heightman et al. (2021) UK	Outpatients	Cohort	1325	$\geq$ 6 weeks	FAS	**Total fatigue**		
						Post-Hospitalised	24 (16-34)	
						Non-Hospitalised	30 (24-38)	
						Post-Emergency	28 (23-36)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						CFS	10 (0.8)	
						Return to full-time work		
						Hospitalised	OR = 0.29	
						Non-Hospitalised	OR = 0.67	
						Functional recovery		
						Hospitalised	OR = 0.47	
						Non-Hospitalised	OR = 0.49	
						Post-Emergency	OR = 0.40	
Hellemons et al. (2021) Netherlands	Outpatients Survey	Prospective cohort	92	3-6 months	FAS	**Post -Covid Time**		
						6 weeks to 3 months	-	.863
						3 months to 6 months	-	.006
						Gender (F)	β = 4.05	.027
						Physical functioning	β = -2.88	<.001
Hossain et al. 2021 Bangladesh	Outpatients	Prospective cohort	2198	12 weeks	ADQ	**Gender**		
						Female	96 (27)	.763
						Male	199 (55.9)	
						Age	X^2 5.59	.241
						Marital status	X^2 2.95	.304
						Education	X^2 2.59	.659
						Rural/Urban location	X^2 1.17	.351
						Occupation	X^2 1.48	.928
						Disease severity	X^2 0.51	.540
						Post-covid functional status score	B 0.094	.001
Iqbal et al. (2021) Pakistan	Survey	Cross-sectional	158	38 days	ADQ	**Female**	92 (58)	.05
						Days since recovery		
						Fatigued	33.98 (15.62)	<.001
						Not fatigued	58.07 (26.37)	
						Disease severity		
						Mild	86 (65.6)	.005
						Moderate	33 (25.2)	
						Severe	12 (9.2)	
Jacobs et al. (2020) USA	Survey	Cohort	149	35 days	PROMIS	**Physical health rating**		
						Poor/fair	OR = 0.128	<.001
						Quality of life rating		
						Moderate	OR = 0.785	NS
						Mild to none	OR = 0.104	NS
Kanberg et al. (2021) Sweden	Outpatients	Prospective cohort	100	6 months	KEDS	**Disease severity**		
						Mild	9 (38)	0.59
						Moderate	11 (42)	
						Severe	20 (42)	
Karaarslan et al. (2021) Turkey	Survey	Cohort	300	1 month	ADQ	**Fatigue severity**		
						Mild	93 (31.0)	
						Moderate	30 (10.0)	
						Severe	9 (3.0)	
						Very severe	1 (0.3)	
						None	167 (55.7)	
						Multivariate		
						Age	OR = 0.98	.060
						Female	OR = 1.42	.145
						BMI	OR = 1.08	.003

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						LOS	OR = 0.98	*.468*
Kashif et al. 2021 Pakistan	Telephone	Cohort	242	3 months	Questionnaire	**Gender** Female Male **Comorbidities** With Without	 38 (51) 63 (38) 13/29 (44.8) 88/213 (41.3)	 .039 .647
Labarca et al. (2021) Chile	Outpatients	Cross-sectional	60	4 months	CFQ	**Disease severity** Mild Moderate Severe	 5 (11.1) 10 (47) 10 (36)	 *.05*
Liang et al. (2020) China	Outpatients	Prospective cohort	76	3 months	Questionnaire	**3 months fatigue** TN1 at acute phase	 r = . 782	 *.008*
Lindahl et al. (2021) Finland	Survey	Cohort	101	6 months	SF-36	 54.2 (23.6) **Gender** Women Men **Mild fatigue** Women Men **Severe fatigue** Women Men	**M (SD)** 36 (83.7) 39 (7) 26 (60.5) 32 (61) 17 (39.5) 7 (13)	 .033
Liu et al. (2021) China	Outpatients	Prospective cohort	594	3, 6, 12 months	Questionnaire	**3 months** Total Moderate Severe Critical **6 months** Total Moderate Severe Critical **12 months** Total Moderate Severe Critical	 48/502 (9.6) 7/63 (11.1) 34/378 (9.0) 7/61 (11.5) 27/422 (6.4) 5/52 (9.6) 20/313 (6.4) 2/57 (3.5) 18/486 (3.7) 0 (0) 16/379 (4.2) 2/55 (3.6)	
Liyanage-Don et al. 2021 USA	Survey	Cross-sectional	153	3 months	ADQ	**Depression v No Depression** **Anxiety v. No Anxiety**	NR NR	*<.01* *<.01*
Lombardo et al. (2021) Italy	Telephone	Prospective cohort	303	12 months	ADQ	**Age** 18-47 47-58 59-90	 OR =1.52 OR = 3.30 OR = 0.78	 *<.001* *<.001* *.044*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Gender (F)	OR = 0.57	*.022*
						Hospitalised	OR = −0.069	*.801*
Maamar et al. (2021) Spain	Outpatients	Cross-sectional	121	3 months	Interview	**Neutrophil count (x103/µL)**		
						Post-Covid fatigue	OR = 4.68	*.041*
						No fatigue	OR = 3.37	
						Post-Covid Men	OR = 4.07	*.047*
Mazza et al. 2021 Italy	Outpatients Online	Prospective cohort	402	1, 6, 12 months	FSS	Age	r = .01	*NS*
						LOS	r = -.06	*NS*
						Severity of Depression at 6 months	r = .47	*NS*
						Severity of PTSD at 6 months	r = .32	q = .05
						Severity of Anxiety at 6 months	r = .37	q = .05
						Severity of Depression at 12 months	r = .56	q = .05
						Severity of PTSD at 12 months	r = .52	q = .05
						Severity of Anxiety at 12 months	r = .48	q = .05
						FSS M (SD)		
						Men	3.17 ± 1.42	q = .004
						Women	3.88 ± 1.73	
						Comorbid Psychiatric history	4.05 (1.62)	**q =.001**
						No psychiatric history	3.18 (1.48)	
Menges et al. (2021) Switzerland	Survey	Prospective cohort	431	6-8 months	FAS	**Age**		
						18-39	105 (64.0)	
						40–64	104 (51.0)	
						65+	24 (41.4)	
						Gender		
						Female	125 (59.2)	*NS*
						Male	108 (50.2)	
						Not hospitalised	195 (55.9)	*NS*
						Hospitalised	38 (49.4)	
						Healthcare utilisation	OR = 1.61	*NR*
						Age 18-39	OR = 0.59	*NR*
						Female	OR = 1.38	*NR*
						Initial symptoms (v severe)	OR = 1.36	*NR*
						ICU admission	OR = 4.63	*NR*
						Ex-smoker	OR = 1.58	*NR*
						BMI	OR = 1.04	*NR*
						Comorbidities	OR = 1.27	*NR*
						Time since diagnosis	OR = 1.00	*NR*
Mirfazeli et al. (2021) Iran	Survey Interview	Prospective cohort	94	9 months	CDC Criteria for Fatigue Scale	**Chronic fatigue syndrome**		
						Total 21 (22.9)		
						Female	-	*.02*
						Age	-	*NS*
						Constitutional neuropsychiatric	-	
						symptoms in the acute phase		*.01*
						Initial Covid severity		
							-	*NS*
Molnar et al. (2021) Hungary	Outpatients	Prospective cohort	101	> 4 weeks	CFQ-11		**M (SD)**	
						Total fatigue score	15.7 (5.9)	
						4-12 weeks	15.8 (5.5)	*.951*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						> 12 weeks **Fatigue severity** Age **Antibody levels** Total CFQ-11 score	5.6 (6.7) OR = 1.18 OR = 9.03	 *.178* *.003*
Morin et al. (2021) France	Telephone	Prospective cohort	478	3-4 months	MFI	 MFI Score Mental fatigue score Intubated Non-intubated	**M (IQR)** 4.5 (I3.0-5.0) 3.7 (3.0-4.5 **N (%)** 110 (29.9) 24 (38.1)	
Munblit et al. (2021) Russia	Telephone	Longitudinal cohort	2599	218 days	Questionnaire	**Chronic fatigue** Chronic pulmonary disease Female Hypertension RT- PCR "+"	 OR = 1.68 OR = 1.67 OR = 1.27 OR = 1.23	 *.05* *.05* *.05* *.05*
Nehme et al. (2021) Switerland	Survey	Cohort	410	7-9 months	Questionnaire	**Female** **Male** **Age** 18-39 40-59 > 60	65 (23.6) 20 (14.8) 30 (17.3) 43 (21.7) 12 (30.8)	- -
Noviello et al. (2021) Italy	Survey	Case control	164 patients 184 controls	4.8 months	SAGIS	**Chronic fatigue** Patients **Disease severity** Mild Moderate Severe **Diarrhoea** **Somatisation** Fatigued Not fatigued	 RR = 2.24 (33.3) (25.9) (40.1) - **M (SD)** 61.7 (10.8) 50.9 10.9)	*<.001* *.41* *.05* *<.001*
Nune et al. (2021) UK	Telephone	Prospective cohort	271	3, 6, 9 months	ADQ VAS	**3 months** Evidence of pneumonia in CXR ITU/HDU admission	 OR = 3.22 OR = 5.58	 *.008* *.020*
O'Keefe et al. (2021) USA	Survey	Cross-sectional	290	1-6 months	ADQ	**Fatigue post-acute** Median 61 days Median 139 days **Worse physical health (than before Covid)** **Physical health affects daily activities** **Emotional health affects daily activities**	 17 (19.3) 42 (21.2) OR = 10.48 OR = 10.35 OR = 2.56	 *.710*
Pauley et al. (2021) UK	Telephone/ Outpatients	Prospective cohort	332	3 months 12 months	VAS	**Fatigue severity** **Age** Male 50-69 Male > 70	β = 0.09 β = 1.33 β = 0.96	*.242* *.101* *.295*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Female < 50 Female 50 - 69 **≥ 1 comorbidities** **Ventilated (ICU)**	β = 2.56 β = 1.32 β = 1.20 OR = 0.50	*.037* *.101* *.037* *NR*
Peghin et al. 2021 Italy	Telephone	Prospective cohort	599	6 months	PRO	**Disease Severity @ Onset** Asymptomatic Mild Moderate Severe Critical	**N (%)** 1/55 (1.8) 45/409 (11.0) 21/93 (22.6) 5/24 (20.8) 6/15 (40.0)	*<.001*
Pérez-González et al. (2021) Spain	Telephone	Prospective cohort	284	6 months	Questionnaire	**Hospitalised** **Not hospitalised** **Gender** Female Male **COPD v No COPD**	36 (20.9) 4 (5.3) 22 (22) 18 (12.2) -	*.001* *.00* *NS*
Pilotto et al. (2021) Italy	Outpatients	Cohort	165	6 months	Questionnaire	**Disease severity** Moderate/Severe	OR = 2.1	*NR*
Rass et al. (2021) Austria	Outpatients	Prospective cohort	90	3 months	NR	**Quality of life (SF-36)** MCS ≥ 40 MCS < 40 PCS ≥ 40 PCS < 40	13 (19.7) 9 (40.9) 12 (15.8) 9 (81.8)	*.009* *.001*
Rauch et al. (2021) Germany	Survey	Prospective cohort	127	3, 6, 12 months	ADQ	**Disease severity** Mild Moderate Severe **Age** 18 - 19 40 - 59 > 60 **Gender** Female Male	3 (8) 19 (31) 10 (39) 8 (28) 13 (21) 11 (31) 24 (28) 8 (20)	.004 *.471* *.390*
Righi et al. (2021) Italy	Outpatients Telephone	Prospective cohort	448	4-12 weeks	Questionnaire	**Duration of fatigue** Inpatients Outpatients	22 days 14 days	*<.001*
Romero-Duarte et al. (2021) Spain	EHR	Retrospective cohort	797	6 months	Reported symptoms	**Gender** Men Women	81 (18.9) 95 (25.7)	*.021*
Sami et al. (2020) Iran	Telephone	Cohort	452	4 weeks	Questionnaire	**Disease severity** Non-Severe Severe	43/400 (10.75) 7/52 (13.46)	*.320*
Sathyamurthy et al. (2021) India	Telephone	Prospective cohort	279	90 days	Questionnaire	**Gender** Men	16/101 (9)	*.277*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Women	9/178 (8.9)	
						Disease Severity		
						Mild/moderate	9/163 (5.5)	*.077*
						Severe/critical	16/116 (13.8)	
Scherlinger et al. (2021) France	Outpatients	Prospective cohort	30	152 days	VAS	**Immunised**	13 (86.7)	*NS*
						Not immunised	12 (80)	
Seeßle et al. (2021) Germany	Outpatients	Prospective cohort	96	5/12 months	Questionnaire			*.043*
Shang et al. (2021) China	Telephone	Cohort	796	6 months	Questionnaire	**Disease Severity**		
						Severe	183 (25.3)	*.902*
						Critical	18 (24.7)	
						Gender		
						Men	86 (21.3)	*.009*
						Women	115 (29.3)	
						Age		
						< 65	125 (26.1)	*.500*
						> 65	76 (24.0)	
Shendy et al. (2021) Egypt	Telephone	Cross-sectional	81	3-5 months	MFIS	**Fatigued v Not fatigued**		
						Gender	-	*.40*
						Age	-	*.80*
						BMI	-	*.44*
						Smoking status	-	*.89*
						O² supplementation	-	*.53*
						Hospitalised	-	*.52*
						Dyspnoea level		
						None	-	
						Mild	-	*.04*
						Moderate	-	
						Severe	-	
						NRS Scores		
						Physical MFIS	r = 0.44	*<.001*
						Cognitive MFIS	r = 0.31	*.005*
						Psychosocial MFIS	r = 0.27	*.01*
Sigfrid et al. (2021) UK	Outpatients Survey	Prospective cohort	308	222 days	VAS		**M (IQR)**	
						Gender		
						Men	4.0 (2.0 – 6)	*<.001*
						Women	6.0 (2.0 - 7.0)	
						Women		*.001*
						< 50 years	OR = 2.06	*.012*
						> 50 years	OR = 1.20	*.362*
						> 70 years	OR= 0.29	*.194*
						Males		
						< 70 years	OR = 0.44	*.194*
						> 70 years	OR = 0.38	*.272*
						≥ 1 comorbidity	OR = 0.95	*.001*
						Age	-	*NS*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Disease severity	**VAS Score**	
						WHO Scale 4	OR = -0.26	*.266*
						WHO Scale 5	OR = -0.20	*.354*
						WHO Scale 6/7	OR = -0.18	*.354*
Silva et al. (2021) Brazil	Outpatients	Cross-sectional	87	54 days	Questionnaire CFQ-11	**CFQ-11 Score**	15 (0-32)	
						Sleep	r = .440	<.001
						Depression	r = .470	<.001
Staudt et al. 2021 Germany	Outpatients	Prospective cohort	101	10 months	Questionnaire	Age	OR = 1.00	*NS*
						Gender	OR = 0.52	*NS*
						Smoking	OR = 0.80	*NS*
						SpO_2	OR = 0.99	*NS*
						BMI	OR = 1.02	*NS*
						FEV_1	OR = 0.97	*NS*
						TLC/RV	OR = 1.00	*NS*
						6MWT	OR = 1.02	*NS*
						Depression PHQ-9	OR = 1.27	*.05*
						Respiratory symptoms SGRQ	OR = 1.06	*.05*
						Haemoglobin levels (g/dL)	OR = 1.26	*NS*
						Somatization index SOMS-SAD	OR = 0.90	*NS*
Stavem et al. (2021) Norway	Survey	Cohort	458	1.5-6 months	CFQ-11 RAND-36		**M (SD)**	
						CFQ Physical	10.1 (3.8)	
						CFQ Mental	5.0 (1.8)	
						Vitality	56.8 (23.9)	
						CFQ-11		
						Age		
						Marital status	OR = 1.02	*.081*
						Female gender	OR = 0.56	*.022*
						Education (university)	OR = 0.49	*.002*
						No. comorbidities >2	OR = 1.17	*.070*
						Previous depression	OR = 1.52	*.230*
						Symptoms during COVID	OR = 1.10	*.840*
						No. covid symptoms (10-23)	OR = 3.66	*.001*
						Dyspnoea	OR = 1.56	*.069*
						Confusion	OR = 2.25	*.022*
						BMI	OR = 1.03	*.130*
						Smoking	OR = 1.34	*.210*
						Days since symptom onset (128-200)	OR = 0.55	*.034*
						RAND-36 (Vitality)		
						Age	β = 1.51	*.057*
						Gender (f)	β = 9.63	*<.001*
						Marital status	β = 3.53	*<.001*
						Education (university)	β = 4.42	*.230*
						Previous depression	β = -12.05	*.005*
						Covid symptoms (#10-23)	β = −15.59	*<.001*
						Confusion during covid	β = -7.35	*.018*
						BMI	β = -0.50	*.010*
						Days since symptom onset (128-200)	β = 6.09	*.015*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Sykes et al. (2021) UK	Outpatients	Retrospective cohort	134	113 days	Questionnaire	**Gender**		
						Males	27 (30)	*.004*
						Females	26 (56.5)	
						ICU/Ward		
						Ward	44/107 (41.1)	NR
						ICU	9/27 (33.3)	
						Follow-up days		
						47-75	5 (71.4)	NR
						76-100	13 (50)	
						101-125	26(33.3)	
						126-167	9 (39.1)	
						BMI (>)	NR	*.046*
Taboada et al. (2021) Spain	NR	Prospective cohort	91	6 months	Questionnaire	**With a decrease in functional status v. no decrease**	OR = 12.321	*.01*
						With a decrease in QoL v. no decrease	OR = 15.448	*.01*
Taylor et al. (2021) UK	Telephone Survey	Cohort	675	> 12 weeks	Amplitude Questionnaire	**High risk for post-covid healthcare needs**	169 (50.3)	-
						Low risk for post-covid healthcare needs	376 (46.8)	
Tomasoni et al. (2021) Italy	Outpatients	Cross-sectional	105	1-3 months	Questionnaire	**HADS Anxiety Scores**		
						'Normal'	18/70 (25.7)	.044
						'Pathological'	15/30 (30)	
Townsend et al. (2020) Ireland	Outpatients	Cross-sectional	128	10 weeks	CFQ	**Physical fatigue**	11.38 (4.22)	
						Psychological fatigue	4.72 (1.99)	
						Severe fatigue group:		
						Female	45 (52.3)	*.002*
						Anxiety/Depression/anti-depressant history	-	*.002*
						Days since onset		*NS*
						Critical care		*NS*
						LOS		*NS*
						BMI		*NS*
						Lab tests (NLR, LDH, CRP)		*NS*
						COVID severity		*NS*
van den Borst et al. (2021) Netherlands	Outpatients	Prospective cohort	124	3 months	NCSI	**Disease severity**	NR	*.05*
Venturelli et al. (2021) Italy	Telephone	Cohort	767	49 days 81 days	BFI	**Male**	93 (18.1)	*NR*
						Female	93 (36.9)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Voruz et al. (2021) Switzerland	Outpatients Survey	Cohort	75	6-9 months	FIS SF-36	**Disease Severity**		
						Mild	2/15 (13.3)	*.088*
						Moderate	3/15 (20)	
						Severe	1/15 (6.6)	
						Quality of Life	-	*.040*
						Vitality Score		
						Mild	38.66	*.039*
						Moderate	49.00	
						Severe	56.00	
Wu et al. (2021) China	Outpatients	Cohort	54	6 months	ADQ	**Disease Severity**	**N(%)**	
						Severe	6/23 (19.4)	*NR*
						Moderate	7/31 (30.4)	
Yomogida et al. (2021) USA	Telephone	Prospective cohort	366	1, 2, 6 months	Questionnaire	Gender (F)	aOR = 3.90	<.001
						≥ 1 comorbidity	aOR = 4.39	<.001
						Age ≥40	aOR = 2.25	0.01
Zhang et al. (2021) China	Telephone	Cohort	2433	1 year	ADQ	**Disease Severity**		
						Severe v. Not severe	OR = 1.36	.004
						Oder age	OR = 1.02	< .001
						Gender (F)	OR = 1.27	.008
						Severe disease during hospital-stay	OR = 1.43	< .001
Zhou et al. (2021) China	Outpatients	Case-control	15 patients 14 controls	3 months	NR	Intestinibacter bartlettii	r = 0.545	.036
						Escherichia unclassified	r = 0.567	.028

Table 1 continued - Continuous fatigue outcomes

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Bardakci et al. (2021) Turkey	Outpatients	Cohort	65	6-7 months	SF-36	**6MWT**	r = .526	*<.001*
						Pulmonary functions		
						FVC%	r = .242	*.064*
						FEV_1%	r = .290	*.026*
Chen et al. (2020) China	Outpatients	Cross-sectional	361	1 month	SF-36	**Gender**		
						Women	81.80 (16.32)	<.001
						Men	83.25 (16.13)	
						Multivariate		
						LOS	β .113	.040
						Age	β .128	.04
Dalbosco-Salas et al. (2021) Chile	Outpatients	Prospective cohort	115	30 days	SF-36 VAS Fatigue	**Pre-rehabilitation (VT)**		
						Total	40.7	*.001*
						Hospitalised	38.3	*.001*
						Not hospitalised	42.9	*.001*
						Post-rehabilitation (VT)		
						Total	58.5	-
						Hospitalised	58.3	-
						Not hospitalised	58.7	-
						Post intervention intergroup	-	*.912*
						Non-ICU (VAS)		
						Pre-rehabilitation		
						Post-rehabilitation	3 (0–4)	*.053*
						ICU	1 (0–3.25)	
						Pre-rehabilitation		
						Post-rehabilitation	3 (1.75–5)	*.004*
						Post-intervention intergroup	1.5 (0–2.75)	
							-	*.473*
Elanwar et al. (2021) Egypt	Outpatients	Case control	46 fatigue 46 no fatigue	6 months	CFQ	**Fatigue**		
						Physical	4 (2-7)	
						Mental	2 (0-3)	
						Fatigued v. no fatigue		
						Duration of acute illness	β = 0.099	.05
						Increased ferritin (ng/mL		
						Mean consecutive difference for ECD	R = .425	.003
						Decremental response in ADM (Y/N)	40.7 (36.7,44.8)	<.001
						Decremental response in trapezius		
						(Y/N)	9 (13%)	.011
							20 (43%)	<.001

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Elkan et al. (2021) Israel	Survey	Case control	42 cases 42 controls	9 months	SF-36	**Age**		.914
						Gender		
						Males	55 (27.5-87.5)	.720
						Females	60 (30-70)	
						Smoking		
						Never	55 (30-75)	.992
						Ever	60 (10.0-87.5)	
						Physical comorbidities	-	NS
						Obesity		
						No	60 (30-81.2)	.197
						Yes	50 (27.5-63.7)	
						BMI	r = -0.13	.310
						LOS	r = 0.03	.798
						Disease Severity		
						Mild	55 (30-75)	.440
						Moderate	60 (50-78.7)	
						Severe	45 (25-85)	
						O² support		
						Yes	47.5 (21.2-81.2)	.435
						No	60 (33.7-76.2)	
						Follow-up (months)	r = 0.138	.270
Evans et al. (2021) UK	Outpatients	Prospective cohort	1077	5 months	FACIT	**Disease severity**		
						WHO Class 3-4	18·5 (14·3)	NR
						WHO Class 5	14·6 (12·1)	
						WHO Class 6	16·4 (13·1)	
						WHO Class 7-9	18·5 (13·4)	
Gamberini et al. (2021) Italy	Telephone	Prospective cohort	205	3, 12 months	15D	**Full Recovery**	0.931(0.125)	
						Partial Recovery Mental	0.718 (0.160)	
						Partial Recovery Physical	0.806 (0.227)	<.001
						Bad Recovery	0.499 (0.185)	
Guo et al. (2020) China	Outpatients	Prospective cohort	259	1 month	SF-36	**Positive nucleic-acid duration > 14 days (Age 46-69)**		*.047*
						Gender		
						Age	NR	*NS*
						Smoking	NR	*NS*
						Corticosteroids	NR	*NS*
							NR	*NS*
Henneghan et al. (2021) USA	Survey	Cross-sectional	52	4 months	PROMIS	**Younger age**	r = .280	*<.05*
						Total symptoms (n.)	r = .300	*<.05*

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Kedor et al. (2021) Germany	Outpatients	Prospective cohort	42	6 months	CFQ	**Covid-19 Syndrome**	7 (2-10)	*.687*
						CFS v. CCS		
						Stress intolerance	-	*.042*
						Post-exertional malaise	-	*.007*
						Temperature sensitivity	-	*.024*
						Sensitivity to light	-	*.014*
						Sensitivity to noise	-	*.029*
						Autonomic dysfunction	-	*NS*
Liu et al. (2020) China	Outpatients	RCT	72	6 weeks	SF-36	**Intervention Group**		
						Pre-rehab	60.6 (6.9)	*< .05*
						Post-rehab	75.6 (7.1)	
						Control Group		
						Pre-rehab	60.5 (7.1)	*NS*
						Post-rehab	61.2 (6.3)	
Mantovani et al. (2021) Italy	Outpatients	Cohort	37	6 months	Clinical interview BORG	**MFI - FG - General fatigue**		
						All	**9**.5 (4.8)	.002
						CFS	13.6 (4.6)	
						No CFS	7.9 (3.9)	
						MFI-FF Physical Fatigue		
						All	8.7 (4.7)	.001
						CFS	13.1 (5.0)	
						No CFS	7.0 (3.4)	
						MFI-RA Reduced Activity		
						All	8.7 (4.8)	<.001
						CFS	13.6 (4.7)	
						No CFS	6.9 (3.4)	
						MFI-RM Reduced Motivation		
						All	7.5 (3.8)	.001
						CFS	10.9 (4.1)	
						No CFS	6.3 (2.9)	
						MFI-FM Mental Fatigue		
						All	8.0 (4.3)	<.001
						CFS	13.2 (3.5)	
						No CFS	6.0 (2.7)	
						Between CFS +Ve and CFS -Ve		
						Lung functions (all)	-	NS
						6MWT	-	NS
						BORG dyspnoea (baseline)	-	.014
						Subjective neuropsychological complaints (Y/N)	-	<.001
						Anxiety	-	.11
						Depression	-	.002
						SARS-CoV-2 Inflammatory markers	-	NS
						Hospitalisation	-	NS
						ICU	-	NS

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Qin et al. (2021) USA		Cross-sectional	55	30 days	PROMIS 7a	**Gender (F)** **Anxiety** **Depression** **Age ≥ 65** **Initial symptoms (n.)** **Longer LOS** **ICU admission** **Each day of hospitalisation**	β = 5.4 β = 1.47 β = 0.89 OR = 0.36 OR = 1.33 OR = 1.15 OR = 5.18 OR = 1.2	*.05* *.05* *.05* *.05* *.04* *.03* *.02* *.08*
van der Sar -van der Brugge (2021) Netherlands	Outpatients	Prospective cohort	101	6 weeks	SF-36	**Disease severity v. Pop Norms** Moderate (lowest VT)	NR	*.001*
Yildirim et al. (2021) Turkey	Outpatients	Prospective cohort	70	6 months	SF-36	**Vitality Score** ICU Non-ICU	**Median (IQR)** 65 (40-80) 60 (45-80)	*.680*
Zhao et al. (2021) China	Outpatients	Prospective cohort	94	1 year	SF-36 Questionnaire	**Disease severity (VT)** Mild/moderate Severe/critical **Muscle fatigue (MF)** Total **Disease Severity (MF)** Mild/moderate Severe/critical **Age** < 60 > 60	80 (65, 90) 70 (60, 85) 37/94 (39.36) 15/51 (29.41) 22/43 (51.16) 34/81 (41.98) 3/13 (23.08)	*.108* .032 .195

NA = Not analysed; NR = Not reported; NS = not significant; r = Pearson's correlation; OR = Odds Ratio; CFS = chronic fatigue syndrome; 6MWT = 6-minute walking test; FEV_1 = forced expiratory volume; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for CO^2; KCO = carbon monoxide transfer coefficient; TLco = gas transfer capacity; ECLA = extracorporeal lung assist; ARDS = acute respiratory distress syndrome; FMA = fibromyalgia; BFHX = Bufei Huoxue supplement, PTSD = post-traumatic stress disorder; CXR = chest X-ray; WBC – white blood cell; CRP = c-reactive protein; ADQ = author designed questionnaire; BFI = Brief Fatigue Inventory; BORG = Borg rating of perceived exertion scale; BRAF-NRS, V2 Revised = Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale-Revised; CFQ = Chalder Fatigue Scale; ECOG = Eastern Cooperative Oncology Group performance scale; EHR = electronic health records; FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue; FAI = Fatigue Assessment Inventory; FIC = Functional Impairment Checklist; FSS = Fatigue Severity Scale; FAS = Fatigue Assessment Scale; FIS = Fatigue Impact Scale; FRS = Fatigue Rating Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; KEDS = Karolinska Exhaustion Disorder Scale; NCSI = Nijmegen Clinical Screening Instrument; NRS = Numeric Rating Score; PCL-5 = Post-Traumatic Stress Disorder Checklist; PRO = Patient reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS-7a = short-form Fatigue; SAGIS = Structured Assessment of Gastrointestinal Symptoms Scale; SF-36 = 36-Item Short-Form Survey; SPHERE-34 = Somatic & Psychological Health Report; VAS-F = Visual Analogue Scale- Fatigue.

Supplementary Table 1. Summary of included studies with fatigue and vitality outcomes

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Agergaard et al. (2021) Denmark	Outpatients	Case-control	20	77-255 days	ADQ	NR	18 (90)	
Albu et al. (2021) Spain	Outpatients	Cross-sectional	30	> 3 months	MFIS	Range = 0 - 84 Higher score = severe impact	26 (86)	
Amin-Chowdhury et al. (2021) UK	Survey	Prospective cohort	1671	7 months	ADQ	NR	**+Ve cases** 55 (39.3) **-Ve controls** 203 (17.5)	<.001
Anaya et al. (2021) Colombia	Survey	Case series	100	219 days	ADQ	NR	34 (34)	
Andrade Barreto et al. (2021) Brazil	Outpatients	Cross-sectional	602	> 1 month	ADQ	NR	371 (61.6)	
Aparisi et al. (2021) Italy	Outpatients	Prospective cohort	70	3 months	NR	NR	20 (28.6)	
Aranda et al. (2021) Spain	Outpatients	Prospective cohort	113	240 days	ADQ	Range 0 - 10	51 (45)	
Arnold et al. (2020) UK	Outpatients	Prospective cohort	110	8-12 weeks	ADQ	NR	32/81 (39)	
Asadi-Pooya et al. (2021) Iran	Telephone	Retrospective cohort	4681	3-6 months 6-12 months	ADQ	NR	**3 months** 859/2685 (32) **6 months** 499/1996 (25)	.001
Augustin et al. (2021) Germany	Outpatients	Prospective cohort	958	4 months 7 months	ADQ	NR	**4 months** 43/442 (9.7) **7 months** 50/353 (14.2)	
Aul et al. (2021) UK	Telephone	Cross-sectional	387	6 weeks	ADQ	NR	165/366 (45.1)	
Aydin et al. (2021) Turkey	Outpatients	Cross-sectional	116	44 days	ADQ	NR	29 (25)	
Bai et al. 2021 Italy	Outpatients	Prospective cohort	377	102 days	Clinical interview	NR	149 (39.5)	
Barizien et al. (2021) France	Outpatients	Prospective cohort	39	7 months	Clinician assessment	NR	-	
Becker et al. 2021 Switzerland	Outpatients	Prospective cohort	90	12 months	ADQ VAS for severity	NR Range 0-10	41/90 (46%) M 5.54 (SD 2.34)	
Bek et al. (2021) Netherlands	Outpatients	Prospective cohort	492	3, 6, 12 months	FAS	> 36 = caseness	**3 months** 248/385 (64.5) **6 months** 277/483 (63.1) **12 months** 156/271 (60.2)	.932

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Bell et al. (2021) USA	Survey	Prospective cohort	303	> 30 days	ADQ	NR	**>30 days** 78/208 (37.5) **30-59 days** 21/87 (24.1) **> 60 days** 57/121 (47.1)	
Bliddal et al. (2021) Denmark	Survey	Cohort	445	> 4 weeks	ADQ	NR	**4 weeks** 32/198 (16) **12 weeks** 21/129 (16)	
Boari et al. (2021) Italy	Outpatients	Prospective cohort	91	4 months	ADQ	NR	47 (52)	
Boesl et al. (2021) Italy	Outpatients	Cross-sectional cohort	100	$\geq$ 12 weeks	FSS	4-7 impairment due to fatigue $\geq$ 36 = caseness	**N (%)** 67 (67)	
Boscolo-Rizzo et20 al. (2021) Italy	Outpatients	Cohort	304	12 months	ADQ	NR	83 (27.3)	
Bottemanne et al. (2021) France	Outpatients Telephone	Prospective cohort	84	1, 3 months	Clinical interview	NR	**1 month** 50/84 (59.5) **3 months** 38/82 (46.3)	
Bozzetti et al. (2021) Italy	Outpatients	Prospective cohort	49	6 months	Modified BORG Scale	6 = No exertion 20 = Maximal exertion	28 (57.1)	
Cao et al. (2021) China	Survey	Cohort	81	1-3 months	ADQ	NR	**1 month** 7 (11) **3 months** 5 (8)	
Carfi et al. (2020) Italy	Outpatients	Cohort	143	60 days	ADQ	NR	76 (53.1)	
Carvalho-Schneider et al. (2021) France	Survey	Prospective cohort	150	30-60 days	WHO Performance Status Classification	Grade 3 Grade 4	**Day 30** 74 (49.3) **Day 60** 52 (40)	
Castro et al. (2021) USA	EHR	Retrospective case-control	6619	> 30 days	EHR	NR	**31-90 days** 887 (13.4) **91-150 days** 721 (10.9)	
Catalan et al. (2021) Spain	Telephone	Cohort	76	12 months	ADQ SF-36 Vitality	NR	**No steroids** 19/44 (43.2) **Steroids** 11/32 (34.4)	
Chen, Li et al. (2021) China	Telephone	Longitudinal cohort	715	M 225 days	ADQ	NR	137 (19.2%)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Chopra et al. (2021) India	Survey	Cohort	53	30 days	ADQ	NR	12 (22.6)	
Chudzik et al. (2021) Poland	Outpatients	RCT	50	4 weeks	FAS	Score ≥4 = severe	-	
Clavario et al. (2020) Italy	Outpatients	Prospective cohort	110	3 months	ADQ	NR	54 (49.1)	
Creamer et al. (2021) UK	Outpatients Telephone	Cohort	57	6, 9 weeks	NR	NR	14 (25)	
Daher et al. (2020) Germany	Outpatients	Prospective cohort	33	6 weeks	BORG	Range 6 - 20	15 (45)	
Danesh et al. (2021) USA	Telephone	Cross-sectional	200	2-10 months	ADQ	NR	32/62 (52)	
Darley et al. (2021) Australia	Outpatients	Longitudinal cohort	66	8 months	SPHERE-34 VAS-F	NR Range 0 – 10 ≥ 7 = severe	15 (23) 2.0 (0.38-5.0)	
D'Cruz et al. (2020) UK	Outpatients	Prospective cohort	119	61 days	NRS	NR	78/115 (67.8)	
Daugherty et al. (2021) USA	EHR	Retrospective cohort	27074	1-6 months	ICD10	-	-	
Dennis et al. (2021) UK	Outpatients	Prospective cohort	201	Median 141 days	NR	-	197 (98)	
Desgranges et al. (2021) Switzerland	Telephone	Cohort	413	3-10 months	ADQ	NR	**Cases** 132 (32) **Controls** 15 (17)	.006
Dini et al. (2021) Italy	Outpatients	Cross-sectional	50	5 months	ADQ	NR	3637 (71)	
Eloy et al. (2021) France	Survey	Prospective cohort	324	3-6 months	ADQ	NR	**3 months** 159 (49) **6 months** 152 (47)	.05
Fang et al. (2021) China	Telephone	Prospective cohort	1233	12 months	Physician interview	NR	400 (32.4)	
Fatima et al. (2021) India	Survey	Cohort	160	40 days	ADQ	NR	90 (56.2)	
Fernandez-de-Las-Penas et al. (2021) Spain	Survey	Cohort	1142	7 months	FIC ADQ	Mild = 25% Moderate = 50% Severe = 75%%	695 (61)	
Ferraro et al. (2020) Italy	Outpatients	Case-series	7	Post-discharge	BORG Scale	Range 6 - 20	6 (85.7)	
Fortini et al. (2021) Italy	Outpatients	Prospective cohort	59	4 months	ADQ	NR	25 (42.4)	
Froidure et al. (2021) Italy	Outpatients	Cohort	126	3 months	ADQ	NR	32 (25)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Frontera et al. (2021) USA	Survey	Prospective cohort	272	6 months	ADQ	NR	98 (36)	
Ganesh et al. (2021) USA	Survey	Cross-sectional	817	6 months	PROMIS-Fatigue	NR	132 (16.2)	
Garcia-Abellan et al. (2021) Spain	Outpatients	Prospective cohort	116	1-6 months	ADQ	NR	**6 months** 12 (10.3)	
Garrigues et al. (2020) France	Outpatients	Cohort	120	110.9 days	ADQ	NR	66 (55)	
Gautam et al. (2021) UK	Outpatients	Case series	200	4-7 months	ADQ	NR	77/144 (53.5)	
Gebhard et al. (2021) Switzerland	Survey	Cohort	1024	6.5 months	ADQ	NR	84 (8.2)	
Goertz et al. (2020) Belgium Netherlands	Survey	Cohort	457	3 months	ADQ	NR	398 (87)	
Gonzalez-Hermosillo et al. (2021) Mexico	Survey	Prospective cohort	130	3 months 6 months	ADQ	NR	**3 months** 69 (53) **6 months** 61 (46.9)	.019
Graham et al. (2021) USA	Survey	Cohort	50	7 months	PROMIS	≥ 50 = average	43 (85)	
Gupta et al. (2021) Pakistan	Outpatients	Case series	371	30 days	ADQ	NR	51/123 (41.4)	
Halpin et al. (2020) UK	Telephone	Cross-sectional	100	4-8 weeks	ADQ	Mild = 0-3 Moderate = 4-6 Severe = 7-10	64(64)	
Heightman et al. (2021) UK	Outpatients	Cohort	1325	≥ 6 weeks	FAS	< 22 = no fatigue ≥ 22 = fatigue	644 (48.6)	
Hellemons et al. (2021) Netherlands	Outpatients Survey	Prospective cohort	92	3-6 months	FAS	≥ 22 = fatigue	**6 months** 32/63 (50.8)	
Horwitz et al. (2021) USA	Survey	Prospective cohort	126	6 months	PROMIS-10	≥ 50 = average > 0 = fatigued	107 (85)	
Hossain et al.(2021) Bangladesh	Outpatients	Prospective cohort	2198	12 weeks	ADQ	NR	295/356 (82.9)	
Iqbal et al. (2021) Pakistan	Survey	Cross-sectional	158	38 days	ADQ	NR	131 (82.9)	
Jacobs et al. (2020) USA	Survey	Cohort	149	35 days	PROMIS	NR	82 (55)	
Kanberg et al. (2021) Sweden	Outpatients	Prospective cohort	100	6 months	KEDS	19 points	40 (41)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Karaarslan et al. (2021) Turkey	Survey	Cohort	300	1 month	ADQ	NR	133 (44.3)	
Kashif et al. 2021 Pakistan	Telephone	Cross-sectional	242	3 months	ADQ	NR	101 (41.7)	
Khalaf et al. (2021) Egypt	Survey	Cross-sectional	538	83 days	ADQ	NR	318 (59.1)	
Kozak et al. (2021) Canada	EHR	Retrospective cohort	223	3 months	ADQ	NR	31/62 (50)	
Labarca et al. (2021) Chile	Outpatients	Cross-sectional	60	4 months	CFQ	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	25 (41.7)	
Lemhofer et al. 2021 Germany	Survey	Cross-sectional	365	3 months	ADQ SF-36 Vitlity	NR Range 0 – 100 100 = max vitality	137 (37.5) M 54.6	
Leth et al. (2021) Denmark	Outpatients Telephone	Prospective cohort	49	6 weeks 12 weeks	ADQ	NR	**6 weeks** 32 (65) **12 weeks** 31 (63)	
Liang et al. (2020) China	Outpatients	Prospective cohort	76	3 months	ADQ	NR	45 (59)	
Lindahl et al. (2021) Finland	Survey	Cohort	101	6 months	ADQ SF-36 Vitality	Range 0 – 100 100 = max vitality	75 (79) **M (SD)** 54.2 (23.6)	
Liu et al. (2021) China	Outpatients	Prospective cohort	594	3, 6, 12 months	ADQ	NR	-	
Liyanage-Don et al. (2021) USA	Survey	Cross-sectional	153	3 months	ADQ	NR	31 (20.3)	
Logue et al. (2021) USA	Survey	Prospective cohort	177	3 months 9 months	ADQ	NR	24 (13.6)	
Lombardo et al. (2021) Italy	Telephone	Cohort	303	12 months	ADQ	NR	158 (52)	
Maamar et al. (2021) Spain	Outpatients	Cross-sectional	121	3 months	Interview	NR	52 (42.8)	
Mahmud et al. (2021)	Telephone	Prospective cohort	355	30 days	ADQ	NR	117 (33)	
Mandal et al. (2020) UK	Outpatients Telephone	Cross-sectional	384	54 days	ADQ	NR	265 (69)	
Mazza et al. (2021) Italy	Outpatients Online	Prospective cohort	402	1, 6, 12 months	FSS	Range 0 – 63 ≥ 36 = caseness	**12 months** 63/192 (33)	
Menges et al. (2021) Switzerland	Survey	Prospective cohort	431	6-8 months	FAS	≥ 22 = fatigue	233/426 (54.7)	
Mirfazeli et al. (2021)	Survey	Prospective cohort	94	9 months	CDC Criteria for	≥ 25 = fatigue	48 (51.0)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Iran	Interview				Fatigue Scale			
Miyazato et al.(2020) Japan	Telephone	Retrospective cohort	63	1-4 months	ADQ	NR	10 (16) 6 (9.5)	
Molnar et al. (2021) Hungary	Outpatients	Prospective cohort	101	> 4 weeks	CFQ-11	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	69 (68.3) 4-12 weeks 15.8 (5.5) >12 weeks 5.6 (6.7)	.951
Moradian et al. (2020) Iran	Telephone	Cross-sectional	300	6 weeks	ADQ	NR	39 (19.5)	
Moreno-Perez et al. (2021) Spain	Outpatients	Prospective cohort	277	8 – 12 weeks	ADQ	NR	96 (34.8)	
Morin et al. (2021) France	Telephone	Prospective cohort	478	3-4 months	MFI	Range 4 – 20 ≥ 15 severe	134/431 (31)	
Munblit et al. (2021) Russia	Telephone	Prospective cohort	2599	218 days	ADQ	NR	551 (21.2)	
Naik et al. (2021) India	Outpatients	Prospective cohort	1234	3-6 months	ADQ	NR	45 (3.7)	
Nehme et al. (2021) Switzerland	Survey	Cohort	410	7-9 months	ADQ ECOG	NR 0 no limitations – 4 disabled	85 (20)	
Noviello et al. (2021) Italy	Survey	Case-control	164 cases 184 controls	4.8 months	SAGIS	NR	**Cases v. Controls** 52 (31.7) v. 25 (13.7) = <.001	
Nune et al. (2021) UK	Telephone	Prospective cohort	271	3, 6, 9 months	ADQ VAS	NR Range 0 – 10 ≥ 7 = severe	**9 months** 24/41 (58) M 5.8	
O'Keefe et al. (2021) USA	Survey	Cross-sectional	290	1-6 months	ADQ	NR	59 (20.3)	
Pauley et al. (2021) UK	Telephone/ Outpatients	Prospective cohort	332	3 months 12 months	VAS	Range 0 – 10 ≥ 7 = severe	**3 months (Cases v. Controls)** 7 (8.9) v. 51 (27.1) **6 months** 3 (10.3) v. 54 (32.5)	.809 .001
Peghin et al. (2021) Italy	Telephone	Prospective cohort	599	6 months	PRO	NA	78 (13.1)	
Pérez-González et al. (2021) Spain	Telephone	Prospective cohort	248	6 months	ADQ	NR	40 (16.1)	
Pilotto et al. (2021) Italy	Outpatients	Cohort	165	6 months	ADQ	NR	56 (33.9)	
Poyraz et al. (2021)	Survey	Cross-sectional cohort	118	50 days	ADQ	Range 0 - 8	47 (40)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Turkey								
Raman et al. (2020) UK	Outpatients	Cohort	58	2-3 months	FSS	Range 0 – 63 ≥ 36 = caseness	33 (55)	
Rass et al. (2021) Austria	Outpatients	Prospective cohort	90	3 months	SF-36 Vitality	< 40 = low energy/vitality	-	
Rauch et al. (2021) Germany	Survey	Prospective cohort	127	3, 6, 12 months	ADQ	NR	**6 months** 32 (25)	
Righi et al. (2021) Italy	Outpatients Telephone	Prospective cohort	448	6 - 12 weeks	ADQ	NR	**T1** = 45/175 (26) **T2** = 7/83 (9)	
Romero-Duarte et al. (2021) Spain	EHR	Retrospective cohort	797	6 months	EHR	NR	176 (22.1)	
Rosales- Castillo et al. (2021) Spain	Outpatients	Retrospective cohort	118	50 days	Question	NR	22/74 (30.5)	
Sami et al. (2020) Iran	Telephone	Cohort	452	4 weeks	ADQ	NR	50 (11)	
Sathyamurthy et al. (2021) India	Telephone	Prospective cohort	279	90 days	ADQ	NR	25 (8.9)	
Savarraj et al. (2021) USA	Telephone	Prospective cohort	48	3 months	FSS	Range 0 – 63 ≥ 36 = caseness	20 (42)	
Scherlinger et al. (2021) France	Outpatients	Prospective cohort	30	152 days	VAS	Range 0 – 10 ≥ 7 = severe	T1 28 (93) T2 25 (82)	
Shoucri et al. (2021) USA	EHR	Case series	929	3, 6 months	EHR	NA	**3 months** 44/488 (9.0) **6 months** 38/364 (10.4)	
Seeßle et al. (2021) Germany	Outpatients	Prospective cohort	96	5, 12 months	ADQ	NR	**5 months** 40 (41.7) **12 months** 51 (53.1)	.043
Senjam et al. (2021) India	Online	Cross-sectional	773	1 month	ADQ	NR	204/257 (79·3)	
Shang et al. (2021) China	Telephone	Cohort	796	6 months	ADQ	NR	201 (25.3)	
Shendy et al. (2021) Egypt	Telephone	Cross-sectional	81	3-5 months	MFIS	Range 0 – 84 ≥ 38 caseness	52 (64.2)	
Sigfrid et al. (2021) UK	Outpatients Survey	Prospective cohort	308	90, 200 M 222 days	VAS	Range 0 – 10 ≥ 7 = severe	255 (82.8)	
Silva et al. (2021) Brazil	Outpatients	Cross-sectional	87	54 days	ADQ CFQ-11	NR Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	38 (43.7)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Smet et al. (2021) Belgium	Outpatients	Cross-sectional	220	10 weeks	ADQ	NR	90/137 (66)	
Sollini et al. (2021) Italy	Outpatients	Case control	39	98 days	NR	NR	Cases 8/18 (62)	
Soraas et al. (2021) Norway	Survey	Cohort	794	3-8 months	ADQ	NR	157/597 (23)	
Staudt et al. 2021 Germany	Outpatients	Prospective cohort	101	10 months	ADQ	NR	50 (49.5)	
Stavem et al.(2021) Norway	Survey	Cross-sectional	458	1.5-6 months	CFQ-11 RAND-36	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	211 (46)	
Steinbeis et al. (2022) Germany	Outpatients	Prospective cohort	72	3, 6, 12 months	ADQ	NR	44 (60.8)	
Strumiliene et al. (2021) Lithuania	Outpatients	Cohort	51	2 months	ADQ	NR	35 (68.6)	
Suarez-Robles et a. (2021) Spain	Telephone	Cross-sectional	134	90 days	ADQ	NR	73 (54.5)	
Sultana et al. (2021) Bangladesh	Telephone	Cross-sectional	186	30-60 days	ADQ	NR	**≥ 60 days** 15 (8.1)	
Sykes et al. (2021) UK	Outpatients	Retrospective cohort	134	113 days	ADQ	NR	53 (39.6) 47-75 days 5 (71.4) 76-100 days 13(50) 101-125 days 26 (33.3) 126-167 days 9 (39.1)	
Szekely et al. (2021) Israel	Outpatients	Prospective cohort	71	90 days	Modified BORG Scale	6 - 20 17 = very hard exertion	COVID 24 (34) Control 9/35 (26)	
Taboada et al. (2021) Spain	NR	Prospective cohort	91	6 months	ADQ	NR	34 (37.4)	
Taylor et al. (2021) UK	Telephone Survey	Cohort	675	> 12 weeks	Amplitude Questionnaire	NR	-	
Tessitore et al. (2021) Switzerland	Telephone	Prospective cohort	184	1, 12 months	PROMIS	NR	**1 month** 113 (61) **12 months** 45/165 (27)	
Tiwari et al. (2021) Nepal	Outpatients	Cross-sectional	132	2 months	ADQ	NR	17 (13)	
Tleyjeh et al. (2021) Saudi Arabia	Telephone	Prospective cohort	222	122 days	ADQ	NR	T1 48 (21.6) T2 66 (29.7)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Tomasoni et al. (2021) Italy	Outpatients	Cross-sectional	105	1-3 months	ADQ	NR	33 (31.4)	
Tosato et al. (2021) Italy	Outpatients	Cross-sectional	165	76 days	ADQ	NR	104/137 (75.9)	
Townsend et al. (2020) Ireland	Outpatients	Cross-sectional cohort	128	Median 10 weeks <8, 8-10, 10-12, >12 weeks	CFQ-11	Range 0 – 33 > 29 = caseness 0 – 11 $\geq$ 4 = caseness	67 (52.3)	
van den Borst et al. (2021) Netherlands	Outpatients	Prospective cohort	124	3 months	NCSI	Range 0 - 64	86 (69)	
Vanichkachom et al. (2021) USA	Outpatients	Case series	100	3 months	NR	NR	80 (80)	
van Veenendaal et al. (2021) Netherlands	Survey	Prospective cohort	50	3, 6 months	ADQ	NR	17 (33)	
Venturelli et al. (2021) Italy	Telephone	Cohort	767	49 days 81 days	BFI	Range 1 - 10 8-10 = Severe	334 (44.1)	
Voruz et al. (2021) Switzerland	Outpatients Survey	Cohort	75	6-9 months	FIS SF-36 Vitality	Range 0 - 84	6 (8)	
Wang et al. (2021) USA	Outpatients	Cohort	126	5 months	NR	-	53 (42)	
Wong-Chew et al. 2022 Mexico	Telephone	Prospective cohort	1303	1, 3 months	ADQ	NR	**30 days** 449/1303 (34.5) **90 days** 299/928 (32.2)	.001
Wu et al. (2021) China	Outpatients	Cohort	54	6 months	ADQ	NR	13 (24.1)	
Yomogida et al. (2021) USA	Telephone	Prospective cohort	366	1, 2, 6 months	ADQ	NR	**1 month** 88 (24.0) **2 months** 62 (16.9) **6 months** 50 (13.7)	
Zayet et al. (2021) France	Telephone	Retrospective cohort	354	289 days	ADQ	NR	68 (53.5)	
Zhang et al. (2021) China	Telephone	Cohort	2433	1 year	ADQ	NR	673 (27.7)	
Zhou et al. (2021) China	Outpatients	Case-control	15 patients 14 controls	3 months	NR	-	6 (40)	
Zulu et al. (2020) Zambia	Telephone	Cohort	302	54 days	ADQ	NR	4/27 (14.8)	
CONTINUOUS FATIGUE OUTCOMES								
Bardakci et al. (2021) Turkey	Outpatients	Cohort	65	6-7 months	SF-36 Vitality	Range 0 – 100 100 = max vitality	**M (SD)** 70.8 (NR)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Chen, Liu et al. (2021) China	Outpatients	RCT	129	94 days	FAI	> 4 = severe fatigue	**BFHX group (n. 64)** 85.5 ± 27.6 **Placebo group (n. 65)** 100.4 ± 25.7	.0019
Dalbosco-Salas et al. (2021) Chile	Outpatients	Prospective cohort	115	30 days	SF-36 Vitality VAS Fatigue	Range 0 – 10 ≥ 7 = severe	- **VAS Fatigue** Pre-rehab = 3 (0-5) Post-rehab = 1 (0-3)	
dal et al. (2021) UK	Outpatients	Cohort	30		FACIT	Range 0 - 52 < 30 = severe	**Pre rehabilitation** 29 (14) **Post rehabilitation** 34 (13)	
Donaghy et al. (2021) N. Ireland	Outpatients/ Telephone	Prospective cohort	113	3 months	FIS	Range 0-160	**M** =65	
Elanwar et al. (2021) Egypt	Outpatients	Case-control	46 fatigue 46 no fatigue	6 months	CFQ	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	**Fatigued** 6 (3-9)	
Elkan et al. (2021) Israel	Survey	Case-control	66 Cases 42 Controls	9 months	SF-36 Vitality	"	**Cases v Controls** 57.5 (30–76.2) v. 50 (23.7-80)	NS
Evans et al. (2021) UK	Outpatients	Prospective cohort	1077	5 months	FACIT	Range 0 - 52 < 30 = severe	16·8 (13·2)	
Gamberini et al. (2021) Italy	Telephone	Prospective cohort	205	3, 12 months	15D	5 = worst 1 = best	**12 months** M 0.816 (0.196)	
Guo et al. (2020) China	Outpatients	Prospective cohort	259	1 month	SF-36	"	-	
Henneghan et al. (2021) USA	Survey	Cross-sectional	52	4 months	PROMIS	NR	51.14 (7.61)	
Kayaaslan et al. (2021) Turkey	Outpatients Survey	Prospective cohort	1007	3 months	ADQ	4 (3–5) (Range 0-10)	24 (24.3)	
Kedor et al. (2021) Germany	Outpatients	Prospective cohort	42	6 months	CFQ	0 – 11 ≥ 4 = caseness	**Chronic Covid Syndrome** 7 (2-10) **CFS** 8 (5-10)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Latronico et al. (2021) Italy	Survey	Prospective cohort	114	3-12 months	SF-36	Range 0 – 100 100 = max vitality	**M (IQR)** **3 months** 53 (46–59) **6 months** 77 (44–59) **12 months** 54 (47–59)	.600
Liu et al. (2020) China	Outpatients	RCT	72	6 weeks	SF-36	"	**Post-pulmonary rehabilitation** 75.6 (7.1) **Controls** 61.2 (6.3)	
Mancini et al. (2021) USA	Outpatients	Prospective cohort	41	3 months	BORG	Range 6 - 20	**M (SD)** 15 (NR)	
Mantovani et al. (2021) Italy	Outpatients	Cohort	37	6 months	Clinical interview BORG	NR Range 6 - 20	**M (SD)** 42.5 (20.0-36.0) 0.16 (0.45-0.0	
Novak et al. (2021) USA	Outpatients	Retrospective cohort	24	> 4 weeks	BRAF-NRS, V2 Revised	Range 0-70 > 3 (0-10)	**PASC** 9/9 (100) **Controls** 0/5 (0) **POTS** 10/10 (100)	.001
Ortelli et al (2021) Italy	Outpatients	Case-control	12 cases 12 controls	11 weeks	FRS FSS	≥ 6 = casenes Range 0 – 10 ≥ 36 = caseness Range 0–63	**M (SD)** **Cases** 8.1 (1.7) 31.6 (10.8) **Controls** 0.7 (0.5) 9.5 (0.5)	<.001
Qin et al. (2021) USA	Telephone	Cross-sectional	55	1 month	PROMIS-7a	Standard T-score = 50 (SD 10)	**Before hospitalisation** 44.2 (7.4) **After hospitalisation** 54.5 (9.8)	
Schandl et al. (2021) Sweden	Outpatients	Prospective cohort	113	5 months	SF-36	Range 0 – 100 100 = max vitality	**M (95% CI)** **High-flow nasal O^2/ Non-Invasive ventilation** 44 (32- 56) **Invasive mechanical ventilation** 50 (44- 57)	
Valent et al. (2020) France	Outpatients	Retrospective cohort	19	3 months	SF-36	Range 0 – 100 100 = max vitality	60 (IQR - 50-65)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
van der Sar -van der Brugge (2021) Netherlands	Outpatients	Prospective cohort	101	6 weeks	SF-36	"	NR	
Weerahandi et al. (2020) USA	Telephone	Prospective cohort	152	37 days	PROMIS	NR	**Before Covid** 4 (IQR 4-5) **After Covid** 3 (3-4)	
Yildirim et al. (2021) Turkey	Outpatients	Prospective cohort	70	6 months	SF-36	Range 0 – 100 100 = max vitality	NR	
Zhao et al. (2021) China	Outpatients	Prospective cohort	94	1 year	SF-36	"	75 (63.75, 90)	

NA = Not analysed; NR = Not reported; NS = not significant; r = Pearson's correlation; OR = Odds Ratio; CFS = chronic fatigue syndrome; 6MWT = 6-minute walking test; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for CO^2; KCO = carbon monoxide transfer coefficient; TLco = gas transfer capacity; ECLA = extracorporeal lung assist; ARDS = acute respiratory distress syndrome; FMA = fibromyalgia; BFHX = Bufei Huoxue supplement, PTSD = post-traumatic stress disorder; CXR = chest X-ray; WBC – white blood cell; CRP = c-reactive protein; ADQ = author designed ADQ; BFI = Brief Fatigue Inventory; BORG = Borg rating of perceived exertion scale; BRAF-NRS, V2 Revised = Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale-Revised; CFQ = Chalder Fatigue Scale; ECOG = Eastern Cooperative Oncology Group performance scale; EHR = electronic health records; FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue; FAI = Fatigue Assessment Inventory; FIC = Functional Impairment Checklist; FSS = Fatigue Severity Scale; FAS = Fatigue Assessment Scale; FIS = Fatigue Impact Scale; FRS = Fatigue Rating Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; KEDS = Karolinska Exhaustion Disorder Scale; NCSI = Nijmegen Clinical Screening Instrument; NRS = Numeric Rating Score; PCL-5 = Post-Traumatic Stress Disorder Checklist; PRO = Patient reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS-7a = short-form Fatigue; SAGIS = Structured Assessment of Gastrointestinal Symptoms Scale; SF-36 = 36-Item Short-Form Survey; SPHERE-34 = Somatic & Psychological Health Report; VAS-F = Visual Analogue Scale- Fatigue.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 1-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 1-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplemental
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5 & 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages 6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 6-7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 6 &7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pages 6-7
Study characteristics	17	Cite each included study and present its characteristics.	Pages 8-19 & supplemental
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplemental
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8-19
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 20
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 20-21 & 21-25 for Risk factors
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 21 & supplemental
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 21 & supplemental
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 21 & supplemental
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 25-26
	23b	Discuss any limitations of the evidence included in the review.	Page 27-28
	23c	Discuss any limitations of the review processes used.	Page 27-28
	23d	Discuss implications of the results for practice, policy, and future research.	Page 27
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5 Supplemental
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplemental
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 28
Competing interests	26	Declare any competing interests of review authors.	Page 28

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 28

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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Fatigue outcomes following COVID-19: A systematic review and meta-analysis

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Title **Fatigue outcomes following COVID-19: A systematic review and meta-analysis**

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ABSTRACT

Objectives Fatigue is a pervasive clinical symptom in coronaviruses and may continue beyond the acute phase, lasting for several months or years. This systematic review and meta-analysis aimed to incorporate the current evidence for post-infection fatigue among survivors of SARS-CoV-2 and investigate associated factors.

Methods Embase, PsyINFO, Medline, CINAHL, CDSR, Open Grey, BioRxiv and MedRxiv were systematically searched from January 2019 to December 2021. Eligible records included all study designs in English. Outcomes were fatigue or vitality in adults with a confirmed diagnosis of SARS-CoV-2 measured at $\geq$ 30 days post-infection. Non-confirmed cases were excluded. JBI risk of bias was assessed by 3 reviewers. Random-effects model was used for the pooled proportion with 95% CIs. A mixed-effects meta-regression of 35 prospective articles calculated change in fatigue overtime. Subgroup analyses explored specific group characteristics of study methodology. Heterogeneity was assessed using Cochran's Q and I^2 statistic. Egger's tests for publication bias.

Results Database searches returned 14,262 records. Following deduplication and screening, 178 records were identified. 147 (n=48,466 participants) were included for the meta-analyses. Pooled prevalence was 41% (95% CI: 37-45%, k=147, I^2=98%). Fatigue significantly reduced over time (-0.057, 95% CI: -107 - -0.008, k=35, I^2=99.3%, p=0.05). A higher proportion of fatigue was found in studies using a

valid scale (51%, 95% CI: 43- 58%, k=36,I^2=96.2%, p=.004). No significant difference was found for fatigue by study design (p=0.272). Egger's test indicated publication bias for all analyses except valid scales. Quality assessments indicated 4% at low risk of bias, 77% at moderate risk and 19% at high risk. Frequently reported associations were female gender, age, physical functioning, breathlessness, and psychological distress.

Conclusion This study revealed that a significant proportion of survivors experienced fatigue following SARS-CoV-2 and their fatigue reduced overtime. Non-modifiable factors and psychological morbidity may contribute to ongoing fatigue and impede recovery.

Prospero Registration No. CRD42020201247

Strengths &Limitations

- This review and meta-analysis was conducted using a significant sample size from a comprehensive search of the literature, including only confirmed cases;
- Substantial unexplained heterogeneity between studies limits generalisability of our findings;
- Only one reviewer screened and extracted the data from each study leaving the potential for missing articles and selection errors;
- Outcome measures of fatigue were unvalidated in the majority of studies, limiting confidence in our estimates;

- Total point-prevalence was likely impacted by predominance of hospitalised patients with potentially more severe disease.

INTRODUCTION

Fatigue may be characterised as tiredness or exhaustion as a result of physical or mental exertion or as a result of an illness or disease. The experience of fatigue is common and is usually short-lived but, for a small number of people, it can become long-lasting, associated with a number of impairments in daily living and quality of life.[1] It is one of the most common presenting symptoms of coronaviruses.[2] The current pandemic has also revealed a considerable burden of lasting symptoms [3–12] with approximately 1 in 4 people experiencing fatigue by one estimate.[13] Systematic reviews indicate a pooled-prevalence of post-COVID-19 fatigue to vary between 45% [14], 52% [15] and 64%.[16] In previous epidemics, fatigue was enduring. In a follow-up of 90 SARS survivors 30 months post-illness, for instance, 1 study found significantly lower vitality scores compared to Hong Kong population norms.[17] A small study of Middle East Respiratory Syndrome patients, revealed 32.7% had clinically relevant chronic fatigue, according to their FSS scores, at 18 months follow-up.[18] Likewise, for a considerable number of COVID-19 patients, tiredness symptoms extend beyond 3 months and represent a larger burden of post-infection symptomology.[19–41] A large study of 1,142 hospitalised patients found that 61% had fatigue 7 months post-COVID-19.[42] Similarly, those who perceived themselves as experiencing 'poor recovery' had lower vitality on the 15D instrument, compared to those making a 'full recovery' ($p<.001$) 1 year post-illness.[43]

More severe disease, associated with being hospitalised or ICU admission, has been related to post-illness fatigue.[44–51] In a small cohort of 55 people, 30 days post-discharge for COVID-19, each additional day of hospitalisation increased fatigue by 1.2.[52] Apart from hospitalised patients, among non-hospitalised or those treated for milder disease, fatigue is persistent.[53–61] In 359 patients 63.4% reported significant fatigue up to 12 months post-infection and were more likely than admitted patients to require referral for fatigue symptomology.[62]

Determinants of post-illness fatigue include female gender,[63–66] and older age, although the latter relationship was not consistent. Being over 50 years was associated with fatigue severity in some studies,[52,67,68] but not in others.[69,70] Exercise impairments are a common feature of post-Covid sequelae.[71–77] Poorer performance on the six-minute walk test (6MWT) was associated with fatigue and lower vitality at 6 months despite no concomitant impairments in pulmonary functions.[78] Indeed, impairments in lung functions have not thus far fully explained worse fatigue in COVID-19.[78–81] Nevertheless, patients often report persistent dyspnoea, which was consistently related to their fatigue,[82–85] suggestive of multi-dimensional functional consequences. For instance, quality of life,[86] functional status [87] and an increased risk for post-infection healthcare needs [88] were all related to fatigue.

Anxiety, post-traumatic stress and depressive symptoms are prevalent in survivors of respiratory viral infections.[85,89–94] A meta-analysis of 36 COVID-19 articles found high rates of anxiety (29%) and depressive symptoms (23%) 4-12 weeks post-illness.[95] The relationship between mental health outcomes and fatigue is consistent among convalescing COVID-19 patients. Depressive symptoms for example were associated with lower vitality [96] and fatigue.[79,97] In a retrospective study of 55 patients, baseline anxiety was related to higher fatigue 30 days after hospitalisation.[52] Moreover, these relationships can be present at 12 months follow-up. Mazza et al. (2021) found depression ($r=0.56$, $q=0.05$) and PTSD ($r=0.52$, $q=0.05$) were related to fatigue severity in 402 post-Covid patients. Neuropsychiatric symptoms comprising anxiety, mood swings, irritability and depression and others, predicted chronic fatigue 9 months later for those with mild/moderate disease ($p=0.01$).[98]

Summary and aims

For the majority of patients acute fatigue diminishes during the course of a virus, but current evidence suggests some experience longer lasting symptoms, and these affect functional and psychological recovery. Meta-analyses have focused on post-acute sequelae of COVID-19 (PASC) or clusters of symptoms and therefore fewer studies have investigated solely fatigue outcomes. Moreover, a proportion of these reviews were narrative in design, which did not provide a pooled estimate for fatigue. Furthermore, fatigue is reported as the most prominent factor of post-infection symptomology indicative of its importance in understanding recovery. Therefore, the objectives of this systematic review were to a) investigate the prevalence of persistent fatigue among survivors of COVID-19; b) integrate the findings by conducting a meta-analysis and c) investigate current evidence for factors associated with fatigue outcomes in this context.

METHODS

Search strategy

The protocol and PICO framework for this study (supplementary file 1) was developed utilising the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[99] Embase, PsyINFO, Medline, CINAHL, Cochrane Database of Systematic Reviews, Open Grey, MedRxiv and BioRxiv were systematically searched from January 2019 to 31 December 2021. Search terms: severe acute respiratory syndrome or severe acute respiratory adj2 syndrome or coronavirus or corona virus or corona adj1 virus or COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV or nCoV19 or nCoV2 or covid19 or covid-19 or covid and "chronic fatigue" or fatigue or tired* or exhaust* or quality adj2 life or QoL or health related quality) adj2 life or HRQoL. We incorporated 'health related quality of life' into our search terms in order to capture 'vitality', which we used as proxy for fatigue. Reference lists of the review studies were manually searched for additional articles. Full search protocols for each database are available in supplementary file 2. Duplicate references were removed electronically and imported into Rayyan [100] for screening and inclusion decisions.

Inclusion and exclusion criteria

Included were original articles with primary data, published in English between January 2019-December 2021. Adult patients ($\geq$18 years) must have had a diagnosis of SARS-CoV-2 confirmed by

RT-PCR, IgM/IgG serology or clinical assessment (e.g., chest X-ray, CT scan). ‘Probable’ or self-reported cases were excluded. All study designs were incorporated except qualitative and case reports. Main outcomes were fatigue/vitality reported as ‘post-discharge’, ‘post-hospitalisation’, ‘post-acute’, ‘post-illness’ or ‘post-onset’. Outcomes were included if measured at a median/mean time of ≥ 30 days post-infection as defined. All associations with fatigue/vitality were included if reported/quantified (e.g., anxiety, dyspnoea). We excluded pandemic fatigue (defined as ‘worn out’ by pandemic warnings, government safety instructions, media coverage or compliance requirements), healthcare worker fatigue in the context of their work (e.g., burnout, compassion fatigue), comorbid physical disease or pregnant populations. We excluded ‘muscle fatigue’, ‘leg fatigue’ and fatigue combined with ‘malaise’ or ‘muscle weakness’. Protocols, vaccination studies, newspaper articles, conference papers, commentaries, opinions or editorials were also omitted.

Data extraction

Titles and abstracts were screened by 1 reviewer (KPW). Full texts were screened by KPW. A data spreadsheet was created to record extracted data from the included studies. Spreadsheet variables were citation, population, sample size, control group, location, virus type and diagnostic method, follow-up period, study design, inclusion/exclusion criteria, objectives, outcome variable of interest (e.g., fatigue, vitality), associated variables (e.g. PTSD, dyspnoea), scales/measures employed, results, power calculation (Y/N). The senior researcher (TC) reviewed 10% of the final included studies. Discrepancies were resolved via discussion and consensus. A PRISMA flow diagram is available in Figure 1.

Figure 1. PRISMA 2020 flow diagram

Quality Assessments

Risk of bias was assessed by the JBI Critical Appraisal Tools.[101] Items related to bias included “Were confounding factors identified?”, which demanded a ‘yes’, ‘no’, ‘unclear’ or ‘not applicable’. An overall assessment was made by assigning a grade of low quality, moderate quality or good quality. Three researchers (KPW, OS, CC) independently graded 13%, 14% and 73% each of the total articles and, for the purposes of interrater estimation, researchers graded the same 10% of the articles. Interrater agreement was assessed by Fleiss' kappa, which indicated moderate agreement (k=0.534, p=.004).

Statistical analysis

We computed pooled mean prevalence for fatigue outcomes with 95% confidence intervals using a random effects model as high heterogeneity was anticipated. A number of studies investigated fatigue across multiple time points. Therefore, in order to maintain the independence of observations for the pooled prevalence, we selected 1 time-point with accompanying prevalence from each study using 1 of 3 methods: (a) fatigue reported at the stated mean/median time of the follow-up assessment, e.g. 127 days post-illness, (b) fatigue at the 3-month follow-up (being the mode for all 147 studies), or (c) for studies investigating fatigue > 4 months, we selected the shortest timepoint. Studies with missing data were excluded from analyses. Where studies investigated both 'fatigue' and CFS outcomes, we incorporated the 'fatigue' data only. This was because a confirmed diagnosis of CFS could not be established. To determine the trend for fatigue, 35 prospective studies, with available data for ≥ 2 follow-up times, were included in a meta-regression using the mixed-effects framework for meta-analyses developed by Sera et al. (2019).[102] Meta-regression coefficients were estimated using a Restricted Maximum Likelihood (REML) estimator. To determine the proportion of fatigued participants by study design, and to increase the power, we categorised studies into 2: 'cross-sectional' and 'prospective'. The latter included longitudinal and retrospective designs. The cross-sectional category comprised the remaining designs. Two categories were used to investigate proportions for 'ongoing symptomatic COVID-19' (1-3 months) and 'post-COVID-19 syndrome' (>3 months) following NICE guidelines (nice.org.uk). The robustness of the main pooled prevalence was checked by controlling for the presence of outliers. Studies with 95% confidence intervals falling outside the 95% confidence interval of the total pooled effect were defined as 'outliers'. Sensitivity analysis was performed on the mean pooled prevalence by excluding high risk of bias studies and unpublished studies. To investigate the proportion of fatigued by scale, 2 categories were used: (a) studies with a valid fatigue scale and (b) studies without a valid fatigue scale. Meta-analyses were conducted using R Studio, Version 1.3.1073[103] using packages meta, metafor, dmetar, metareg, mixmeta and irr. Heterogeneity was assessed using Cochran Q statistic. We obtained the I^2 statistic with the degree of heterogeneity categorised as 'not important' (0-40%), 'moderate' (30-60%), 'substantial' (50-90%) and 'considerable' (75-100%).[104] We conducted Egger's tests and produced funnel plots to explore potential publication bias for all proportional analyses. For 'vitality' outcomes, lack of comparable controls and missing data precluded a means difference analysis.

Patient and public involvement: No patient was involved in this study.

RESULTS

Search results

A total of 14,262 articles were identified using the database search protocols. Following the removal of duplicates 13,210 articles remained for title and abstract screening. Of these a total of 3,222 were selected for full text screening producing a final total of 178 studies and 22 systematic reviews. We identified 147 as eligible for a quantitative analysis. A summary of the 147 included articles is available as supplementary Table 1. The studies are tabulated according to categorical and continuous fatigue outcome measures. Summary table of systematic reviews is available in supplementary file 3.

Study characteristics

A total of 178 articles comprising 48,466 participants and 22 systematic reviews were included.[13–16,91,95,105–120] 14(8%) were pre-prints, 30(17%) used a fatigue scale and 27(15%) used a validated measure with a fatigue item(s). 13(7%) utilised the 'vitality' subscale of the SF-36 and 108(61%) employed a questionnaire, interview or health records. The most common countries were

Italy with 25 studies and USA with 23 studies. UK had 19 studies and China 14 studies. Spain had 12 and France had 9 studies. Germany had 8 and Switzerland had 7 studies. The Netherlands and Turkey had 6 studies each and India had 5. Iran had 4 studies. Bangladesh, Denmark, Egypt and Pakistan had 3 studies each. Brazil, Chile, Israel, Mexico, Norway and Sweden all had 2 studies. Austria, Australia, Belgium, Canada, Colombia, Finland, Ireland, Hungary, Japan, Lithuania, Mexico, Nepal, Poland, Russia, Saudi Arabia and Zambia each had 1 study. There were 80 prospective and 11 retrospective cohort deigns. Six longitudinal studies, 29 cross-sectional, 8 case-controls, 5 case series, 36 cohort, 3 randomised-controlled trials and 22 systematic reviews. The most frequent follow-up times were 3 months (46 studies), 6 months (22 studies), 1 month (20 studies), 12 months (12 studies) and 2 months (12 studies). All other time-points had $\leq$ 8 studies. JBI quality assessments resulted in most studies receiving a moderate rating. Full ratings are available as supplementary file 4. In summary, 30 were assigned a 'high' risk of bias, 139 received a 'moderate' risk assessment and only 9 were considered 'low' risk. Lower grades were assigned for selection bias, lack of adequate control groups, small samples, study design and methodological bias (employment of unvalidated/unreliable scales).

Meta-analyses

A total of 48,466 participants were included for the meta-analysis of proportions using a random-effects model. A pooled prevalence from 147 studies was found to be 41% (95% CI: 37-45%, I^2 =98%). A forest plot of this analysis is available in Figure 2. Fatigue was present between 1 month to 1-year post-infection with a median time of 3 months (IQR=2-6). An Egger's test was conducted to assess possible publication bias for our proportional analysis. The results indicated funnel plot asymmetry (bias=3.35, p=0.001) (supplementary file 5).

Figure 2 Forest plot for proportion of fatigued

To explore potential origins of heterogeneity and to test the robustness of our pooled prevalence, outliers were controlled for. A 1% difference was found once n=84 outlier studies were removed 42% (95% CI: 40-45%, I^2= 67%), although heterogeneity was reduced to 'substantial'. Given the range of post-infection assessment periods, the effect of time on fatigue was investigated by a linear mixed-effects model meta-regression. The outcome variable was the proportion of individuals reporting fatigue, with 'Months' (number of months since infection) and 'Hospitalisation' (whether someone was hospitalised) as predictors. 35 studies with available fatigue data and multiple time points ($\geq$ 2 follow-ups) were included. We found an effect of time, with the proportion of fatigued participants decreasing by 5.7% per month (95% CI: 1-10%, p=0.05). There was no effect of Hospitalisation and no interaction between Hospitalisation and time (Table 1).

Table 1 Results of linear mixed-effect meta-regression of time and hospitalisation

Parameter	*Estimate*	*SE*	*AIC*	*p*	*95% CI*	
					Lower	*Upper*
Months	-0.0577	0.0252	501.933	.05	-0.1070	-0.0084
Hospitalisation	-0.0871	0.1088	-	.445	-0.3013	0.1326
Months: Hospitalised	0.0324	0.0674	505.680	.630	-0.0997	0.1645

AIC Akaike Information Criterion

We conducted 2 subgroup analyses to explore the origins of heterogeneity arising from study methodology and investigate between group differences. No significant difference in fatigue was found between n=67 cross-sectional studies (44%, CI: 38-50%, !^{2}=97.6%) and n=80 prospective studies (39%, CI: 33-45%, !^{2}=98%), p=0.272.

A higher proportion of fatigued participants was found in n=36 studies using a scale (51%, 95% CI: 43-58%, I^2= 96.2%) compared to n=111 studies using an unvalidated questionnaire (38%, 95% CI: 33-43%, I^2=98%), p=0.004. To assess fatigue occurring at (a) 1-3 months ('ongoing symptomatic COVID-19') and (b) > 3 months ('post-COVID-19 syndrome'), 2 random effects subgroup analyses were conducted. Between 1-3 months the proportion of fatigued was 41% (95% CI: 36-47%, k=86, I^2=98.3%). At > 3 months, the proportion was 41% (95% CI: 34-48%, k=61, I^2= 97.4%). Sensitivity analysis was performed by excluding n=30 quality assessments (graded 'low') and removing unpublished results from the main analysis (n=8). Results found the pooled prevalence to be 40% (95% CI: 36-45%, I^2 =98.3%) and 41% (95% CI: 37-46%, k=139, I^2 =98%) respectively, indicating little impact on the main results. Egger's tests indicated publication bias for both time categories and sensitivity. Plots available in supplementary files 6-15.

Factors associated with fatigue

Not all studies investigated or reported factors associated with fatigue. For some, the available data for each risk factor were too few to conduct a quantified analysis. Studies also used diverse outcome measures or non-validated scales. In addition, some risk factors were reported but not accompanied by quantified data making comparisons between studies problematic. Consequently, reported associations were arranged in tabular form illustrating the direction of the association with fatigue (Table 2). A positive symbol (+) indicated a positive association, a negative symbol (-) indicated a negative association and a zero (0) indicated no significant association between the investigated variable and fatigue.[121] Associations with fatigue measured in prospective cohort designs were demonstrated by superscript figures contained within parentheses, representing the time period the relationships were examined. Where a risk factor was examined with another (e.g. ICU admission with age), one set of results was included. Full details of the associations are available in supplementary file 16.

Table 2. Variables associated with fatigue

Factor	Cross-sectional		Prospective Cohort	
	Bivariate	*Multivariate*	*Bivariate*	*Multivariate*
PTSD↑	+ +		+ +	
Anxiety symptoms↑	+ 0 +	+	+	0
Depression↑	+ + + + + +	+ +	+ (0^6 $+^{12}$)	+ 0

Psychiatric morbidity↑			+	
Physical comorbidities	0 0 0	+ +	0 0	+ + + + + + +
Psychological distress			0	
Somatisation			+	0
Pulmonary functions	+ 0 0	0		0
Pneumonia (CXR)		+		
Disease Severity↑	+ 0 - + 0 0 0 0	+	+ 0 + 0 0 0 + 0 0 0 0 + + + 0 0	0 0
Age↑	0 - 0 + - 0 0 -	- + 0 0 0 + 0 0	0 0 + 0 0 0 0 - 0	+ 0 – + 0 +
ICU Admission	0 0 + + + + 0	0 0 +	+ 0 + +	
Female gender	+ + - 0 + + 0 + + + 0 + + + + 0 + + + +	+ + + + 0	+ + 0 + 0 + + 0 + 0 + + + 0	+ + ++ 0 0 +
Ethnicity	0 0	0		
Marital status			0	
Rural/Urban habitat			0	
Occupation type			0	
BMI/obesity/weight↑	0 + + 0	0 0 + 0	0 0 0	0
Returned to work	+	+	0	
Employed				+
Retired				-
Exercise capacity <	+ + - -		0	0 0
Intubated/IMV	+		- (-[3] +[6]) 0	+
Serum troponin-1 (TN1)			+	
Nucleic-acid test (> 14 days, 46-69 years old)	+	+		
Reduction of serum NfL levels			0	
Blood (e.g. lymphocytes10^9/L, IgG)	0 + -	+	0	0
SpO^2				0 0
Gut microbiota	+			
% Predicted VO2			0	
Mean consecutive difference (MCD) in extensor digitorum communis (EDC)	+			
Alcohol consumption	0	0		
Smoking history	0 0 0	0 0		0 0
Response to follow-up <				
Length of stay (LOS) >	0 + 0 0	+	0 +	
Hospital readmission				+
Education↑	0	0		
Physical health↓	0 +			+
Pain	+		+	
Post functional status/daily functioning↓	+ + + +			
Frailty↑			+	

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Resilience↓	-			
Sleep (quality & quantity)	+ + +		+ 0	
Steroid treatment	0 0			
Days since onset >	0	+		
Cognitive problems↑	+ + +		+	
Breathlessness/Dyspnoea/Hyperventilation↑	+ 0 +	+ 0	+ +	+ +
Post Covid-19 functioning↓			+	+

Non-modifiable factors

Older age was reported in 30 studies with mixed results. Six reported an association with, or an increased likelihood of fatigue (OR=1.02) in participants >50.[52,66–68,122,123] Two reported higher fatigue in > 60 year olds [124] and >40-year olds.[83] Some, however, reported that younger age related to fatigue [125–128] or no difference in fatigue severity between <65 and >65 year olds.[129] The remaining 17 studies did not find a relationship to fatigue.[69,70,79,80,84,85,96,98,130–138] However, studies reporting non-significant results had small to modest sample sizes and were therefore potentially underpowered. Gender was investigated by 46 studies. Thirty reported a significant association with fatigue, found more women were fatigued or found higher fatigue in women.[42,52,63–66,68,96,98,122,124,127,129,132,135,138–152] Females (54.3%) reported more severe/moderate fatigue than males (29.6%),[86,128] and had significantly lower vitality scores (M=81.80) compared to men (M=83.25).[123] However, 16 utilised an unvalidated instrument potentially affecting results. Those finding no significant difference [70,79,80,83,84,130,131,134,136,137,153,154] had small sample sizes and only 3 used a fatigue scale.

Physical factors

The key physical factors associated with fatigue were dyspnoea, pulmonary functions, exercise capacity, comorbidities and ICU admission. An association between breathlessness and fatigue was found in 3 studies [79,84,85] and those with fatigue had a higher prevalence of breathlessness in 4 other studies.[82,83,128,155] At 3-6 months post-infection 2 did not find a relationship,[80,96] suggestive of improvements over time. Staudt et al. (2021) found that 'respiratory symptoms' on the SGRQ were related to fatigue in multivariate analyses at 10 months post-infection (OR=1.06, p=0.05). However, only 2 used a dyspnoea scale or a fatigue scale. All had small sample sizes, therefore potentially underpowered. Pulmonary functions were reported in 5 studies. FEV_1 related to higher vitality in 1 (r=.0.23, p<.05),[78] but non-significant in the others.[79,80,155] These studies assessed survivors ≥ 3 months, suggesting results are indicative of functional improvements overtime. Exercise capacity was generally poor in survivors[156] and 7 studies examined its relationship with fatigue, with mixed results. Better exercise performance was associated with vitality (r = 0.526, p<.001),[78] but not with 4-meter gait speed test [85] or 6MWT.[79] Two others found improved fatigue following a physical rehabilitation programme.[97,157] At 3 months post-infection, fatigue was cited as the reason for halting a cardiopulmonary performance test or limiting exercise in 3 studies.[158–160] Myopathy was associated with fatigue in another small study of 20 people [161] suggestive of poor conditioning contributing to limited capacity. Generally, fatigue had an inverse relationship with exercise capacity in the early months. Where the relationship remained beyond 3 months,[78] patients were overweight/obese, which possibly affected performance. Also, all studies had small sample sizes limiting generalisability.

Physical comorbidities such as hypertension, asthma and diabetes were related to fatigue in 9 studies.[52,63,68,125,127,135,146,148,162] Four found no relationship.[131,132,136,147]. A large study of 4,755 participants found hypertension increased the likelihood (OR=1.27, p=0.05) of persistent fatigue > 6 months.[148] Yomogida et al. (2021) reported that having at least 1 comorbidity increased the risk for fatigue (OR=4.39, p<.001). Moreover, worse physical health was related to fatigue (OR = 10.48)[65,163,164] implying general poorer functioning among survivors.[165]

For those admitted to ICU, some experienced high fatigue (8 studies),[83,128,130] and lower vitality,[166,167] or had an increased likelihood for fatigue. (OR=4.63).[52,127,168] Four studies found no association between ICU admission and worse fatigue or vitality.[42,169–171] Patients who received mechanical ventilation had lower vitality (M=50, 95% CI: 44-57) than a sex and age matched group (M=68, 95% CI: 67-69).[172] Similarly, more intubated patients had fatigue (38.1%) than non-intubated(29.9%).[173] One study found the proportion of fatigued participants was higher in the ward group (74%) compared to ICU (33%).[143] Disease severity also had an inconsistent impact on fatigue, with most studies finding no association with severe acute disease or fatigue prevalence in severity categories.[80,86,93,129,135,136,153,174–180] Six studies found a significant association with critical illness or a significantly higher proportion of fatigued in severe illness.[122,134,145,181–183] Two studies found a relationship between severity of acute illness and vitality,[184,185] although both had small samples and were single-centre designs. Interestingly, moderately severe COVID-19 related to fatigue (OR=2.1) in 1 study.[186] Even after a longer hospital stay, the relationship with fatigue was inconsistent with 2 finding significance,[52,123] while 4 did not.[69,136,138,149] Taken together these results indicate an uncertain contribution of critical illness to fatigue, although the non-significant results chiefly occurred > 6 months. However, the classification of disease severity varied between studies and countries making comparisons difficult.

Psychological factors

A relationship with anxiety was found up to 6 months post-infection in 3 studies.[52,83,149] The fatigued had higher anxiety (56.3%) compared to non-fatigued (24.6%, $p<.001$).[83,149] In contrast, no significant interaction between anxiety and fatigue at 1 month related to later fatigue.[187] Similar results were found for depression. Previous depression was associated with lower vitality (-12.05, $p=0.005$) in 1 study [96] and a higher proportion of fatigued had depressive symptoms in 4 other studies ($p = .004$).[83,90,155,188] Other studies found consistently moderate positive correlations ($r=0.470$).[138,171,189] or increased fatigue scores ($b=0.89$, $p=0.05$) in those with depressive symptoms.[52] The relationship continued up until 12 months.[79,138] Four studies found that those with PTSD symptoms were fatigued [90,128] and PTSD was associated with fatigue at 6 and 12 months after infection.[138] Barizien et al. (2021) found higher scores on the PCL-5 (PTSD Checklist for DSM-5) in those with fatigue (M=31, IQR=18) compared to those without fatigue (M=18, IQR=19, p<.001). Generalisability of these results, however, are likely limited due to modest sample sizes and single-centre designs. In addition, only 3 studies used a valid fatigue scale.

DISCUSSION

This review investigated the prevalence of persistent fatigue in survivors who had a confirmed diagnosis of SARS-CoV-2, using a mean of $\geq$ 30 days post-infection. We found a considerable proportion of patients continued to experience fatigue up to 12 months after their initial illness, which was associated with some non-modifiable factors including female gender, age and modifiable factors such as anxiety, depression and post-traumatic stress. Our findings support other research indicating that fatigue is an important symptom in persistent post-acute sequelae.[14,111,150,190–196] Rates of fatigue may depend on when it was measured and, in this respect, we found overall rates of fatigue decreased by 6% per month. Fatigue did not differ by hospitalisation status, indicating that the contribution of severe disease was not related to fatigue recovery for most people. This is consistent with previous reviews, which did not find support for the effects of critical illness on fatigue outcomes.[116,197] Respiratory impairments, a key clinical indicator, were associated with worse vitality post-recovery (r=0.290, p=0.026),[78] although at 10 months, FEV_1 was not associated [79] implying that, as lung function improved, fatigue diminished. Indeed, rehabilitation aimed at improving functioning by incorporating aerobic exercises, improved vitality scores.[97,167,198] Some survivors, however, continued to experience dyspnoea, which was associated with their fatigue,[83–85] despite normal pulmonary tests.[80,159] Similarly, reduced exercise capacity, as a result of critical illness, is thought to contribute to reduced HRQoL and fatigue outcomes in recovered patients.[199] However, our review did not find a consistent relationship between exercise performance and worse fatigue in those who had more severe disease. It is possible that these limitations are related to diminished muscle function [199] and deconditioning. Rehabilitation programmes have led to improved vitality [157,198] and lower fatigue.[97,157] A 9-week telerehabilitation study of 115 participants, incorporating 2/3 aerobic exercises per week to improve physical capacity, reported significantly increased vitality scores from pre =40.7(SD=21.7) to post =58.5(SD=21.2), p=0.001.[167] While deconditioning could explain fatigue, persistent fatigue may be related to other variables including psychological factors.

Depression and anxiety were found to be correlated with fatigue in our review.[52,171] Moreover, these relationships were found some distance from the initial infection.[138,155] In a prospective study of 402 participants using a fatigue scale, Mazza et al. (2021) found that both anxiety (r=0.48) and PTSD (r=0.52) were moderately correlated with fatigue at 6 and 12 months, post-illness. These findings accord with critical illness studies[200] and systematic reviews suggesting that symptoms of depression, anxiety, PTSD and fatigue persist long after discharge.[197] For COVID-19, we cannot be certain of the longevity of psychological factors or their relationship to fatigue because the body of evidence is too small, but current literature indicates the relationship remains up to 6 months.[83,131] This fits with previous coronavirus research indicating those with chronic fatigue were more likely to have psychiatric morbidity 4 years following a SARS infection.[201] Similarly, those with psychiatric illness reported higher fatigue than those without (p<.05) in survivors of SARS.[202]

Theoretical implications

The associations of fatigue persistence were multidimensional. Factors such as dyspnoea and comorbidities (e.g., hypertension) were likely risk factors for fatigue in the shorter term whereas psychological factors appeared more likely to be associated with fatigue longer term. The psychological risk factors could have been related to adverse effects of the pandemic as well as infection.[203,204] Taken together, these factors, alongside other mechanisms such as skeletal muscle deficits,[205] could lead to poorer global functioning and lower engagement in activities or exercise. Lower scores on objective walking tests and reduced physical functioning were associated with fatigue in some studies We have summarised diagrammatically the factors associated with post-coronavirus fatigue (see Figure 3).

Figure 3 Diagram of post-COVID-19 fatigue findings

Practical implications

Our review suggests post-coronavirus fatigue is complex, affecting multiple domains of physical and psychological well-being. While there were small improvements in fatigue over time, our review indicates that fatigue remains a significant problem for patients beyond their anticipated recovery time.[206] Pulmonary and exercise programmes have shown promise.[97,167,198] Our results also suggest that psychological interventions may benefit some survivors. Given fatigue is one of a number of post-Covid symptoms,[207–210] an integrated management approach has been suggested.[211] Care pathways should identify those most at risk for long-term symptoms such as women and older people with comorbidities.

Future directions

Few studies have examined correlates between fatigue, physical and pulmonary functioning, psychological and social functioning in hospitalised and outpatients. Some research focuses on symptom 'clusters' or 'post-covid syndrome'[212–215] limiting understanding of fatigue processes specifically. Future studies should interrogate risk factors further to help inform the development of clinical interventions to address persistent fatigue. Furthermore, fatigue is the principal symptom for post-illness patients, but there is little research into what mechanisms may ameliorate distress resulting from infection, and thus protect against long symptoms. Severity of the illness, for instance, was not conclusive in our study and nor was length of hospital stay, pointing to the importance of individual differences.

Limitations

The generalisability of our results should be applied with caution due to a number of limitations. Firstly, we found considerable, unexplained between-study heterogeneity. Measurement error was not found to explain the inconsistency. However, diverse tools were used to measure fatigue in different populations. Non-validated questionnaires were unlikely to capture fatigue dimensions accurately given most only had 1-2 fatigue-related items. Moreover, scoring and cut-offs were underreported, contributing to variability. Included studies could not adequately exclude 'pandemic related fatigue' in their selections or definitions. Therefore, we recognise that our results could not completely exclude such fatigue and its potential influence on participants in the included studies. Some studies used particular populations, including older age or only those admitted to ICU, meaning they were not representative. Furthermore, our sample comprised primarily of hospitalised patients with potentially more severe disease. This was complicated by different admission and discharge protocols across countries, with some admitting all confirmed patients regardless of disease severity. This could explain why there was no difference between hospitalised and non-hospitalised survivors. We also encountered missing data, which reduced the reliability of our results. Moreover, Egger's tests suggested all but one analyses were asymmetric representing a high likelihood of publication bias. Small study effects were likely to affect precision. Larger studies, with more precise confidence intervals are likely to be a more reliable indicator of fatigue proportions. Moreover, sample bias probably occurred due to recruitment from single-centre post-covid clinics [216–218] for persistent symptoms and therefore could be expected to have higher fatigue than controls or population norms. Different admission and discharge protocols and lung function reference ranges vary between countries.[219] Our results, therefore, should be viewed with this in mind. Methodologically, our study had only one reviewer for screening and data extraction, and we did not contact authors for missing data meaning our study was at higher risk for excluding relevant data. Other limitations include the inclusion of non-peer reviewed articles and those limited to English. For the meta-analysis, given the multiple assessment times, we incorporated one median follow-up time obtained from each study, which may not denote actual fatigue prevalence. Despite these limitations, we incorporated a substantial sample size likely to be a reasonable estimate of fatigue in this population.

CONCLUSION

This large review provides a broad illustration of fatigue outcomes and complements the body of information for persistent symptoms in those recovering from COVID-19. We report that fatigue decreases over time, but recovery pathways are potentially impeded by a number of risk factors, independent of disease severity or hospitalisation. Our study indicates the need for long-term clinical and psychological rehabilitation support for survivors of COVID-19.

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TC is the author of several self-help books on chronic fatigue for which she has received royalties. TC(KCL) has received ad hoc payments for workshops carried out in long-term conditions. TC is on the Expert Advisory Panel for Covid-19 Rapid Guidelines. She is also in receipt of grants from NIHR and St Thomas' Charity. TC collaborates with The Post-hospitalisation Covid-19 Study (PHOSP-COVID). TC is the Director of the Persistent Physical Symptoms Service. There are no other relationships or activities that could have influenced submitted work.

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References

1 Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue. *J Psychosom Res* 2004;**56**:157–70. doi:10.1016/S0022-3999(03)00371-4

2 Grant MC, Geoghegan L, Arbyn M, *et al.* The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. *PLoS One* 2020;**15**:e0234765. doi:http://dx.doi.org/10.1371/journal.pone.0234765

3 Lemhöfer C, Sturm C, Loudovici-Krug D, *et al.* The impact of Post-COVID-Syndrome on functioning – results from a community survey in patients after mild and moderate SARS-CoV-2-infections in Germany. *Journal of Occupational Medicine & Toxicology* 2021;**16**:1–9. doi:10.1186/s12995-021-00337-9

4 Leth S, Gunst JD, Mathiasen V, *et al.* Persistent Symptoms in Patients Recovering From COVID-19 in Denmark. *Open Forum Infect Dis* 2021;**8**:ofab042. doi:https://dx.doi.org/10.1093/ofid/ofab042

5 Liang L, Yang B, Jiang N, *et al.* Three-Month Follow-Up Study of Survivors of Coronavirus Disease 2019 after Discharge. *J Korean Med Sci* 2020;**35**. doi:10.3346/jkms.2020.35.e418

6 Miyazato Y, Akashi M, Osanai Y, *et al.* Prolonged and late-onset symptoms of coronavirus disease 2019. *Open Forum Infect Dis* 2020;**7**:ofaa507. doi:10.1093/ofid/ofaa507

7 Ortelli P, Ferrazzoli D, Sebastianelli L, *et al.* Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19:

Insights into a challenging symptom. *J Neurol Sci* 2021;**420**:117271. doi:http://dx.doi.org/10.1016/j.jns.2020.117271

8 Rosales-Castillo A, García de los Ríos C, Mediavilla García JD. Persistent symptoms after acute COVID-19 infection: importance of follow-up. *Med Clin (Barc)* 2021;**156**:35–6. doi:10.1016/j.medcli.2020.08.001

9 Shoucri SM, Purpura L, DeLaurentis C, *et al.* Characterising the long-term clinical outcomes of 1190 hospitalised patients with COVID-19 in New York City: a retrospective case series. *BMJ Open* 2021;**11**:e049488. doi:10.1136/bmjopen-2021-049488

10 Søraas A, Kalleberg KT, Dahl JA, *et al.* Persisting symptoms three to eight months after non-hospitalized COVID-19, a prospective cohort study. *PLoS One* 2021;**16**:e0256142. doi:10.1371/journal.pone.0256142

11 Sultana S, Islam MT, Salwa M, *et al.* Duration and Risk Factors of Post-COVID Symptoms Following Recovery Among the Medical Doctors in Bangladesh. *Cureus* 2021;**13**:e15351. doi:https://dx.doi.org/10.7759/cureus.15351

12 Zhou Y, Zhang J, Zhang D, *et al.* Linking the gut microbiota to persistent symptoms in survivors of COVID-19 after discharge. *J Microbiol* 2021;**59**:941–8. doi:https://dx.doi.org/10.1007/s12275-021-1206-5

13 Badenoch JB, Rengasamy ER, Watson CJ, *et al.* Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.30.21256413. doi:10.1101/2021.04.30.21256413

14 Hoshijima H, Mihara T, Seki H, *et al.* Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. *medRxiv* 2021;:2021.04.08.21255109. doi:10.1101/2021.04.08.21255109

15 Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, *et al.* Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chron Respir Dis* 2021;**18**:147997312110022. doi:10.1177/14799731211002240

16 Malik P, Patel K, Pinto C, *et al.* Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* Published Online First: 2021. doi:https://dx.doi.org/10.1002/jmv.27309

17 Mak IWC, Chu CM, Pan PC, *et al.* Long-term psychiatric morbidities among SARS survivors. *Gen Hosp Psychiatry* 2009;**31**:318–26. doi:10.1016/j.genhosppsych.2009.03.001

18 Lee SH, Shin H-S, Park HY, *et al.* Depression as a Mediator of Chronic Fatigue and Post-Traumatic Stress Symptoms in Middle East Respiratory Syndrome Survivors. *Psychiatry Investig* 2019;**16**:59–64. doi:10.30773/pi.2018.10.22.3

19 Arnold DT, Hamilton FWFW, Morley MA, *et al.* Patient outcomes after hospitalisation with COVID-19 and implications for follow-up; results from a prospective UK cohort. *medRxiv* 2020;:2020.08.12.20173526. doi:10.1101/2020.08.12.20173526

20 Becker C, Beck K, Zumbrunn S, *et al.* Long COVID 1 year after hospitalisation for COVID-19: a prospective bicentric cohort study. *Swiss Med Wkly* 2021;**151**:w30091. doi:https://dx.doi.org/10.4414/smw.2021.w30091

21 Bozzetti S, Ferrari S, Zanzoni S, *et al.* Neurological symptoms and axonal damage in COVID-19 survivors: are there sequelae? *Immunol Res* Published Online First: 7 August 2021. doi:10.1007/s12026-021-09220-5

22 Catalan IP, Marti CR, Sota DP de la, *et al.* Corticosteroids for COVID-19 symptoms and quality of life at 1 year from admission. *J Med Virol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/jmv.27296

23 Eloy P, Tardivon C, Martin-Blondel G, *et al.* Severity of self-reported symptoms and psychological burden 6-months after hospital admission for COVID-19: a prospective cohort study. *Int J Infect Dis* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.ijid.2021.09.011

24 Evans RA, McAuley H, Harrison EM, *et al.* Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* Published Online First: 2021. doi:https://dx.doi.org/10.1016/S2213-2600(21)00383-0

25 Fatima G, Bhatt D, Idrees J, *et al.* Elucidating Post-COVID-19 manifestations in India. *medRxiv* 2021;:2021.07.06.21260115. doi:10.1101/2021.07.06.21260115

26 Fortini A, Torrigiani A, Sbaragli S, *et al.* COVID-19: persistence of symptoms and lung alterations after 3-6 months from hospital discharge. *Infection* 2021;**49**:1007–15. doi:http://dx.doi.org/10.1007/s15010-021-01638-1

27 Ganesh R, Ghosh AK, Nyman MA, *et al.* PROMIS scales for assessment of the impact of post-COVID syndrome: A Cross Sectional Study. *medRxiv* 2021;:2021.05.25.21257817. doi:10.1101/2021.05.25.21257817

28 García-Abellán J, Padilla S, Fernández-González M, *et al.* Antibody Response to SARS-CoV-2 is Associated with Long-term Clinical Outcome in Patients with COVID-19: a Longitudinal Study. *J Clin Immunol* 2021;**41**:1490–501. doi:10.1007/s10875-021-01083-7

29 Kayaaslan B, Eser F, Kalem AK, *et al.* Post-COVID syndrome: A single-center questionnaire study on 1007 participants recovered from COVID-19. *J Med Virol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/jmv.27198

2

30 Khalaf M, Bazeed SE, Abdel-Gawad M, *et al.* Prevalence and Predictors of Persistent Symptoms after Clearance of SARS-CoV-2 Infection: A Report from Egypt. *SSRN Electronic Journal* Published Online First: 2020. doi:10.2139/ssrn.3727954

31 Mahmud R, Rassel MA, Rahman MM, *et al.* Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. *PLoS One* 2021;**16**:e0249644. doi:http://dx.doi.org/10.1371/journal.pone.0249644

32 Moreno-Perez O, Merino E, Leon-Ramirez JM, *et al.* Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *Journal of Infection* 2021;**82**:378–83. doi:http://dx.doi.org/10.1016/j.jinf.2021.01.004

33 Poyraz BÇ, Poyraz CA, Olgun Y, *et al.* Psychiatric morbidity and protracted symptoms after COVID-19. *Psychiatry Res* 2021;**295**:113604. doi:10.1016/j.psychres.2020.113604

34 Righi E, Mirandola M, Mazzaferri F, *et al.* Long-Term Patient-Centred Follow-up in a Prospective Cohort of Patients with COVID-19. *Infect Dis Ther* 2021;**10**:1579–90. doi:http://dx.doi.org/10.1007/s40121-021-00461-3

35 Scherlinger M, Felten R, Gallais F, *et al.* Refining “Long-COVID” by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection. *Infect Dis Ther* 2021;**10**:1747–63. doi:10.1007/s40121-021-00484-w

36 Seeßle J, Waterboer T, Hippchen T, *et al.* Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. *Clinical Infectious Diseases* 2022;**74**:1191–8. doi:10.1093/cid/ciab611 Published online 2021, July 5.

37 Steinbeis F, Thibeault C, Doellinger F, *et al.* Severity of respiratory failure and computed chest tomography in acute COVID-19 correlates with pulmonary function and respiratory symptoms after infection with SARS-CoV-2: An observational longitudinal study over 12 months. *Respir Med* 2021;**191**:106709. doi:https://dx.doi.org/10.1016/j.rmed.2021.106709

38 Tleyjeh IM, Saddik B, AlSwaidan N, *et al.* Prevalence and predictors of Post-Acute COVID-19 Syndrome (PACS) after hospital discharge: A cohort study with 4 months median follow-up. *PLoS One* 2021;**16**:e0260568. doi:https://dx.doi.org/10.1371/journal.pone.0260568

39 van Veenendaal N, van der Meulen IC, Onrust M, *et al.* Six-Month Outcomes in COVID-19 ICU Patients and Their Family Members: A Prospective Cohort Study. Healthcare . 2021;**9**. doi:10.3390/healthcare9070865

40 Wu Q, Zhong L, Li H, *et al.* A Follow-Up Study of Lung Function and Chest Computed Tomography at 6 Months after Discharge in Patients with Coronavirus Disease 2019. *Can Respir J* 2021;**2021**:6692409. doi:http://dx.doi.org/10.1155/2021/6692409

41 Zayet S, Zahra H, Royer P-YY, *et al.* Post-COVID-19 Syndrome: Nine Months after SARS-CoV-2 Infection in a Cohort of 354 Patients: Data from the First Wave of COVID-19 in Nord

Franche-Comte Hospital, France. *Microorganisms* 2021;**9**. doi:https://dx.doi.org/10.3390/microorganisms9081719

42 Fernandez-De-Las-Penas C, Palacios-Cena D, Palacios-Cena M, *et al.* Fatigue and Dyspnoea as Main Persistent Post-COVID-19 Symptoms in Previously Hospitalized Patients: Related Functional Limitations and Disability. *Respiration* Published Online First: 2021. doi:http://dx.doi.org/10.1159/000518854

43 Gamberini L, Mazzoli CA, Prediletto I, *et al.* Health-related quality of life profiles, trajectories, persistent symptoms and pulmonary function one year after ICU discharge in invasively ventilated COVID-19 patients, a prospective follow-up study. *Respir Med* 2021;**189**:106665. doi:10.1016/j.rmed.2021.106665

44 Boari GEM, Bonetti S, Braglia-Orlandini F, *et al.* Short-Term Consequences of SARS-CoV-2-Related Pneumonia: A Follow Up Study. *High Blood Press Cardiovasc Prev* 2021;**28**:373–81. doi:https://dx.doi.org/10.1007/s40292-021-00454-w

45 Creamer AW, Alaee S, Iftikhar H, *et al.* Clinico-radiological recovery following Severe covid-19 pneumonia. *Thorax* 2021;**76**:A185. doi:http://dx.doi.org/10.1136/thorax-2020-BTSabstracts.320

46 Horwitz LI, Garry K, Prete AM, *et al.* Six-Month Outcomes in Patients Hospitalized with Severe COVID-19. *J Gen Intern Med* Published Online First: 2021. doi:https://dx.doi.org/10.1007/s11606-021-07032-9

47 Naik S, Haldar SN, Soneja M, *et al.* Post COVID-19 sequelae: A prospective observational study from Northern India. *Drug Discov Ther* 2021;**15**:254–60. doi:10.5582/ddt.2021.01093

48 Frontera JA, Yang D, Lewis A, *et al.* A Prospective Study of Long-Term Outcomes Among Hospitalized COVID-19 Patients with and without Neurological Complications. *medRxiv* 2021;:2021.03.18.21253881. doi:10.1101/2021.03.18.21253881

49 Gupta A, Garg I, Iqbal A, *et al.* Long-Term X-ray Findings in Patients With Coronavirus Disease-2019. *Cureus* 2021;**13**:e15304. doi:https://dx.doi.org/10.7759/cureus.15304

50 Kozak R, Armstrong SM, Salvant E, *et al.* Recognition of Long-COVID-19 Patients in a Canadian Tertiary Hospital Setting: A Retrospective Analysis of Their Clinical and Laboratory Characteristics. *Pathogens* 2021;**10**:1246. doi:10.3390/pathogens10101246

51 Liu T, Wu D, Yan W, *et al.* Twelve-month systemic consequences of COVID-19 in patients discharged from hospital: a prospective cohort study in Wuhan, China. *Clin Infect Dis* Published Online First: 2021. doi:https://dx.doi.org/10.1093/cid/ciab703

52 Qin ES, Gold LS, Hough CL, *et al.* Patient-Reported Functional Outcomes Thirty Days after Hospitalization for COVID-19. *PM R* Published Online First: 2021. doi:https://dx.doi.org/10.1002/pmrj.12716

53 Bell ML, Catalfamo CJ, Farland L V, *et al.* Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT. *medRxiv* 2021;:2021.03.29.21254588. doi:10.1101/2021.03.29.21254588

54 Carvalho-Schneider C, Laurent E, Lemaignen A, *et al.* Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021;**27**:258–63. doi:10.1016/j.cmi.2020.09.052

55 Graham EL, Clark JR, Orban ZS, *et al.* Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 'long haulers'. *Ann Clin Transl Neurol* Published Online First: 2021. doi:http://dx.doi.org/10.1002/acn3.51350

56 Savarraj JPJ, Burkett AB, Hinds SN, *et al.* Three-month outcomes in hospitalized COVID-19 patients. *medRxiv* 2020;:2020.10.16.20211029. doi:10.1101/2020.10.16.20211029

57 Senjam SS, Balhara YPS, Kumar P, *et al.* Assessment of Post COVID-19 Health Problems and its Determinants in North India: A descriptive cross section study. *medRxiv* 2021;:2021.10.03.21264490. doi:10.1101/2021.10.03.21264490

58 Boscolo-Rizzo P, Guida F, Polesel J, *et al.* Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol* 2021;**11**:1685–8. doi:10.1002/alr.22832

59 Bliddal S, Banasik K, Pedersen OB, *et al.* Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. *Sci Rep* 2021;**11**:13153. doi:10.1038/s41598-021-92045-x

60 Logue JK, Franko NM, McCulloch DJ, *et al.* Sequelae in Adults at 6 Months After COVID-19 Infection. *JAMA Netw Open* 2021;**4**:e210830. doi:10.1001/jamanetworkopen.2021.0830

61 Castro VM, Rosand J, Giacino JT, *et al.* Case-control study of neuropsychiatric symptoms following COVID-19 hospitalization in 2 academic health systems. *medRxiv* 2021;:2021.07.09.21252353. doi:10.1101/2021.07.09.21252353

62 Heightman M, Prashar J, Hillman TE, *et al.* Post-COVID assessment in a specialist clinical service: a 12-month, single-centre analysis of symptoms and healthcare needs in 1325 individuals. *medRxiv* 2021;:2021.05.25.21257730. doi:10.1101/2021.05.25.21257730

63 Amin-Chowdhury Z, Harris RJ, Aiano F, *et al.* Characterising post-COVID syndrome more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. *medRxiv* 2021;:2021.03.18.21253633. doi:10.1101/2021.03.18.21253633

64 Bai F, Tomasoni D, Falcinella C, *et al.* Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.cmi.2021.11.002

65 Hellemons ME, Huijts S, Bek L, *et al.* Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for SARS-CoV-2; A Longitudinal Study of

Respiratory, Physical and Psychological Outcomes. *Ann Am Thorac Soc* Published Online First: 2021. doi:https://dx.doi.org/10.1513/AnnalsATS.202103-340OC

66 Lombardo MDM, Foppiani A, Peretti GM, *et al.* Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. *Open Forum Infect Dis* 2021;**8**:ofab384. doi:https://dx.doi.org/10.1093/ofid/ofab384

67 Daugherty SE, Guo Y, Heath K, *et al.* Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021;**373**:n1098. doi:https://dx.doi.org/10.1136/bmj.n1098

68 Yomogida K, Zhu S, Rubino F, *et al.* Post-Acute Sequelae of SARS-CoV-2 Infection Among Adults Aged ≥18 Years — Long Beach, California, April 1–December 10, 2020. *MMWR Morb Mortal Wkly Rep* 2021;**70**:1274–7. doi:10.15585/mmwr.mm7037a2

69 Karaarslan F, Demircioğlu Güneri F, Kardeș S. Postdischarge rheumatic and musculoskeletal symptoms following hospitalization for COVID-19: prospective follow-up by phone interviews. *Rheumatol Int* 2021;**41**:1263–71. doi:10.1007/s00296-021-04882-8

70 Hossain MA, Hossain KMA, Saunders K, *et al.* Prevalence of Long COVID symptoms in Bangladesh: a prospective Inception Cohort Study of COVID-19 survivors. *BMJ Glob Health* 2021;**6**. doi:https://dx.doi.org/10.1136/bmjgh-2021-006838

71 Cao J, Chen X, Zheng X, *et al.* Three-month outcomes of recovered COVID-19 patients: prospective observational study. *Ther Adv Respir Dis* 2021;**15**. doi:http://dx.doi.org/10.1177/17534666211009410

72 Aranda J, Oriol I, Martín M, *et al.* Long-term impact of COVID-19 associated acute respiratory distress syndrome. *Journal of Infection* Published Online First: August 2021. doi:10.1016/j.jinf.2021.08.018

73 Szekely Y, Lichter Y, Sadon S, *et al.* Cardiorespiratory Abnormalities in Patients Recovering from Coronavirus Disease 2019. *J Am Soc Echocardiogr* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.echo.2021.08.022

74 Wang SY, Adejumo P, See C, *et al.* Characteristics of Patients Referred to a Cardiovascular Disease Clinic for Post-Acute Sequelae of SARS-CoV-2 Infection. *medRxiv* 2021;:2021.12.04.21267294. doi:10.1101/2021.12.04.21267294

75 Donaghy M, McKeegan D, Walker J, *et al.* Follow up for COVID-19 in Belfast City Hospital. *Ulster Med J* 2021;**90**:157–61.

76 Chudzik M, Kapusta J, Burzyńska M. Use of 1-MNA to Improve Exercise Tolerance and Fatigue in Patients After COVID-19. *medRxiv* 2021;:2021.07.14.21259081. doi:10.1101/2021.07.14.21259081

77 Chen Y, Liu C, Wang T, *et al.* Efficacy and safety of Bufei Huoxue capsules in the management of convalescent patients with COVID-19 infection: A multicentre, double-blind,

and randomised controlled trial. *J Ethnopharmacol* 2021;**284**:114830. doi:10.1016/j.jep.2021.114830

78 Bardakci MI, Ozkarafakili MA, Ozturk EN, *et al.* Evaluation of long-term radiological findings, pulmonary functions, and health-related quality of life in survivors of severe COVID-19. *J Med Virol* 2021;**93**:5574–81. doi:http://dx.doi.org/10.1002/jmv.27101

79 Staudt A, Jorres RA, Hinterberger T, *et al.* Associations of Post-Acute COVID syndrome with physiological and clinical measures 10 months after hospitalization in patients of the first wave. *Eur J Intern Med* 2022;**95**:50–60. doi:https://dx.doi.org/10.1016/j.ejim.2021.10.031 Published online 2021, November 25.

80 Froidure A, Mahsouli A, Liistro G, *et al.* Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. *Respir Med* 2021;**181**:106383. doi:10.1016/j.rmed.2021.106383

81 Smet J, Stylemans D, Hanon S, *et al.* Clinical status and lung function 10 weeks after severe SARS-CoV-2 infection. *Respir Med* 2021;**176**:106276. doi:10.1016/j.rmed.2020.106276

82 Aparisi Á, Ybarra-Falcón C, García-Gómez M, *et al.* Exercise Ventilatory Inefficiency in Post-COVID-19 Syndrome: Insights from a Prospective Evaluation. *J Clin Med* 2021;**10**:2591. doi:10.3390/jcm10122591

83 Gonzalez-Hermosillo JA, Martinez-Lopez JP, Carrillo-Lampon SA, *et al.* Post-Acute COVID-19 Symptoms, a Potential Link with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A 6-Month Survey in a Mexican Cohort. *Brain Sci* 2021;**11**. doi:https://dx.doi.org/10.3390/brainsci11060760

84 Shendy W, Elsherif AA, Ezzat MM, *et al.* Prevalence of fatigue in patients post Covid-19. *European Journal of Molecular and Clinical Medicine* 2021;**8**:1330–40.

85 D'cruz RF, Waller MD, Perrin F, *et al.* Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res* 2020;**7**:00655–2020. doi:10.1183/23120541.00655-2020

86 Andrade Barreto AP, Duarte LC, Cerqueira-Silva T, *et al.* Post-Acute COVID Syndrome, the Aftermath of Mild to Severe COVID-19 in Brazilian Patients. *medRxiv* 2021;:2021.06.07.21258520. doi:10.1101/2021.06.07.21258520

87 Taboada M, Moreno E, Cariñena A, *et al.* Quality of life, functional status, and persistent symptoms after intensive care of COVID-19 patients. *Br J Anaesth* 2021;**126**:e110–3. doi:10.1016/j.bja.2020.12.007

88 Taylor RR, Trivedi B, Patel N, *et al.* Post-COVID symptoms reported at asynchronous virtual review and stratified follow-up after COVID-19 pneumonia. *Clinical Medicine, Journal of the Royal College of Physicians of London* 2021;**21**. doi:http://dx.doi.org/10.7861/CLINMED.2021-0037

89 Daher A, Balfanz P, Cornelissen C, *et al.* Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020;**174**:106197. doi:http://dx.doi.org/10.1016/j.rmed.2020.106197

90 Liyanage-Don NA, Cornelius T, Sanchez JE, *et al.* Psychological Distress, Persistent Physical Symptoms, and Perceived Recovery After COVID-19 Illness. *J Gen Intern Med* 2021;**36**:2525–7. doi:10.1007/s11606-021-06855-w

91 Rogers JP, Chesney E, Oliver D, *et al.* Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 2020;**7**:611–27. doi:10.1016/S2215-0366(20)30203-0

92 Suarez-Robles M, Iguaran-Bermudez MDR, Garcia-Klepizg JL, *et al.* Ninety days post-hospitalization evaluation of residual covid-19 symptoms through a phone call check list. *Pan African Medical Journal* 2020;**37**:1–4. doi:http://dx.doi.org/10.11604/pamj.2020.37.289.27110

93 Voruz P, Allali G, Benzakour L, *et al.* Long COVID neuropsychological deficits after severe, moderate or mild infection. *medRxiv* 2021;:2021.02.24.21252329. doi:10.1101/2021.02.24.21252329

94 Weerahandi H, Hochman KA, Simon E, *et al.* Post-discharge health status and symptoms in patients with severe COVID-19. *medRxiv* 2020;:2020.08.11.20172742. doi:10.1101/2020.08.11.20172742

95 Domingo FR, Waddell LA, Cheung AM, *et al.* Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review. *medRxiv* 2021;:2021.06.03.21258317. doi:10.1101/2021.06.03.21258317

96 Stavem K, Einvik G, Ghanima W, *et al.* Prevalence and determinants of fatigue after covid-19 in non-hospitalized subjects: A population-based study. *Int J Environ Res Public Health* 2021;**18**:1–11. doi:http://dx.doi.org/10.3390/ijerph18042030

97 Daynes E, Gerlis C, Chaplin E, *et al.* Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort study. *Chron Respir Dis* 2021;**18**:14799731211015692. doi:https://dx.doi.org/10.1177/14799731211015691

98 Mirfazeli FS, Sarabi-Jamab A, kordi A, *et al.* Acute phase clinical manifestation of COVID-19 is linked to long-COVID symptoms; A 9-month follow-up study. *medRxiv* 2021;:2021.07.13.21260482. doi:10.1101/2021.07.13.21260482

99 Page MJ, Moher D, Bossuyt PM, *et al.* PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;:n160. doi:10.1136/bmj.n160

100 Ouzzani M, Hammady H, Fedorowicz Z, *et al.* Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;**5**:1–10. doi:10.1186/s13643-016-0384-4

101 Moola S, Munn Z, Tufanaru C, *et al.* Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. *JBI Manual for Evidence Synthesis*. 2020.

102 Sera F, Armstrong B, Blangiardo M, *et al.* An extended mixed-effects framework for meta-analysis. *Stat Med* 2019;**38**:5429–44. doi:10.1002/sim.8362

103 RStudio. RStudio: Integrated development environment for R. RStudio. 2020.

104 Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60. doi:10.1136/bmj.327.7414.557

105 Aiyegbusi OL, Hughes SE, Turner G, *et al.* Symptoms, complications and management of long COVID: a review. *J R Soc Med* 2021;**114**:428–42. doi:10.1177/01410768211032850

106 Falk RS, Amdal CD, Pe M, *et al.* Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review. *Quality of Life Research* Published Online First: 2021. doi:http://dx.doi.org/10.1007/s11136-021-02908-z

107 Cabrera Martimbianco AL, Pacheco RL, Bagattini AM, *et al.* Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. *Int J Clin Pract* 2021;**75**:e14357. doi:http://dx.doi.org/10.1111/ijcp.14357

108 Cha C, Baek G. Symptoms and management of long COVID: A scoping review. *J Clin Nurs* 2021;:No-Specified. doi:https://dx.doi.org/10.1111/jocn.16150

109 Fernandez-de-Las-Penas C, Palacios-Cena D, Gomez-Mayordomo V, *et al.* Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. *Eur J Intern Med* 2021;**92**:55–70. doi:https://dx.doi.org/10.1016/j.ejim.2021.06.009

110 Garg M, Maralakunte M, Bhatia V, *et al.* The conundrum of ‘long-covid-19’: A narrative review. *Int J Gen Med* 2021;**14**:2491–506. doi:http://dx.doi.org/10.2147/IJGM.S316708

111 Jennings G, Monaghan A, Xue F, *et al.* A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: Ongoing symptomatic phase vs. post-COVID-19 syndrome. *medRxiv* 2021;:2021.06.25.21259372. doi:10.1101/2021.06.25.21259372

112 Gavriatopoulou M, Ntanasis-Stathopoulos I, Kastritis E, *et al.* Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. *Journal of Infection* 2021;**83**:1–16. doi:http://dx.doi.org/10.1016/j.jinf.2021.05.004

113 Long Q, Li J, Hu X, *et al.* Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis. *Front Med (Lausanne)* 2021;**8**. doi:10.3389/fmed.2021.702635

114 Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open* 2021;**4**:e2111417. doi:https://dx.doi.org/10.1001/jamanetworkopen.2021.11417

115 Poudel AN, Zhu S, Cooper N, *et al.* Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One* 2021;**16**:e0259164. doi:https://dx.doi.org/10.1371/journal.pone.0259164

116 Rao S, Benzouak T, Gunpat S, *et al.* Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.23.21256006. doi:10.1101/2021.04.23.21256006

117 Sanchez-Ramirez DC, Normand K, Zhaoyun Y, *et al.* Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis. *Biomedicines* 2021;**9**. doi:https://dx.doi.org/10.3390/biomedicines9080900

118 Shanbehzadeh S, Tavahomi M, Ebrahimi-Takamjani I, *et al.* Physical and mental health complications post-COVID-19: Scoping review. *J Psychosom Res* 2021;**147**:110525. doi:http://dx.doi.org/10.1016/j.jpsychores.2021.110525

119 Wong TL, Weitzer DJ. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-A Systemic Review and Comparison of Clinical Presentation and Symptomatology. *Medicina (Kaunas)* 2021;**57**. doi:http://dx.doi.org/10.3390/medicina57050418

120 Chen C, Haupert SR, Zimmermann L, *et al.* Global prevalence of post-acute sequelae of COVID-19 (PASC) or long COVID: A meta-analysis and systematic review. *medRxiv* Published Online First: 2021. doi:https://dx.doi.org/10.1101/2021.11.15.21266377

121 Matcham F, Ali S, Hotopf M, *et al.* Psychological correlates of fatigue in rheumatoid arthritis: A systematic review. *Clin Psychol Rev* 2015;**39**:16–29. doi:10.1016/j.cpr.2015.03.004

122 Zhang X, Wang F, Shen Y, *et al.* Symptoms and Health Outcomes among Survivors of COVID-19 Infection 1 Year after Discharge from Hospitals in Wuhan, China. *JAMA Netw Open* 2021;**4**:e2127403. doi:http://dx.doi.org/10.1001/jamanetworkopen.2021.27403

123 Chen YK, Li T, Gong FH, *et al.* Predictors of Health-Related Quality of Life and Influencing Factors for COVID-19 Patients, a Follow-Up at One Month. *Front Psychiatry* 2020;**11**:668. doi:http://dx.doi.org/10.3389/fpsyt.2020.00668

124 Nehme M, Braillard O, Chappuis F, *et al.* Prevalence of Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in an Outpatient Setting. *Ann Intern Med* 2021;**174**:1252–60. doi:http://dx.doi.org/10.7326/M21-0878

125 Pauley E, Drake TM, Griffith DM, *et al.* Recovery from Covid-19 critical illness: a secondary analysis of the ISARIC4C CCP-UK cohort study and the RECOVER trial. *medRxiv* 2021;:2021.06.15.21258879. doi:10.1101/2021.06.15.21258879

126 Henneghan AM, Lewis KA, Gill E, *et al.* Describing cognitive function and psychosocial outcomes of COVID-19 survivors: A cross-sectional analysis. *J Am Assoc Nurse Pract* Published Online First: 2021. doi:http://dx.doi.org/10.1097/JXX.0000000000000647

127 Menges D, Ballouz T, Anagnostopoulos A, *et al.* Burden of Post-COVID-19 Syndrome and Implications for Healthcare Service Planning: A Population-based Cohort Study. *medRxiv* 2021;:2021.02.27.21252572. doi:10.1101/2021.02.27.21252572

128 Halpin SJ, McIvor C, Whyatt G, *et al.* Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;**93**:1013–22. doi:10.1002/jmv.26368

129 Shang YF, Liu T, Yu JN, *et al.* Half-year follow-up of patients recovering from severe COVID-19: Analysis of symptoms and their risk factors. *J Intern Med* 2021;**290**:444–50. doi:https://dx.doi.org/10.1111/joim.13284

130 Aul DR, Gates DJ, Draper DA, *et al.* Complications after discharge with COVID-19 infection and risk factors associated with development of post-COVID pulmonary fibrosis. *Respir Med* 2021;**188**:106602. doi:http://dx.doi.org/10.1016/j.rmed.2021.106602

131 Barizien N, Le Guen M, Russel S, *et al.* Clinical characterization of dysautonomia in long COVID-19 patients. *Sci Rep* 2021;**11**:14042. doi:http://dx.doi.org/10.1038/s41598-021-93546-5

132 Desgranges F, Tadini E, Munting A, *et al.* Post-COVID-19 syndrome in outpatients: a cohort study. *medRxiv* 2021;:2021.04.19.21255742. doi:10.1101/2021.04.19.21255742

133 Molnar T, Varnai R, Schranz D, *et al.* Severe Fatigue and Memory Impairment Are Associated with Lower Serum Level of Anti-SARS-CoV-2 Antibodies in Patients with Post-COVID Symptoms. *J Clin Med* 2021;**10**. doi:https://dx.doi.org/10.3390/jcm10194337

134 Rauch B, Kern-Matschilles S, Haschka SJ, *et al.* COVID-19-related symptoms 6 months after the infection - Update on a prospective cohort study in Germany. *medRxiv* 2021;:2021.02.12.21251619. doi:10.1101/2021.02.12.21251619

135 Sigfrid L, Drake TM, Pauley E, *et al.* Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *medRxiv* 2021;:2021.03.18.21253888. doi:10.1101/2021.03.18.21253888

136 Elkan M, Dvir A, Zaidenstein R, *et al.* Patient-Reported Outcome Measures After Hospitalization During the COVID-19 Pandemic: A Survey Among COVID-19 and Non-COVID-19 Patients. *Int J Gen Med* 2021;**14**:4829–36. doi:https://dx.doi.org/10.2147/IJGM.S323316

137 Guo L, Lin J, Ying W, *et al.* Correlation Study of Short-Term Mental Health in Patients Discharged After Coronavirus Disease 2019 (COVID-19) Infection without Comorbidities: A

Prospective Study. *Neuropsychiatr Dis Treat* 2020;**Volume 16**:2661–7. doi:10.2147/NDT.S278245

138 Mazza MG, Palladini M, De Lorenzo R, *et al.* One-year mental health outcomes in a cohort of COVID-19 survivors. *J Psychiatr Res* 2021;**145**:118–24. doi:https://dx.doi.org/10.1016/j.jpsychires.2021.11.031

139 Aydin S, Unver E, Karavas E, *et al.* Computed tomography at every step: Long coronavirus disease. *Respir Investig* 2021;**59**:622–7. doi:https://dx.doi.org/10.1016/j.resinv.2021.05.014

140 Lindahl A, Aro M, Reijula J, *et al.* Women report more symptoms and impaired quality of life: a survey of Finnish COVID-19 survivors. *Infect Dis* Published Online First: 2021. doi:http://dx.doi.org/10.1080/23744235.2021.1965210

141 Pérez-González A, Araújo-Ameijeiras A, Fernández-Villar A, *et al.* Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a prospective cohort study. *medRxiv* 2021;:2021.08.05.21261634. doi:10.1101/2021.08.05.21261634

142 Romero-Duarte Á, Rivera-Izquierdo M, Guerrero-Fernández de Alba I, *et al.* Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med* 2021;**19**. doi:10.1186/s12916-021-02003-7

143 Sykes DL, Holdsworth L, Jawad N, *et al.* Post-COVID-19 Symptom Burden: What is Long-COVID and How Should We Manage It? *Lung* 2021;**199**:113–9. doi:10.1007/s00408-021-00423-z

144 Boesl F, Audebert H, Endres M, *et al.* A Neurological Outpatient Clinic for Patients With Post-COVID-19 Syndrome — A Report on the Clinical Presentations of the First 100 Patients. *Front Neurol* 2021;**12**:738405. doi:10.3389/fneur.2021.738405

145 Iqbal A, Iqbal K, Ali SA, *et al.* The COVID-19 Sequelae: A Cross-Sectional Evaluation of Post-recovery Symptoms and the Need for Rehabilitation of COVID-19 Survivors. *Cureus* 2021;**13**. doi:10.7759/cureus.13080

146 Bek LM, Berentschot JC, Heijenbrok-Kal MH, *et al.* Symptoms persisting after hospitalization for COVID-19: 12 months interim results of the COFLOW study. *medRxiv* 2021;:2021.12.11.21267652. doi:10.1101/2021.12.11.21267652

147 Kashif A, Chaudhry M, Fayyaz T, *et al.* Follow-up of COVID-19 recovered patients with mild disease. *Sci Rep* 2021;**11**:13414. doi:https://dx.doi.org/10.1038/s41598-021-92717-8

148 Munblit D, Bobkova P, Spiridonova E, *et al.* Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clinical and Experimental Allergy* 2021;**51**:1107–20. doi:10.1111/cea.13997

3.

149 Townsend L, Dyer AH, Jones K, *et al.* Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020;**15**:e0240784. doi:http://dx.doi.org/10.1371/journal.pone.0240784

150 Venturelli S, Benatti S V, Casati M, *et al.* Surviving COVID-19 in Bergamo Province: A post-Acute outpatient re-evaluation. *Epidemiol Infect* Published Online First: 2021. doi:http://dx.doi.org/10.1017/S0950268821000145

151 Maamar M, Artime A, Pariente E, *et al.* Post-Covid-19 syndrome, inflammatory markers and sex differences. *medRxiv* 2021;:2021.07.07.21260092. doi:10.1101/2021.07.07.21260092

152 Augustin M, Schommers P, Stecher M, *et al.* Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. *The Lancet regional health Europe* 2021;**6**:100122. doi:https://dx.doi.org/10.1016/j.lanepe.2021.100122

153 Sathyamurthy P, Madhavan S, Pandurangan V. Prevalence, Pattern and Functional Outcome of Post COVID-19 Syndrome in Older Adults. *Cureus* 2021;**13**:e17189. doi:https://dx.doi.org/10.7759/cureus.17189

154 Gebhard CE, Sütsch C, Bengs S, *et al.* Sex- and Gender-specific Risk Factors of Post-COVID-19 Syndrome: A Population-based Cohort Study in Switzerland. *medRxiv* 2021;:2021.06.30.21259757. doi:10.1101/2021.06.30.21259757

155 Mantovani E, Mariotto S, Gabbiani D, *et al.* Chronic fatigue syndrome: an emerging sequela in COVID-19 survivors?. *J Neurovirol* 2021;**27**:631–7. doi:https://dx.doi.org/10.1007/s13365-021-01002-x

156 Latronico N, Peli E, Calza S, *et al.* Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax* 2021;:thoraxjnl-2021-218064. doi:10.1136/thoraxjnl-2021-218064

157 Ferraro F, Calafiore D, Dambruoso F, *et al.* COVID-19 related fatigue: Which role for rehabilitation in post-COVID-19 patients? A case series. *J Med Virol* 2020;:jmv.26717. doi:10.1002/jmv.26717

158 Clavario P, Marzo V De, Lotti R, *et al.* Assessment of functional capacity with cardiopulmonary exercise testing in non-severe COVID-19 patients at three months follow-up. *ERJ Open Res* 2020;**7**:2020.11.15.20231985. doi:10.1101/2020.11.15.20231985

159 Mancini DM, Brunjes DL, Lala A, *et al.* Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post-Coronavirus Disease. *JACC Heart Fail* 2021;**9**:927–37. doi:https://dx.doi.org/10.1016/j.jchf.2021.10.002

160 Raman B, Cassar MP, Tunnicliffe EM, *et al.* Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine* 2021;**31**:100683. doi:https://dx.doi.org/10.1016/j.eclinm.2020.100683

161 Agergaard J, Leth S, Pedersen TH, *et al.* Myopathic changes in patients with long-term fatigue after COVID-19. *Clinical Neurophysiology* 2021;**132**:1974–81. doi:http://dx.doi.org/10.1016/j.clinph.2021.04.009

162 Chen X, Li Y, Shao T-R, *et al.* Some characteristics of clinical sequelae of COVID-19 survivors from Wuhan, China: A multi-center longitudinal study. *Influenza Other Respir Viruses* Published Online First: 2021. doi:https://dx.doi.org/10.1111/irv.12943

163 O'Keefe JB, Minton HC, Morrow M, *et al.* Postacute Sequelae of SARS-CoV-2 Infection and Impact on Quality of Life 1-6 Months After Illness and Association With Initial Symptom Severity. *Open Forum Infect Dis* 2021;**8**:ofab352. doi:https://dx.doi.org/10.1093/ofid/ofab352

164 Jacobs LG, Gupta A, Rasouli L, *et al.* Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. *PLoS One* 2020;**15**:e0243882. doi:http://dx.doi.org/10.1371/journal.pone.0243882

165 Dini M, Poletti B, Tagini S, *et al.* Resilience, Psychological Well-Being and Daily Functioning Following Hospitalization for Respiratory Distress Due to SARS-CoV-2 Infection. *Healthcare (Basel)* 2021;**9**. doi:https://dx.doi.org/10.3390/healthcare9091161

166 Valent A, Dudoignon E, Ressaire Q, *et al.* Three-month quality of life in survivors of ARDS due to COVID-19: A preliminary report from a French academic centre. *Anaesth Crit Care Pain Med* 2020;**39**:740–1. doi:10.1016/j.accpm.2020.10.001

167 Dalbosco-Salas M, Torres-Castro R, Leyton AR, *et al.* Effectiveness of a primary care telerehabilitation program for post-covid-19 patients: A feasibility study. *J Clin Med* 2021;**10**:4428. doi:http://dx.doi.org/10.3390/jcm10194428

168 Nune A, Durkowski V, Titman A, *et al.* Incidence and risk factors of long COVID in the UK: a single-centre observational study. *J R Coll Physicians Edinb* 2021;**51**:338–43. doi:https://dx.doi.org/10.4997/JRCPE.2021.405

169 Garrigues E, Janvier P, Kherabi Y, *et al.* Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *Journal of Infection* 2020;**81**:e4–6. doi:10.1016/j.jinf.2020.08.029

170 Yildirim S, Ediboglu O, Kirakli C, *et al.* Do Covid-19 patients needing ICU admission have worse 6 months follow up outcomes when compared with hospitalized non-ICU patients? A prospective cohort study. *Intensive Care Med Exp* 2021;**9**. doi:http://dx.doi.org/10.1186/s40635-021-00415-6

171 Albu S, Zozaya NR, Murillo N, *et al.* What's going on following acute COVID-19? Clinical characteristics of patients in an out-patient rehabilitation program. *NeuroRehabilitation* 2021;**48**:469–80. doi:http://dx.doi.org/10.3233/NRE-210025

172 Schandl A, Hedman A, Lynga P, *et al.* Long-term consequences in critically ill COVID-19 patients: A prospective cohort study. *Acta Anaesthesiol Scand* 2021;**65**:1285–92. doi:https://dx.doi.org/10.1111/aas.13939

173 Morin L, Savale L, Montani D, *et al.* Four-Month Clinical Status of a Cohort of Patients after Hospitalization for COVID-19. *JAMA - Journal of the American Medical Association* Published Online First: 2021. doi:http://dx.doi.org/10.1001/jama.2021.3331

174 Sami R, Soltaninejad F, Amra B, *et al.* A one-year hospital-based prospective COVID- 19 open-cohort in the Eastern Mediterranean region: The Khorshid COVID Cohort (KCC) study. *PLoS One* 2020;**15**:e0241537. doi:http://dx.doi.org/10.1371/journal.pone.0241537

175 Anaya J-M, Rojas M, Salinas ML, *et al.* Post-COVID Syndrome. A Case Series and Comprehensive Review. *medRxiv* 2021;:2021.07.17.21260655. doi:10.1101/2021.07.17.21260655

176 Kanberg N, Simrén J, Edén A, *et al.* Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. *EBioMedicine* 2021;**70**:103512. doi:10.1016/j.ebiom.2021.103512

177 Noviello D, Costantino A, Muscatello A, *et al.* Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: A controlled cohort study. *Neurogastroenterology & Motility* 2021;:e14187. doi:10.1111/nmo.14187

178 Zhao Y, Yang C, An X, *et al.* Follow-up study on COVID-19 survivors one year after discharge from hospital. *Int J Infect Dis* 2021;**112**:173–82. doi:https://dx.doi.org/10.1016/j.ijid.2021.09.017

179 Strumiliene E, Zeleckiene I, Bliudzius R, *et al.* Follow-Up Analysis of Pulmonary Function, Exercise Capacity, Radiological Changes, and Quality of Life Two Months after Recovery from SARS-CoV-2 Pneumonia. *Medicina (Kaunas)* 2021;**57**. doi:http://dx.doi.org/10.3390/medicina57060568

180 Rass V, Ianosi B-A, Zamarian L, *et al.* Factors associated with impaired quality of life three months after being diagnosed with COVID-19. *Quality of Life Research* Published Online First: 28 September 2021. doi:10.1007/s11136-021-02998-9

181 Peghin M, Palese A, Venturini M, *et al.* Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. *Clinical Microbiology and Infection* 2021;**27**:1507–13. doi:10.1016/j.cmi.2021.05.033

182 Fang X, Ming C, Cen Y, *et al.* Post-sequelae one year after hospital discharge among older COVID-19 patients: A multi-center prospective cohort study. *J Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.jinf.2021.12.005

183 Labarca G, Henriquez-Beltran M, Lastra J, *et al.* Analysis of clinical symptoms, radiological changes and pulmonary function data 4 months after COVID-19. *Clin Respir J* 2021;**15**:992–1002. doi:https://dx.doi.org/10.1111/crj.13403

184 Van Den Borst B, Peters JB, Brink M, *et al.* Comprehensive Health Assessment 3 Months after Recovery from Acute Coronavirus Disease 2019 (COVID-19). *Clinical Infectious Diseases* 2021;**73**:E1089–98. doi:http://dx.doi.org/10.1093/cid/ciaa1750

185 van der Sar - van der Brugge S, Talman S, de Mol M, *et al.* Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respir Med* 2021;**176**:106272. doi:https://dx.doi.org/10.1016/j.rmed.2020.106272

186 Pilotto A, Cristillo V, Piccinelli SC, *et al.* Long-term neurological manifestations of COVID-19: prevalence and predictive factors. *Neurological Sciences* 2021;:2020.12.27.20248903. doi:10.1101/2020.12.27.20248903

187 Bottemanne H, Gouraud C, Hulot J-S, *et al.* Do Anxiety and Depression Predict Persistent Physical Symptoms After a Severe COVID-19 Episode? A Prospective Study. *Front Psychiatry* 2021;**12**:757685. doi:https://dx.doi.org/10.3389/fpsyt.2021.757685

188 Tomasoni D, Bai F, Castoldi R, *et al.* Anxiety and depression symptoms after virological clearance of COVID-19: A cross-sectional study in Milan, Italy. *J Med Virol* 2021;**93**:1175–9. doi:10.1002/jmv.26459

189 Silva LS, Joao RB, Nogueira MH, *et al.* Functional and microstructural brain abnormalities, fatigue, and cognitive dysfunction after mild COVID-19. *medRxiv* 2021;:2021.03.20.21253414. doi:10.1101/2021.03.20.21253414

190 Elanwar R, Hussein M, Magdy R, *et al.* Physical and mental fatigue in subjects recovered from covid-19 infection: A case-control study. *Neuropsychiatr Dis Treat* 2021;**17**:2063–71. doi:http://dx.doi.org/10.2147/NDT.S317027

191 Danesh V, Arroliga AC, Bourgeois JA, *et al.* Post-acute sequelae of COVID-19 in adults referred to COVID recovery clinic services in an integrated health system in Texas. *Baylor University Medical Center Proceedings* 2021;**34**:645–8. doi:10.1080/08998280.2021.1972688

192 Mandal S, Barnett J, Brill SE, *et al.* Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2020;**0**:1–3. doi:http://dx.doi.org/10.1136/thoraxjnl-2020-215818

193 Moradian ST, Parandeh A, Khalili R, *et al.* Delayed Symptoms in Patients Recovered from COVID-19. *Iran J Public Health* 2020;**49**:2120–7. doi:10.18502/ijph.v49i11.4729

194 Tiwari B, Ghimire M, Bhatta G, *et al.* Persistent Symptoms in Non-critical COVID-19 Patients at Two Months Follow-Up in a District Hospital: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc* 2021;**59**:550–3. doi:https://dx.doi.org/10.31729/jnma.6440

195 Tosato M, Carfi A, Martis I, *et al.* Prevalence and Predictors of Persistence of COVID-19 Symptoms in Older Adults: A Single-Center Study. *J Am Med Dir Assoc* 2021;**22**:1840–4. doi:http://dx.doi.org/10.1016/j.jamda.2021.07.003

196 Zulu JE, Banda D, Hines JZ, *et al.* Two-Month Follow-up of Persons with SARS-CoV-2 Infection—Zambia, September 2020. *medRxiv* 2021;:2021.06.15.21258964. doi:10.1101/2021.06.15.21258964

197 Ahmed H, Patel K, Greenwood DC, *et al.* Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. *J Rehabil Med* 2020;**52**:0. doi:10.2340/16501977-2694

198 Liu K, Zhang W, Yang Y, *et al.* Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. *Complement Ther Clin Pract* 2020;**39**:101166. doi:10.1016/j.ctcp.2020.101166

199 Herridge MS, Cheung AM, Tansey CM, *et al.* One-year outcomes in survivors of the acute respiratory distress syndrome. *New England Journal of Medicine* 2003;**348**:683–93. doi:10.1056/NEJMoa022450

200 Hatch R, Young D, Barber V, *et al.* Anxiety, Depression and Post Traumatic Stress Disorder after critical illness: a UK-wide prospective cohort study. *Crit Care* 2018;**22**:310. doi:10.1186/s13054-018-2223-6

201 Lam M, Wing Y, Yu M, *et al.* Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: Long-term follow-up. *Arch Intern Med* 2009;**169**:2142–7. doi:10.1001/archinternmed.2009.384

202 Wing YK, Leung CM. Mental health impact of severe acute respiratory syndrome: a prospective study. *Hong Kong Medical Journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicineedical journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicine* 2012;**18 Suppl 3**:24–7.

203 Morgul E, Jordan TR, Akyel S, *et al.* COVID-19 pandemic and psychological fatigue in Turkey. *Int J Soc Psychiatry* 2020;**67**:20764020941889. doi:http://dx.doi.org/10.1177/0020764020941889

204 Tessitore E, Handgraaf S, Poncet A, *et al.* Symptoms and quality of life at 1-year follow up of patients discharged after an acute COVID-19 episode. *Swiss Med Wkly* 2021;**151**:w30093. doi:https://dx.doi.org/10.4414/smw.2021.w30093

205 Soares MN, Eggelbusch M, Naddaf E, *et al.* Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J Cachexia Sarcopenia Muscle* 2022;**13**:11–22. doi:10.1002/jcsm.12896

206 Goertz YMJ, Van Herck M, Delbressine JM, *et al.* Persistent symptoms 3 months after a SARS-CoV-2 infection: The post-COVID-19 syndrome? *ERJ Open Res* 2020;**6**:1–10. doi:http://dx.doi.org/10.1183/23120541.00542-2020

207 Carfì A, Bernabei R, Landi F, *et al.* Persistent Symptoms in Patients After Acute COVID-19. *JAMA - Journal of the American Medical Association* 2020;**324**:603–5. doi:http://dx.doi.org/10.1001/jama.2020.12603

208 Dennis A, Wamil M, Alberts J, *et al.* Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021;**11**:e048391. doi:https://dx.doi.org/10.1136/bmjopen-2020-048391

209 Gautam N, Goyal S, Qureshi H, *et al.* Medium-term outcome of severe to critically ill patients with SARS-CoV-2 infection. *Clin Infect Dis* Published Online First: 2021. doi:http://dx.doi.org/10.1093/cid/ciab341

210 Darley DR, Dore GJ, Byrne AL, *et al.* Limited recovery from post-acute sequelae of SARS-CoV-2 at 8 months in a prospective cohort. *ERJ Open Res* 2021;**7**:00384–2021. doi:10.1183/23120541.00384-2021

211 Roth A, Chan PS, Jonas W. Addressing the Long COVID Crisis: Integrative Health and Long COVID. *Glob Adv Health Med* 2021;**10**:21649561211056596. doi:https://dx.doi.org/10.1177/21649561211056597

212 Asadi-Pooya AA, Akbari A, Emami A, *et al.* Risk Factors Associated with Long COVID Syndrome: A Retrospective Study. *Iran J Med Sci* 2021;**46**:428–36. doi:https://dx.doi.org/10.30476/ijms.2021.92080.2326

213 Chopra N, Chowdhury M, Kumar A, *et al.* Clinical predictors of long COVID-19 and phenotypes of mild COVID-19 at a tertiary care centre in India. *Drug Discov Ther* 2021;**15**:156–61. doi:http://dx.doi.org/10.5582/DDT.2021.01014

214 Novak P, Mukerji SS, Alabsi HS, *et al.* Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19. *Ann Neurol* Published Online First: 2021. doi:https://dx.doi.org/10.1002/ana.26286

215 Wong-Chew RM, Cabrera EXR, Valdez CAR, *et al.* Symptom Cluster Analysis of long COVID-19 in Patients Discharged from the Temporary COVID-19 Hospital in Mexico City: A Longitudinal Study. Published Online First: 1 June 2021. doi:10.20944/PREPRINTS202106.0011.V1

216 Sollini M, Morbelli S, Ciccarelli M, *et al.* Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study. *Eur J Nucl Med Mol Imaging* 2021;**48**:3187–97. doi:https://dx.doi.org/10.1007/s00259-021-05294-3

217 Vanichkachorn G, Newcomb R, Cowl CT, *et al.* Post-COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at Mayo Clinic and Characteristics of the

Initial Patient Cohort. *Mayo Clin Proc* 2021;**96**:1782–91. doi:https://dx.doi.org/10.1016/j.mayocp.2021.04.024

218 Kedor C, Freitag H, Meyer-Arndt L, *et al.* Chronic COVID-19 Syndrome and Chronic Fatigue Syndrome (ME/CFS) following the first pandemic wave in Germany – a first analysis of a prospective observational study. *medRxiv* 2021;:2021.02.06.21249256. doi:10.1101/2021.02.06.21249256

219 Chan JCK. Recovery pathway of post-SARS patients. Thorax. 2005;**60**:361–2. doi:10.1136/thx.2004.035972

Figure 1. PRISMA 2020 flow diagram

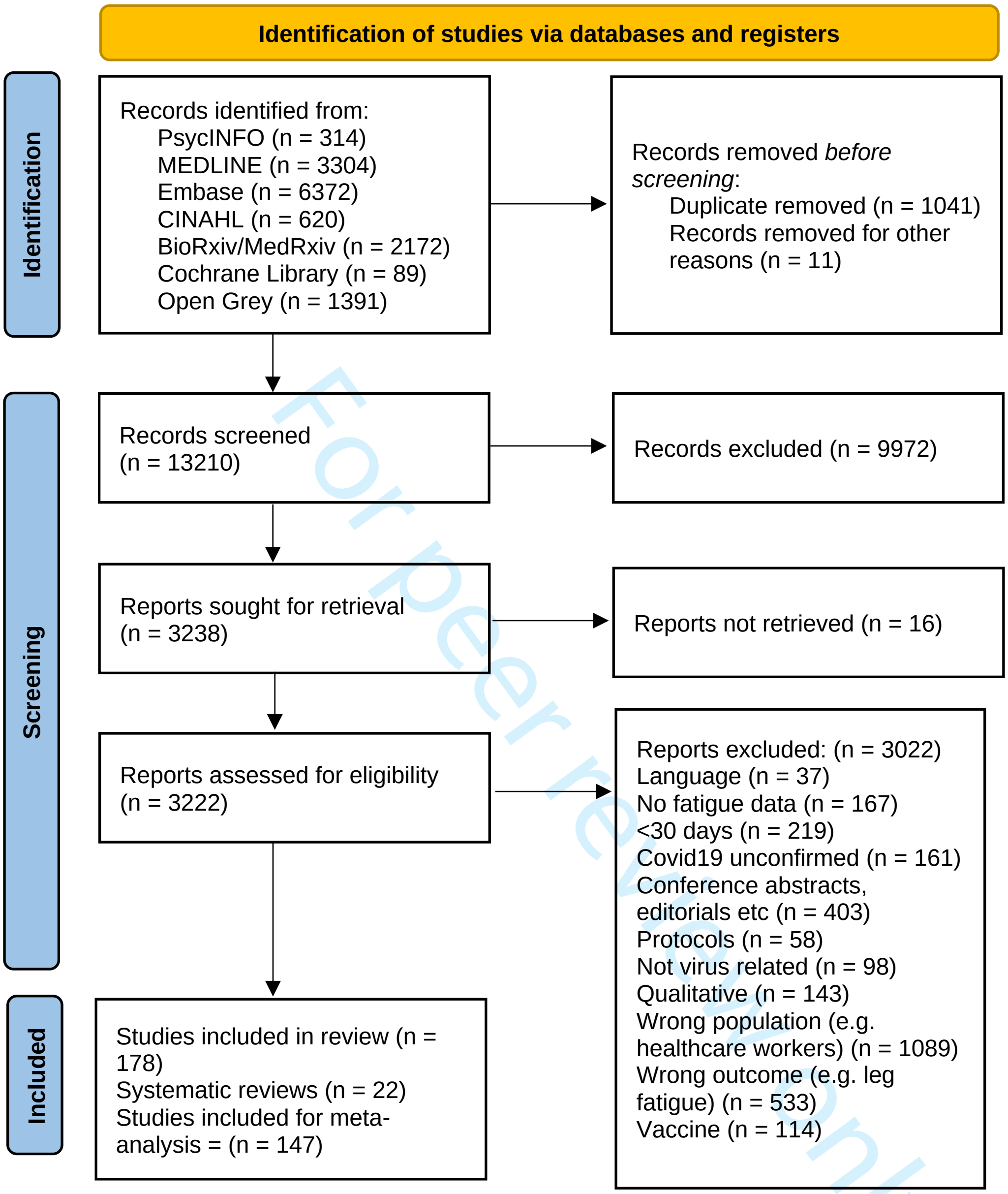


Figure 2. Forest plot for total fatigue proportions

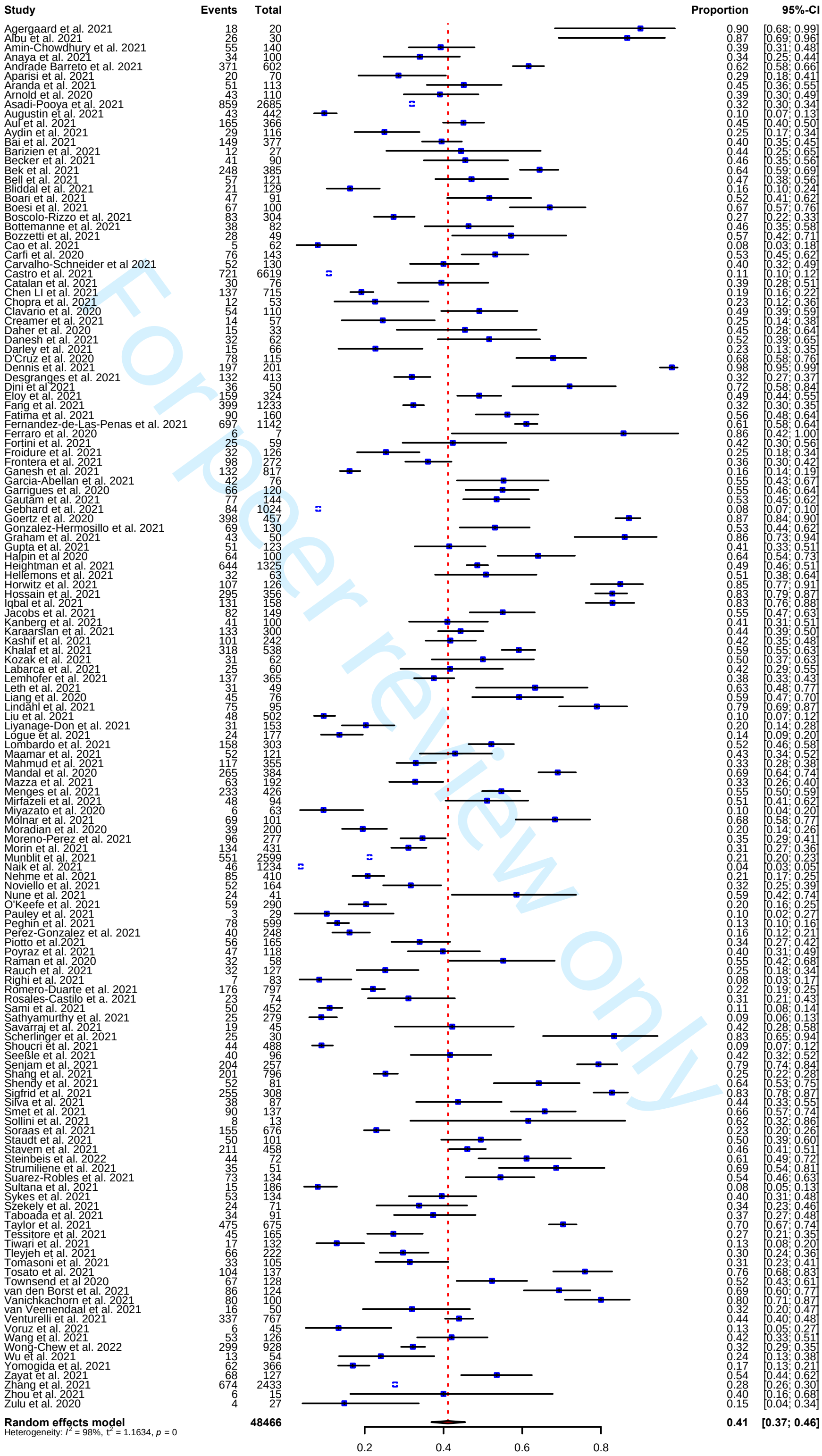
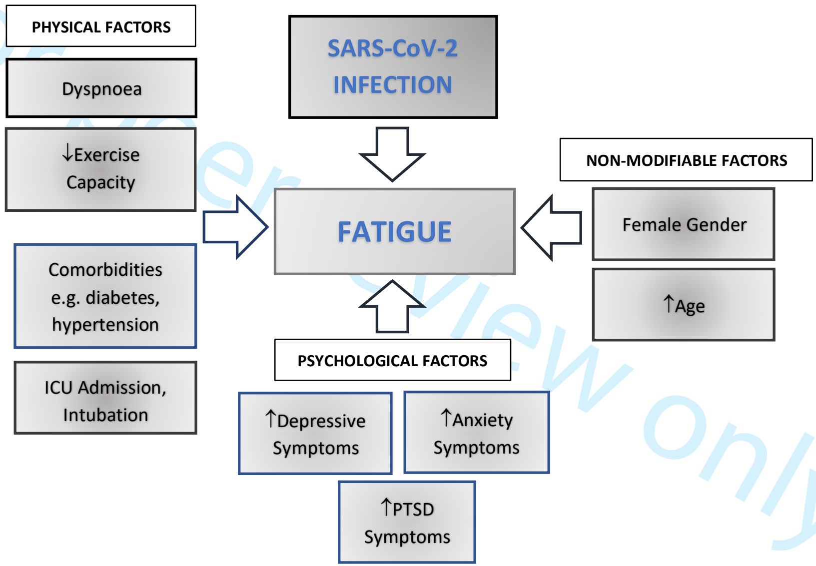


Figure 3. Diagram of fatigue associations



Supplementary File 1. PRISMA-P Protocol

TITLE:	PRISMA-P Protocol for a Systematic Review: Fatigue outcomes following COVID-19: A systematic review and meta-analysis	
REGISTRATION:	PROSPERO 2020 CRD42020201247	
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AMENDMENTS: Protocol amendments will be tracked, dated and numbered. The responsibility for tracking and registering changes to the protocol will be held by the 1st Reviewer with prior agreement and approval from the Senior

Reviewer. Final authorisation for any changes to the protocol will be from the Senior Reviewer.

A summary of changes table (Table 1, Appendix A.) will be utilised to track changes and record authorisations. An explanation and rationale for the amendments will be recorded in Table 2 (Appendix A.)

FUNDING: No specific funding has been obtained for this review.
This protocol was developed and designed in collaboration between all stated authors.

RATIONALE: Fatigue is a commonplace presenting symptom for a number of infectious diseases, including coronaviruses. Studies reporting fatigue in the current COVID-19 epidemic suggest a fatigue prevalence of between 18% in children to 100% in emergency department patients [1] during the acute phase. Fatigue has been implicated in increasing the risk for ICU care in some patients presenting with COVID-19, with a risk ratio of between 1.24 and 1.52. [2] Further, it is an emerging symptom associated with chronic stress among healthy populations during forced lockdown conditions, who reported increased somatic symptomology such as sleepiness, insomnia, headaches, digestive disturbances and fatigue compared to before lockdown conditions. [3]

Apart from acute clinical symptoms, fatigue may continue post-recovery or have a sudden onset following an acute viral infection. The current pandemic has revealed a considerable burden of lasting symptoms with approximately 1 in 4 people experiencing fatigue by one estimate. [4] Studies also indicate fatigue as one of the primary persistent symptoms. Systematic reviews indicate a pooled-prevalence of post-COVID-19 fatigue to vary between 45%, [5] 52% [6] and 64%. [7] For a considerable number of COVID-19 patients, fatigue symptoms extend beyond 3 months and represent the largest burden of post-infection symptomology. [8,9] This accords with evidence for post-viral fatigue in previous coronavirus outbreaks. One study investigating recovered SARS patients, found that 64% suffered continuing fatigue 3 months post-discharge and 60% experienced continuing fatigue at 12 months. [10] Another Hong Kong study reported 40.3% of recovered patients had chronic fatigue 4 years after contracting SARS and around 27% met the criteria for chronic fatigue syndrome.

Factors associated with post-illness fatigue include disease severity at the acute stage, which is more likely to require critical care or hospitalisation. [11–14] Physical factors have also been implicated in some studies. Reduced exercise capacity, for instance, is common in recovered patients even at 6 months post-infection and has been related to lower vitality. This is despite no concurrent impairments in pulmonary functions. [15] Although pulmonary functions are weakly related to fatigue, dyspnoea remains a problem for recovered patients, with studies indicating a positive correlation with fatigue. Other determinants include female gender, [16–19] and older age, particularly over 50 years old [20–22] have been related to worse fatigue following a COVID-19 infection. Psychological factors include anxiety, post-traumatic stress and depressive symptoms, which are frequent in survivors of respiratory viral infections, [23–25] have a consistent relationship with higher fatigue. Depression and PTSD, for instance, were related to fatigue severity in 402 post-Covid patients. [26]

Current systematic reviews and meta-analyses support fatigue as a primary symptom during COVID-19 recovery, which may persist for serval months post-infection. Given the potential to affect recovery, this review will add to the current body of knowledge in both prevalence and associations to potentially aid in developing interventions for fatigue outcomes following the current coronavirus pandemic. The overall aim is to investigate the prevalence of long-term fatigue outcomes in survivors of COVID-19.

This systematic review will comply with the PRISMA-P guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol. [27]

OBJECTIVES: The objective of this review are: (a) to examine the prevalence of continuing/persistent fatigue among recovered patients, (b) to explore potential explanatory variables associated with fatigue outcomes where data is available (e.g. psychological, physical and sociodemographic). The study objectives will utilise a PICO framework (Appendix B.)

METHODS:

Eligibility Criteria

- Original articles available in English;
- Studies with primary data;
- Studies reporting fatigue using a valid fatigue measure (e.g. Chalder Fatigue Questionnaire), the 'vitality' subscale of the SF-36 or SF-12 instruments or studies using a clinical interview, checklist or questionnaire with a fatigue item(s);
- Studies investigating fatigue occurring ≥ 30 days after the acute phase/hospitalisation or post-infection as defined in each article. Fatigue defined as 'post-discharge', 'post-hospitalisation', 'post-acute', 'post-illness' or 'post-onset' must have been measured at a median/mean time of ≥ 30 days.
- Patient populations with a diagnosis of SARS-CoV-2 (COVID-19) confirmed by RT-PCR, IgM/IgG serology or clinical assessment (e.g. CT scan, chest X-ray);
- Adults ≥ 18 years old;
- Letters containing primary data;
- Any study design including cohort, case-control, cross-sectional, randomised control trials, meta-analysis.

Exclusion criteria

- Pandemic fatigue (defined as 'worn out' by pandemic warnings, or by government safety instructions, or with media coverage, or with compliance requirements');
- 'Muscle fatigue', 'leg fatigue' and fatigue data combined with 'malaise' or 'muscle weakness';
- Fatigue associated with physical disorders (e.g. thyroiditis, Parkinson's disease, cancer);
- Pregnant participants; children and adolescents < 18 years old;

- Fatigue measured or reported as a clinical symptom during the 'acute phase' (defined as the period of hospitalisation or fatigue occurring < 30 days post-infection);
- Participants without a confirmed diagnosis of COVID-19 (i.e. participants who self-report a diagnosis), or studies including 'probable' cases;
- Fatigue among healthcare workers, which arising in the context of their work (e.g. burnout, compassion fatigue);
- Newspaper articles, conference papers/abstracts, editorials, opinions, background articles;
- Clinical or treatment procedures or protocols,
- Case reports and qualitative studies;
- COVID-19 vaccination studies, animals;
- Absence of outcome data (i.e. not quantified or reported in text).

Information sources:

PsycINFO, MEDLINE, EMBASE, CINAHL, OpenGrey, Cochrane Database of Systematic Reviews.

Search Strategy:

The search strategy will be piloted and amended where appropriate to select the most appropriate studies. An example of the search strategy is available in Appendix C. The search strategy language will be amended according to each database requirements.

Study Records:

The following data will be extracted and recorded in a spreadsheet: author(s), title, population and participant numbers, follow-up period, control/comparator, location, study inclusion/exclusion criteria, study design, study objectives, outcomes of interest, associations with fatigue, scales/instruments employed, results, effect size and power calculation (Y/N) In addition, the quality of each study (see Risk of Bias) will be indicated. A separate database will be compiled detailing the studies that will be fully-screened but excluded, together with the rationalisation for the exclusion.

Selection Process:

The 1st reviewer will conduct the initial search in the selected databases for relevant studies. The senior reviewer will review a proportion of the identified studies based on the inclusion and exclusion criteria. The senior reviewer will independently audit the selected studies and review the data extraction spreadsheet. Agreement for the final included studies for any meta-analysis and narrative review will be in collaboration. Disagreements will be settled through consensus and agreement. A PRISMA flow chart will be used to record the number of records collected, number of fully-screened records, number of records excluded, studies identified through reference lists and total number of records for inclusion in any meta-analysis.

Data items/collection:

The variables for the data to be recorded will include the following and will be entered into a data extraction spreadsheet:

- citation details
- target population & location (survivors, region/country),
- study eligibility criteria,
- population characteristics (sample size, socio-demographics)
- outcomes under study (fatigue, vitality),
- how the outcomes were measured (Chalder Fatigue Scale), [28] vitality scale of the SF-36/SF-12, including the definition of clinical outcomes for a scale, cut-off points, upper/lower scores, explanation of whether a high or low score is favourable,
- study variables (e.g. PTSD, depressive symptoms, exercise capacity),
- metrics (e.g. changes in fatigue),
- timing of outcome measurements (e.g. assessments at 6-week intervals),
- mean and standard deviations for each group,
- comparator group,
- effect size,
- time (baseline data and follow-up times e.g. 1 month, 3 months),
- study design and setting (e.g. hospital, outpatients, population),

- study methods (single, multicentre, parallel, cluster)

For randomised control trials:

- Intervention or comparator descriptions (e.g. drug type, control group, placebo group),
- Doses, times and frequencies, length of intervention,
- How an intervention was assessed, length of exposure, cumulative exposure,
- Integrity of the intervention (the degree to which the procedures were implemented as stated/planned),
- Post-intervention metrics (e.g. changes in fatigue, pre-post-test),
- Randomisation procedures,
- Adverse effects,

Results

- Number of participants in each stated group (including number of patients lost, withdrawn, lost to follow-up or excluded with reasons),
- Summary data for each group, each outcome and each time point (means and standard deviations for continuous data, OR for dichotomous data),
- Between-group estimates measuring effect of the intervention on the outcome (e.g. OR, RR, mean differences) and their confidence intervals
- Confounders measured.

In the event of incomplete data regarding the exposures or outcomes, effect sizes or other important data, reviewers will request this information from the authors. Where there is no response, the missing data will be calculated according to [29] or the paper will be excluded.

Risk of bias:

Risk of bias (RoB) assessment will be conducted for each included study using the relevant JBI tool. [30] The RoB will be conducted independently by three researchers. The assessments (e.g. good, moderate, poor) will be reported. A selection of reviews will be independently cross-checked by all 3 researchers to establish reliability of the assessments. Methods to summarise the RoB assessments for all the studies and a description of these assessments will be incorporated into the data synthesis (i.e. sensitivity analyses) and their potential influence on the findings will be discussed.

Data synthesis

This systematic review will employ a quantitative approach and provide a summary pooled estimate of the risk for fatigue, combining the results of all the studies where appropriate. Where 3 or more studies can be combined based on the same outcome measure, a meta-analysis will be performed. Where there are less than 3 studies identified for the same outcome, the effect sizes will be described in text. For the meta-analysis, we will compute odds ratios (OR) for binary outcomes to estimate the risk of fatigue relative to the exposure virus and target population (survivors), with 95% confidence intervals as an overall synthesised measure of effect size. For continuous outcomes, standardised mean differences for the combined effect size will be computed. Data from all studies will included in the analysis. Additional statistical tests may be conducted dependent upon data availability (e.g. fatigue outcome relative to gender, socioeconomic status, pre-existing psychiatric conditions etc).

It is expected that there will be considerable heterogeneity in study types and outcome measures, therefore it is expected that a random effects model will be performed for the meta-analysis to provide an estimate of the mean effect size for the included studies. The random effects model is expected to allow for wider heterogeneity and take account of the estimated between-study weight differences. To assess between-study-heterogeneity a Cochran's Q will be performed and the effect of heterogeneity will be quantified using the I^2 statistical-test. A value of 50% or greater for the I^2 will be considered as indicative of greater variability. A value of greater than 75% will be considered as considerable variability. Statistical measures of effect will be extracted from the included studies for calculating pooled effect sizes of the association between an included influenza virus and fatigue outcomes.

Effect sizes, 95% confidence intervals and statistical significance will be presented by quantitative and graphical representations (i.e. forest plots). Statistical significance will be set at $p < 0.05$ (2-tailed) for all analyses. Sensitivity analysis will be conducted utilising the RoB assessments across all the studies. For example, excluding low grade studies, studies with declared conflicts of interest. A funnel plot will be performed to assess publication bias.

Meta-bias(es)

In order to assess publication bias, funnel plots (observed for 10+ studies included in the meta-analysis) with an Egger test [31] to test asymmetry at alpha level 0.1 will be conducted.

Confidence in cumulative evidence

GRADE (Grading of Recommendations, Assessment, Development and Evaluation working group methodology) will be used to assess the quality of evidence for all outcomes. The quality of evidence will be assessed for risk of bias, consistency, directness, precision and publication bias. Quality will be judged as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect)

Reporting standards

The reporting of this systematic review will be in compliance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [32].

References

1 O'Reilly GM, Mitchell RD, Wu J, *et al.* Epidemiology and clinical features of emergency

department patients with suspected COVID-19: Results from the first month of the COVID-19 Emergency Department Quality Improvement Project (COVED-2). *Emerg Med Australas* 2020;:1742-6723.13573. doi:10.1111/1742-6723.13573

2 Zhao J, Gao Y, Huang W, *et al.* Risk factors for the exacerbation of patients with 2019 novel coronavirus: A meta-analysis. *Int J Med Sci* 2020;**17**:1744–50. doi:http://dx.doi.org/10.7150/ijms.47052

3 Majumdar P, Biswas A, Sahu S. COVID-19 pandemic and lockdown: cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. *Chronobiol Int* 2020;**37**:1191–200. doi:10.1080/07420528.2020.1786107

4 Badenoch JB, Rengasamy ER, Watson CJ, *et al.* Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. *medRxiv* 2021;:2021.04.30.21256413. doi:10.1101/2021.04.30.21256413

5 Hoshijima H, Mihara T, Seki H, *et al.* Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. *medRxiv* 2021;:2021.04.08.21255109. doi:10.1101/2021.04.08.21255109

6 Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, *et al.* Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Chron Respir Dis* 2021;**18**:147997312110022. doi:10.1177/14799731211002240

7 Malik P, Patel K, Pinto C, *et al.* Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* Published Online First: 2021. doi:https://dx.doi.org/10.1002/jmv.27309

8 Becker C, Beck K, Zumbrunn S, *et al.* Long COVID 1 year after hospitalisation for COVID-19: a prospective bicentric cohort study. *Swiss Med Wkly* 2021;**151**:w30091. doi:https://dx.doi.org/10.4414/smw.2021.w30091

9 Khalaf M, Bazeed SE, Abdel-Gawad M, *et al.* Prevalence and Predictors of Persistent Symptoms after Clearance of SARS-CoV-2 Infection: A Report from Egypt. *SSRN Electron J* Published Online First: 2020. doi:10.2139/ssrn.3727954

10 Tansey CM, Louie M, Loeb M, *et al.* One-year outcomes and health care utilization in survivors of severe acute respiratory syndrome. *Arch Intern Med* 2007;**167**:1312–20. doi:http://dx.doi.org/10.1001/archinte.167.12.1312

11 Rauch B, Kern-Matschilles S, Haschka SJ, *et al.* COVID-19-related symptoms 6 months after the infection - Update on a prospective cohort study in Germany. *medRxiv* 2021;:2021.02.12.21251619. doi:10.1101/2021.02.12.21251619

12 Zhang X, Wang F, Shen Y, *et al.* Symptoms and Health Outcomes among Survivors of COVID-19 Infection 1 Year after Discharge from Hospitals in Wuhan, China. *JAMA Netw Open* 2021;**4**:e2127403. doi:http://dx.doi.org/10.1001/jamanetworkopen.2021.27403

13 Van Den Borst B, Van Hees HWH, Van Helvoort H, *et al.* Comprehensive Health Assessment 3 Months after Recovery from Acute Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis* 2021;**73**:E1089–98. doi:http://dx.doi.org/10.1093/cid/ciaa1750

14 van der Sar - van der Brugge S, Talman S, de Mol M, *et al.* Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respir Med* 2021;**176**:106272. doi:http://dx.doi.org/10.1016/j.rmed.2020.106272

15 Bardakci MI, Ozkarafakili MA, Ozturk EN, *et al.* Evaluation of long-term radiological findings, pulmonary functions, and health-related quality of life in survivors of severe COVID-19. *J Med Virol* 2021;**93**:5574–81. doi:http://dx.doi.org/10.1002/jmv.27101

16 Amin-Chowdhury Z, Harris RJ, Aiano F, *et al.* Characterising post-COVID syndrome more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. *medRxiv* 2021;:2021.03.18.21253633. doi:10.1101/2021.03.18.21253633

17 Bai F, Tomasoni D, Falcinella C, *et al.* Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect* Published Online First: 2021. doi:https://dx.doi.org/10.1016/j.cmi.2021.11.002

18 Hellemons ME, Huijts S, Bek L, *et al.* Persistent Health Problems beyond Pulmonary Recovery up to 6 Months after Hospitalization for SARS-CoV-2; A Longitudinal Study of Respiratory, Physical and Psychological Outcomes. *Ann Am Thorac Soc* Published Online First: 2021. doi:https://dx.doi.org/10.1513/AnnalsATS.202103-340OC

19 Lombardo MDM, Foppiani A, Peretti GM, *et al.* Long-Term Coronavirus Disease 2019 Complications in Inpatients and Outpatients: A One-Year Follow-up Cohort Study. *Open forum Infect Dis* 2021;**8**:ofab384. doi:https://dx.doi.org/10.1093/ofid/ofab384

20 Daugherty SE, Guo Y, Heath K, *et al.* Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021;**373**:n1098. doi:https://dx.doi.org/10.1136/bmj.n1098

21 Qin ES, Gold LS, Hough CL, *et al.* Patient-Reported Functional Outcomes Thirty Days after Hospitalization for COVID-19. *PM R* Published Online First: 2021. doi:https://dx.doi.org/10.1002/pmrj.12716

22 Yomogida K, Zhu S, Rubino F, *et al.* Post-Acute Sequelae of SARS-CoV-2 Infection Among Adults Aged ≥18 Years — Long Beach, California, April 1–December 10, 2020. *MMWR Morb Mortal Wkly Rep* 2021;**70**:1274–7. doi:10.15585/mmwr.mm7037a2

23 Daher A, Balfanz P, Cornelissen C, *et al.* Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae. *Respir Med* 2020;**174**:106197. doi:http://dx.doi.org/10.1016/j.rmed.2020.106197

24 D'Cruz RF, Patel A, Perrin F, *et al.* Clinical, radiological, functional and psychological characteristics of severe covid-19 pneumonia survivors: A prospective observational cohort study. *Thorax* 2021;**76**:A34–5. doi:http://dx.doi.org/10.1136/thorax-2020-BTSabstracts.60

25 Liyanage-Don NA, Cornelius T, Sanchez JE, *et al.* Psychological Distress, Persistent Physical Symptoms, and Perceived Recovery After COVID-19 Illness. *J Gen Intern Med* 2021;**36**:2525–7. doi:10.1007/s11606-021-06855-w

26 Mazza MG, Palladini M, De Lorenzo R, *et al.* One-year mental health outcomes in a cohort of COVID-19 survivors. *J Psychiatr Res* 2021;**145**:118–24. doi:https://dx.doi.org/10.1016/j.jpsychires.2021.11.031

27 Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;**349**:g7647–g7647. doi:10.1136/bmj.g7647

28 Chalder T, Berelowitz G, Pawlikowska T, *et al.* Development of a fatigue scale. *J Psychosom Res* 1993;**37**:147–53. doi:10.1016/0022-3999(93)90081-P

29 Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60. doi:10.1136/bmj.327.7414.557

30 Moola S, Munn Z, Tufanaru C, *et al.* Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, eds. *JBI Manual for Evidence Synthesis*. 2020. https://synthesismanual.jbi.global

31 Egger M, Smith GD, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34. doi:10.1136/bmj.315.7109.629

32 Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. 2010;**340**:c869.https://doi.org/10.1136/bmj.c869

Appendix A

Table 1. SUMMARY OF CHANGES TABLE

Document	*Protocol Version Number*	*Date*	*Authorisation*
Amendment No. 1			
Amendment No. 2			
Amendment No. 3			
Amendment No. 4			
Current Protocol	*Final*	*12.12.22*	*TC*
Original	1.01	04.08.20	

Table 2. AMENDMENT RATIONALE

Section Number/Heading	***Description of Amendment***	***Rationale Summary***

Appendix B

PICOS

Patient/Population	Exposure	Comparison	Outcome
Adults	**COVID19 diagnosis**	**Where applicable**	**Fatigue**
Patients Survivors Outpatients Inpatients	SARS-CoV-2 COVID-19 n-CoV-2 2019-nCoV2 Coronavirus Socio-demographics COVID-19 severity ICU admission Ventilation status Anxiety symptoms Depressive symptoms PTSD symptoms Stress/distress Sleep Quality of life Physical functioning BMI Clinical factors (lung function, serology, CT scans) Comorbidities	Healthy controls Non-treatment Treatment as usual	Fatigue Vitality Low energy Chronic fatigue Tiredness Exhaustion Asthenia General fatigue Lethargy

Appendix C

Example Search Strategy

	Database	Search
	PSYCINFO	
1		("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").mp
2		exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp.
3		(COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp.
4		(covid19 or covid-19 or covid*).mp.
5		1 OR 2 OR 3 OR 4
6		chronic fatigue*. mp
7		(fatigue or tired*).mp [mesh word]. or exhaust*.tw.
8		((((quality adj2 life) or QoL or health related quality) adj2 life) or HRQoL).tw.
9		6 OR 7 OR 8
10		(5 and 9) not cancer not child* not adolescent* not vaccin* not burnout not HIV Limit 10 to up=”20190101-2021”

Supplementary File 2. Full search protocols

APA PSYCINFO

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").mp.659
2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 9867
3 "chronic fatigue*".mp. 3079
4 (fatigue or tired*).mp [mesh word]. or exhaust*.tw. 47997
5 ((((quality adj2 life) or QoL or health related quality) adj2 life) or HRQoL).tw. 80465
6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 14627
7 (covid19 or covid-19 or covid*).mp. 14685
8 1 or 2 or 6 or 7 15226
9 3 or 4 or 5 124345
10 (8 and 9) not cancer not child* not adolescent* not vaccin* not burnout not HIV 386
11 limit 10 to up="20190101-20211231" 314

MEDLINE(R) ALL

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").ab. 28273
2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 133179
3 "chronic fatigue*".mp. 7798
4 (fatigue or tired*).mp. 128687
5 ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).ab. 53118
6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 237888
7 (covid19 or covid-19 or covid*).mp. 230830
8 1 or 2 or 6 or 7 252264
9 3 or 4 or ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).mp. 182154
10 (8 and 9) not cancer not vaccin* not child* not adolescent* not burnout not HIV.mp. 4117
11 limit 10 to yr="2019-2021" 3304

EMBASE CLASSIC+EMBASE

1 ("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").ab.28257

2 exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp. 83683

3 "chronic fatigue*".mp. 13417

4 (fatigue or tired*).mp. 317550

5 ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).ab. 78429

6 (COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp. 242298

7 (covid19 or covid-19 or covid*).mp. 233333

8 1 or 2 or 6 or 7 269814

9 3 or 4 or ((((quality adj2 life) or QoL or health) adj1 related quality adj2 life) or HRQoL).mp. 394392

10 (8 and 9) not cancer not vaccin* not child* not adolescent* not burnout not HIV.mp. 7449

11 limit 10 to yr="2019-2021" 6372

CINAHL

1 MH coronavirus infections or corona virus or corona* 10,982

2 AB severe acute respiratory syndrome coronavirus 3,719

3 MH severe acute respiratory syndrome 556

4 MH covid-19 or Covid19 or SARS-CoV* or SARS-CoV-2 or SARSCoV2 or SARSCOV-2 or covid19 or covid* 50,545

5 AB ncov-2019 or nCoV-2 or 2019-nCoV* or nCoV2 8,774

6 AB nCov-2019 or nCoV-2 or 2019-nCov* or ncov2 8,570

7 MH fatigue or AB (fatigue or exhaustion or tiredness) or AB (health related quality of life or hrqol) 17,446

8 1 or 2 or 3 or 4 or 5 or 6 not HIV not child* not adolescent* not vaccin* not burnout 64,543

9 7 and 8 Limiters – published date: 20190101-20211231, English language 620

MEDRXIV & BIORXIV

For term "COVID-19 or SARS-CoV-2 or coronavirus AND fatigue or tired" and posted between "01 Jan, 2019 and 21 Dec, 2021"

Returned 2,172 results

COCHRANE LIBRARY

Title abstract keyword COVID-19 or covid19 or or covid-19 or covid* or "corona virus" or "coronavirus infection" or "SARS CoV-2" or "SARS-CoV-2" or "SARS-CoV*" or "SARSCOV2" or "SARSCOV-2" or "nCoV-2" or "2019-nCoV*" or nCoV2" or *keyword* "severe acute respiratory syndrome coronavirus" AND fatigue or "chronic fatigue" or tired* or exhaust* or "health related quality adj1 life" or HRQoL

Selected Facets: 2019-2021 (Publication date)

Returned 89 Cochrane Reviews

OPEN GREY

"COVID-19"

Returned 1,391 results

Supplementary file 3. Summary of systematic reviews

Author	Title	Study Design	Included Articles N.	Follow-up Time	Fatigue Prevalence & Associations	*p*
Aiyegbusi et al. (2021)	Symptoms, complications and management of long COVID: a review	Systematic review & Meta-analysis	24	1 month	47% (CI 31–63) 16 studies	
Badenoch et al. (2021)	Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis	Systematic review & Meta-analysis	51	Mean 77 days (Range 14-182)	24·4% (CI 17·5-32.9)	
Cabera Martimbianco et al. (2021)	Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review	Narrative systematic review	25	Post-infection or discharge	-	
Cares-Marambio et al. (2021)	Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review	Systematic review & Meta-analysis	9	Post-discharge	52% (CI 0.38–0.66)	
Cha & Baek et al. (2021)	Symptoms and management of long COVID: A scoping review	Scoping review	34	> 4 weeks	-	
Chen et al. (2021)	Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review	Systematic review & Meta-analysis	40	> 28 days	**Total (22 studies)** 23 (CI 0.13-0.38) **Hospitalised (8 studies)** 26 (CI 0.17-0.38)	
Domingo et al. (2021)	Prevalence of long-term effects in individuals diagnosed with COVID-19: a living systematic review	Living systematic review & Meta-analysis	36	4-12 weeks ≥ 12 weeks	**4-12 weeks** 51%, (CI: 39-64) **≥ 12 weeks** 47%, (CI: 27-68)	
Falk et al. (2021)	Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review	Narrative systematic review	339	1-4 months post-discharge	-	
Fernandez-de-Las-Penas et al. (2021)	Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis	Systematic review & Meta-analysis	33	30, 60, 90 days post-virus	**30 days** 11.7% (CI 3.1-35.3) **60 days** 56.2% (CI 28.3-80.7) **≥ 90 days** 35.3% (CI 25.3-46.8)	
Garg et al. (2021)	The Conundrum of 'Long-COVID-19': A Narrative Review	Systematic Review	212	-	-	
Gavriatopoulou et al. (2021)	Epidemiology and organ specific sequelae of post-acute COVID 19: A narrative review	Narrative Systematic review	12	> 4 weeks	-	

Author	Title	Study Design	Included Articles N.	Follow-up Time	Fatigue Prevalence & Associations	*p*
Hoshijima et al. (2021)	Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis	Systematic review & Meta-analysis (RAPID)	35	1 month	45% (32-59%)	
Jennings et al. (2021)	A systematic review of persistent symptoms and residual abnormal functioning following acute COVID-19: Ongoing symptomatic phase vs. post-COVID-19 syndrome	Systematic review & Meta-analysis	39	> 4 weeks	**Symptoms (16 studies)** 44% (CI 10-71) **Ongoing Symptoms (19 studies** 43% (CI 5-83)	
Long et al. (2021)	Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis	Systematic review & Meta-analysis	16	> 1 month Post-discharge	47%	
Malik et al. (2021)	Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis	Systematic review & Meta-analysis	22	Post-Covid	**Pooled Total** 64% **Quality of life** OR 1.06	.001
Nasserie et al. (2021)	Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review	Systematic review	45	2 months	Median 39.8% (IQR, 31.4-59.0%) 25 studies	
Poudel et al. (2021)	Impact of Covid-19 on health-related quality of life of patients: A structured review	Rapid review	12	> 4 weeks post-discharge	-	
Rao et al. (2021)	Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; a systematic review and meta-analysis	Systematic review & Meta-analysis	41	1-6 months Post-infection	**1-2 months** 52.7% ER 0.517 **2-3 months** 47.8% ER 0.527 **Female Gender** OR 1.782	
Rogers et al. (2020)	Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: A systematic review and meta-analysis with comparison to the COVID-19 pandemic	Meta-analysis	4	Post-illness	61 (19.3%)	
Sanchez-Ramirez et al. (2021)	Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis	Systematic review & Meta-analysis	24	4 months	38% 15 articles	
Shanbehzadeh et al. (2021)	Physical and mental health complications post-Covid-19: Scoping review	Scoping Systematic Review	34	3 months	-	

Author	Title	Study Design	Included Articles N.	Follow-up Time	Fatigue Prevalence & Associations	*p*
Wong et al. (2021)	Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology	Narrative systematic review	21	> 1 month	-	

Supplementary file 4. Quality Assessments for all included studies

Cohort

Study	*Were the groups similar & recruited from the same population?*	*Were the exposures measured similarly to assign people to exposed & unexposed groups?*	*Was the exposure measured in a valid & reliable way?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?*	*Were the outcomes measured in a valid & reliable way?*	*Was the follow up time reported & sufficient to be long enough for outcomes to occur?*	*Was follow up complete, & if not, were the reasons to loss to follow up described & explored?*	*Were strategies to address incomplete follow up utilized?*	*Was appropriate statistical analysis used?*	*Overall appraisal*
Amin-Chowdhury et al. 2021	Y	Y	Y	Y	Y	N	N	Y	?	N	Y	Low
Aparisi et al. 2021	Y	Y	Y	N	N	N	N	Y	Y	NA	Y	Moderate
Aranda et al. 2021	Y	-	Y	Y	Y	?	N	Y	?	?	Y	Moderate
Arnold et al. 2020	Y	Y	Y	N	N	N	Y	Y	N	N	Y	Moderate
Asadi-Pooya et al. 2021	Y	-	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Augustin et al. 2021	Y	Y	Y	Y	?	N	N	Y	Y	Y	Y	Moderate
Aul et al. 2021	Y	Y	Y	?	Y	?	N	Y	N	N	Y	Moderate
Aydin et al. 2021	-	-	Y	Y	Y	?	Y	Y	N	N	Y	Moderate
Bai et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Moderate
Bardakci et al. 2021	Y	Y	Y	N	N	?	Y	Y	N	N	Y	Moderate
Barizien et al. 2021	Y	Y	Y	N	N	N	N	Y	N	N	Y	Low
Becker et al. 2021	Y	Y	?	Y	Y	?	N	Y	Y	N	Y	Low
Bek et al. 2021	Y	Y	Y	?	?	N	Y	Y	Y	?	Y	Moderate
Bell et al. 2021	Y	Y	Y	?	N	N	N	Y	Y	Y	Y	Moderate
Bliddal et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Boari et al. 2021	Y	Y	Y	?	Y	N	N	Y	Y	Y	Y	Moderate
Boscolo-Rizzo et al. 2021	Y	-	Y	N	Y	?	N	Y	?	N	Y	Moderate
Bottemane et al. 2021	Y	?	Y	Y	Y	N	N	Y	Y	Y	Y	Moderate
Bozzetti et al. 2021	Y	Y	Y	N	N	?	N	Y	N	N	Y	Low
Cao et al. 2021	?	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	High
Carfi et al. 2020	Y	?	Y	Y	N	N	N	Y	?	N	Y	Low
Carvalho-Schneider et al. 2021	Y	Y	Y	?	Y	N	N	Y	Y	Y	Y	Moderate
Catalan et al. 2021	Y	Y	Y	Y	?	N	?	Y	?	?	Y	Low
Chen et al. 2021	Y	-	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Chopra et al. 2021	Y	Y	Y	Y	Y	N	N	Y	-	-	Y	Moderate
Clavario et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Creamer et al. 2021	Y	Y	Y	N	N	?	N	Y	?	?	Y	Low
Daher et al. 2021	Y	-	Y	N	N	?	N	Y	Y	?	Y	Moderate
Dalbosco-Salas et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	?	Y	Moderate
Darley et al. 2021	Y	?	Y	Y	Y	N	Y	Y	Y	Y	Y	High
Daugherty et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	-	-	Y	High
Daynes et al. 2021	Y	?	?	?	?	N	Y	Y	Y	?	Y	Low
D'Cruz et al. 2021	Y	Y	Y	Y	Y	N	Y	Y	-	-	Y	Moderate
Dennis et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	High
Desgranges et al. 2021	Y	Y	Y	Y	Y	?	N	Y	-	-	Y	Moderate
Donaghy et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Eloy et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Moderate
Evans et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Fang et al. 2021	Y	Y	Y	Y	Y	?	?	Y	Y	Y	Y	Moderate
Fatima et al. 2021	Y	Y	Y	N	N	N	N	Y	?	N	Y	Low
Fernandez-de-las-Penas et al. 2021	Y	Y	Y	N	Y	N	Y	Y	-	-	Y	Moderate
Fortini et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate

Study	*Were the groups similar & recruited from the same population?*	*Were the exposures measured similarly to assign people to exposed & unexposed groups?*	*Was the exposure measured in a valid & reliable way?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?*	*Were the outcomes measured in a valid & reliable way?*	*Was the follow up time reported & sufficient to be long enough for outcomes to occur?*	*Was follow up complete, & if not, were the reasons to loss to follow up described & explored?*	*Were strategies to address incomplete follow up utilized?*	*Was appropriate statistical analysis used?*	*Overall appraisal*
Froidure et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Frontera et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Gamberini et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	N	N	Y	Moderate
Garcia-Abellan et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Garrigues et al. 2020	Y	Y	Y	N	N	N	N	Y	Y	N	Y	Low
Gebhard et al. 2021	-	Y	Y	?	Y	?	N	Y	-	-	Y	Moderate
Goertz et al. 2021	N	Y	Y	Y	Y	?	N	Y	-	-	Y	Moderate
Gonzalez-Hermosillo et al. 2021	Y	Y	Y	?	Y	N	Y	Y	N	?	Y	Moderate
Graham et al. 2021	Y	Y	Y	?	Y	?	Y	Y	?	?	Y	Moderate
Guo Lin et al. 2020	Y	?	Y	Y	Y	?	Y	Y	?	?	Y	Moderate
Gupta et al. 2021	Y	?	Y	N	N	?	N	Y	N	N	Y	Moderate
Heightman et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Hellemons et al. 2021	N	N	Y	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Henneghan et al. 2021	Y	-	Y	Y	Y	N	Y	Y	N	N	y	Moderate
Horwitz et al. 2021	Y	-	Y	N	N	?	Y	Y	Y	N	Y	Low
Hossain et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Jacobs et al. 2021	Y	Y	Y	?	Y	N	Y	Y	Y	N	Y	Moderate
Kanberg et al. 2021	Y	Y	Y	?	Y	?	Y	Y	N	N	Y	Moderate
Karaarslan et al. 2021	Y	Y	Y	Y	Y	?	N	Y	?	?	Y	Moderate
Kayaaslan et al. 2021	Y	?	Y	N	N	?	N	Y	N	N	Y	Moderate
Kedor et al. 2021	Y	?	Y	N	N	Y	Y	Y	N	N	Y	Moderate
Khalaf et al. 2021	Y	Y	Y	N	Y	N	N	Y	Y	?	Y	Moderate
Kozak et al. 2021	Y	Y	Y	Y	N	N	N	Y	-	-	Y	Moderate
Latronico et al. 2021	?	Y	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Leth et al. 2021	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Moderate
Liang et al. 2021	Y	Y	Y	Y	N	?	N	Y	Y	N	Y	Moderate
Lindahl et al. 2021	Y	Y	Y	Y	Y	N	Y	Y	Y	-	Y	Moderate
Liu et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	?	Y	Moderate
Logue et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Lombardo et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Mahmud et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	?	Y	Moderate
Mancini et al. 2021	Y	Y	Y	N	N	?	Y	Y	N	N	Y	Moderate
Mantovani et al. 2021	-	Y	Y	N	N	Y	Y	Y	?	?	Y	Low
Mazza et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Menges et al. 2021	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	High
Mirfazeli et al. 2021	Y	Y	Y	N	Y	?	Y	Y	Y	?	Y	Low
Miyazato et al. 2020	Y	?	Y	N	N	N	N	Y	N	N	Y	Low
Molnar et al. 2021	Y	Y	Y	N	Y	?	Y	Y	Y	N	Y	Moderate
Moreno-Perez et al. 2021	Y	-	Y	Y	Y	?	N	Y	Y	?	Y	Moderate
Morin et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	Y	Y	Moderate
Munblit et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	Y	Y	Moderate
Naik et al. 2021	Y	Y	Y	N	Y	?	N	Y	Y	N	Y	Moderate
Nehme et al. 2021	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Moderate
Novak et al. 2021	Y	Y	Y	Y	N	N	Y	?	?	?	Y	Low
Nune et al. 2021	Y	?	Y	Y	Y	?	N	Y	N	?	Y	Moderate

Study	*Were the groups similar & recruited from the same population?*	*Were the exposures measured similarly to assign people to exposed & unexposed groups?*	*Was the exposure measured in a valid & reliable way?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?*	*Were the outcomes measured in a valid & reliable way?*	*Was the follow up time reported & sufficient to be long enough for outcomes to occur?*	*Was follow up complete, & if not, were the reasons to loss to follow up described & explored?*	*Were strategies to address incomplete follow up utilized?*	*Was appropriate statistical analysis used?*	*Overall appraisal*
Pauley et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	N	Y	Moderate
Peghin et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Pérez-González et al. 2021	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Moderate
Pilotto et al. 2021	Y	Y	Y	Y	Y	?	N	Y	N	N	Y	Low
Raman et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	N	?	Y	Moderate
Rass et al. 2021	Y	Y	y	N	Y	?	Y	Y	Y	N	Y	Moderate
Rauch et al. 2021	Y	Y	Y	N	N	?	N	Y	Y	Y	Y	Moderate
Righi et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	?	Y	Moderate
Romero-Duarte et al. 2021	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Moderate
Rosales- Castillo et al. 2021	-	-	Y	N	N	N	?	Y	?	?	Y	Low
Sami et al. 2020	Y	Y	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Sathyamurthy et al. 2021	Y	Y	Y	N	N	?	N	Y	Y	N	Y	Low
Savarraj et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	N	Y	Low
Schandl et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Moderate
Scherlinger et al. 2021	Y	Y	Y	N	Y	N	Y	Y	Y	?	Y	Moderate
Seeßle et al. 2021	Y	?	Y	N	N	?	Y	Y	Y	N	Y	Moderate
Shang et al. 2021	Y	Y	Y	N	Y	?	N	Y	N	N	Y	Low
Sigfrid et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	N	Y	Moderate
Soraas et al. 2021	Y	Y	Y	N	Y	?	Y	Y	N	N	Y	Moderate
Staudt et al. 2021	Y	Y	Y	Y	Y	?	N	Y	Y	Y	Y	Moderate
Steinbeis et al. 2021	Y	?	Y	Y	Y	?	N	Y	Y	N	Y	Moderate
Strumiliene et al. 2021	Y	Y	Y	Y	Y	N	Y	Y	Y	?	Y	Moderate
Sykes et al. 2021	Y	Y	Y	N	Y	N	N	Y	Y	N	Y	Moderate
Szekely et al. 2021	Y	Y	Y	?	Y	?	?	Y	Y	Y	Y	Moderate
Taboada et al. 2021	Y	?	Y	:	Y	?	N	Y	?	?	Y	Low
Taylor et al. 2021	Y	Y	Y	N	N	?	Y	Y	-	-	Y	Moderate
Tessitore et la. 2021	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Moderate
Tleyjeh et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	N	N	Y	Moderate
Valent et al. 2020	?	Y	Y	N	?	?	Y	Y	N	N	Y	Moderate
Van den Borst et al. 2021	Y	Y	Y	N	N	?	N	N	Y	?	Y	Moderate
van der Sar- van der Brugge et al.2021	Y	Y	Y	N	N	?	Y	N	Y	?	Y	Moderate
van Veenendaal et al. 2021	Y	N	Y	N	N	?	N	Y	Y	-	Y	Moderate
Venturelli et al. 2021	Y	Y	Y	N	N	?	Y	Y	Y	-	Y	Moderate
Voruz et al. 2021	Y	Y	Y	Y	Y	?	Y	Y	Y	-	Y	Moderate
Wang et al. 2021	Y	?	Y	N	N	?	?	Y	?	N	Y	Low
Weerahandi et al. 2020	Y	?	Y	N	N	?	N	Y	Y	Y	Y	Low
Wong-Chew et al. 2022	Y	Y	Y	Y	Y	?	N	Y	N	?	Y	Moderate
Wu et al. 2021	Y	Y	Y	N	N	?	N	Y	Y	-	Y	Moderate
Yildirim et al. 2021	Y	Y	Y	N	N	?	Y	Y	N	N	Y	Moderate
Yomogida et al. 2021	Y	?	Y	Y	Y	N	N	Y	Y	?	Y	Moderate
Zayat et al. 2021	Y	Y	Y	N	N	N	N	Y	Y	?	Y	Low
Zhang et al. 2021	Y	Y	Y	?	Y	?	N	Y	Y	Y	Y	Moderate
Zhao Yang et al. 2021	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Moderate
Zulu et al. 2020	Y	?	Y	N	N	?	Y	N	?	N	Y	Low

Cross-sectional

Study	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects & the setting described in detail?	Was the exposure measured in a valid & reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid & reliable way?	Was appropriate statistical analysis used?	*Overall appraisal*
Albu et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Low
Andrade Barreto et al. 2021	Y	Y	Y	Y	N	?	N	Y	Moderate
Boesl et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Danesh et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Dini et al. 2021	Y	Y	Y	Y	N	Y	N	Y	Moderate
Ganesh et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Halpin et al. 2020	Y	Y	Y	Y	N	N	Y	Y	Moderate
Iqbal et al. 2021	Y	Y	Y	Y	N	N	N	Y	Moderate
Kashif et al. 2021	Y	Y	Y	Y	N	N	N	Y	Low
Labarca et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Lemhofer et al. 2021	Y	Y	Y	Y	N	N	Y	Y	Moderate
Liyanage-Don et al. 2021	Y	Y	?	?	Y	Y	N	Y	Low
Maamar et al. 2021	N	Y	Y	Y	?	Y	N	Y	Moderate
Mandal et al. 2020	Y	Y	Y	Y	N	N	N	Y	Moderate
Moradian et al. 2020	Y	Y	Y	Y	N	Y	N	Y	Moderate
O'Keefe et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Moderate
Poyraz et al. 2021	Y	Y	Y	Y	N	Y	N	Y	Moderate
Qin et al. 2021	Y	Y	Y	Y	?	?	Y	Y	Moderate
Senjam et al. 2021	Y	Y	Y	Y	?	Y	N	Y	Low
Shendy et al. 2020	Y	Y	Y	Y	N	N	Y	Y	Moderate
Silva et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Smet et al. 2021	N	N	Y	Y	Y	N	N	Y	Low
Stavem et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Suarez-Robles et al. 2021	Y	Y	Y	Y	N	N	N	Y	Moderate
Sultana et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Moderate
Tiwari et al. 2021	Y	Y	Y	Y	N	N	N	Y	Moderate
Tomasoni et al. 2021	Y	Y	Y	Y	Y	Y	N	Y	Moderate
Tosato et al. 2021	Y	Y	Y	Y	N	Y	N	Y	Moderate
Townsend et al. 2020	Y	Y	Y	Y	?	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

Case series

Study	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	*Overall appraisal*
Anaya et al. 2021	Y	N	Y	Y	N	N	Y	Y	N	Y	Low
Ferraro et al. 2020	Y	Y	Y	Y	N	Y	Y	Y	?	Y	Low
Gautam et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High

Study	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?	*Overall appraisal*
Shoucri et al. 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Vanichkachorn et al. 2021	Y	Y	Y	?	Y	Y	Y	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

Case-control studies

Study	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Were cases & controls matched appropriately?	Were the same criteria used for identification of cases & controls?	Was exposure measured in a standard, valid & reliable way?	Was exposure measured in the same way for cases & controls?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were outcomes assessed in a standard, valid & reliable way for cases & controls?	Was the exposure period of interest long enough to be meaningful?	Was appropriate statistical analysis used?	Overall appraisal
Agergaard et al. 2021	Y	Y	Y	Y	Y	Y	N	?	Y	Y	Moderate
Castro et al. 2021	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	High
Elanwar et al. 2021	Y	?	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Elkan et al. 2021	Y	Y	Y	Y	N	N	N	Y	Y	Y	Moderate
Noviello et al. 2021	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Moderate
Ortelli et al. 2021	Y	Y	?	Y	Y	?	?	Y	Y	Y	Moderate
Sollini et al. 2021	Y	Y	Y	Y	?	Y	N	N	Y	Y	Moderate
Zhou et al. 2021	Y	Y	?	Y	Y	N	N	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

Randomised Controlled Trials

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	Overall appraisal
Chen, Liu et al. 2021	Y	Y	Y	-	Y	Y	Y	?	Y	Y	Y	Y	Y	Moderate
Chudzik et al. 2021	N	?	Y	Y	N	?	Y	?	Y	Y	Y	Y	?	Low
Liu et al. 2020	Y	?	Y	?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate

Low = low quality assessment; moderate = moderate quality assessment; high = good quality assessment

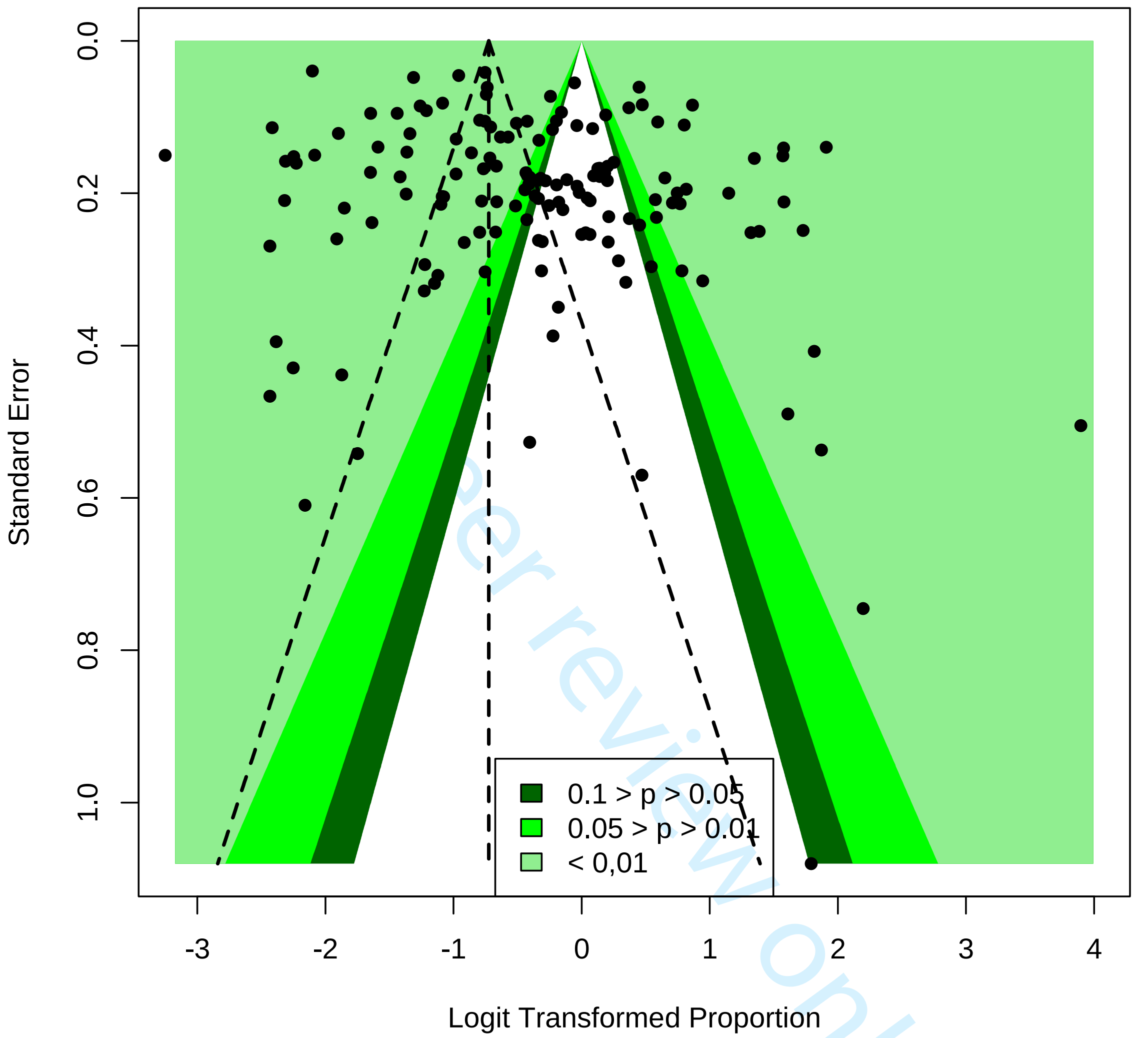
Randomised controlled trials JBI items

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomized?

10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

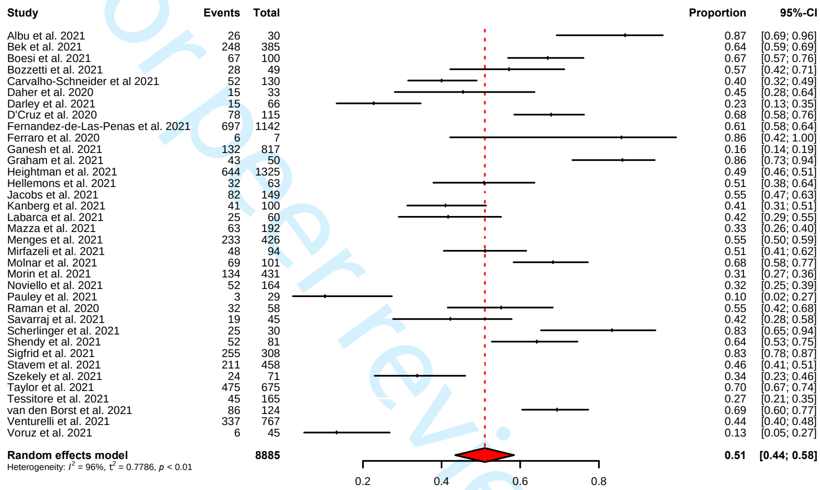
Supplementary file 5.

Funnel plot for total fatigue proportions



Supplementary file 6.

Forest plot for fatigue proportions using a valid scale

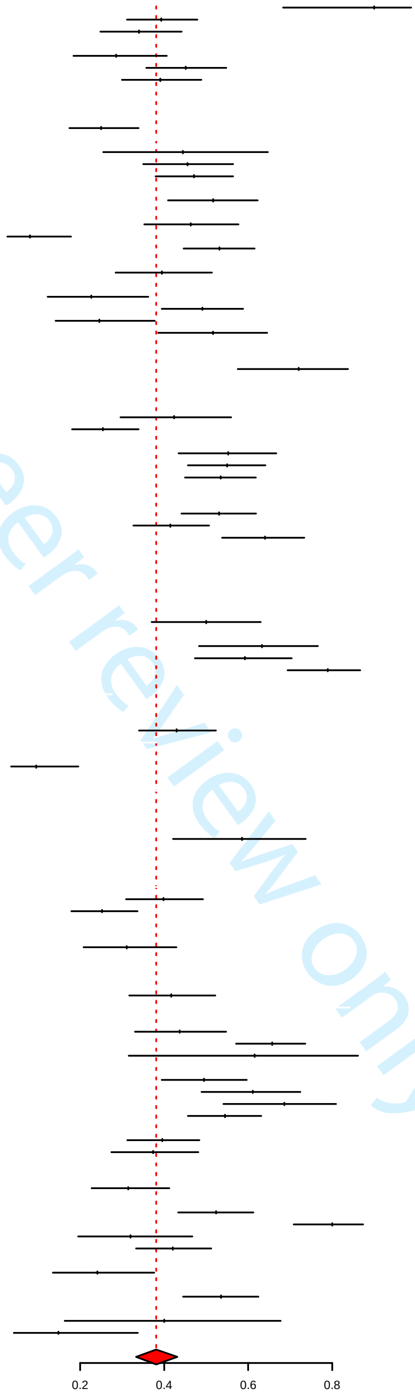


Supplementary file 7.

Forest plot for fatigue proportions without a valid scale

Study	Events	Total	Proportion	95%-CI
Agergaard et al. 2021	18	20	0.90	[0.68; 0.99]
Amin-Chowdhury et al. 2021	55	140	0.39	[0.31; 0.48]
Anaya et al. 2021	34	100	0.34	[0.25; 0.44]
Andrade Barreto et al. 2021	371	602	0.62	[0.58; 0.66]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Aranda et al. 2021	51	113	0.45	[0.36; 0.55]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi-Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Augustin et al. 2021	43	442	0.10	[0.07; 0.13]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Barizien et al. 2021	12	27	0.44	[0.25; 0.65]
Becker et al. 2021	41	90	0.46	[0.35; 0.56]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boari et al. 2021	47	91	0.52	[0.41; 0.62]
Boscolo-Rizzo et al. 2021	83	304	0.27	[0.22; 0.33]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carfi et al. 2020	76	143	0.53	[0.45; 0.62]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Catalan et al. 2021	30	76	0.39	[0.28; 0.51]
Chen LI et al. 2021	137	715	0.19	[0.16; 0.22]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Creamer et al. 2021	14	57	0.25	[0.14; 0.38]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
Dennis et al. 2021	197	201	0.98	[0.95; 0.99]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Dini et al 2021	36	50	0.72	[0.58; 0.84]
Eloy et al. 2021	159	324	0.49	[0.44; 0.55]
Fang et al. 2021	399	1233	0.32	[0.30; 0.35]
Fatima et al. 2021	90	160	0.56	[0.48; 0.64]
Fortini et al. 2021	25	59	0.42	[0.30; 0.56]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Frontera et al. 2021	98	272	0.36	[0.30; 0.42]
Garcia-Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Garrigues et al. 2020	66	120	0.55	[0.46; 0.64]
Gautam et al. 2021	77	144	0.53	[0.45; 0.62]
Gebhard et al. 2021	84	1024	0.08	[0.07; 0.10]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez-Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Horwitz et al. 2021	107	126	0.85	[0.77; 0.91]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Karaarslan et al. 2021	133	300	0.44	[0.39; 0.50]
Kashif et al. 2021	101	242	0.42	[0.35; 0.48]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Lindahl et al. 2021	75	95	0.79	[0.69; 0.87]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Liyanage-Don et al. 2021	31	153	0.20	[0.14; 0.28]
Logue et al. 2021	24	177	0.14	[0.09; 0.20]
Lombardo et al. 2021	158	303	0.52	[0.46; 0.58]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Miyazato et al. 2020	6	63	0.10	[0.04; 0.20]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno-Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Munblit et al. 2021	551	2599	0.21	[0.20; 0.23]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Nehme et al. 2021	85	410	0.21	[0.17; 0.25]
Nune et al. 2021	24	41	0.59	[0.42; 0.74]
O'Keefe et al. 2021	59	290	0.20	[0.16; 0.25]
Peghin et al. 2021	78	599	0.13	[0.10; 0.16]
Perez-Gonzalez et al. 2021	40	248	0.16	[0.12; 0.21]
Piotto et al.2021	56	165	0.34	[0.27; 0.42]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Rauch et al. 2021	32	127	0.25	[0.18; 0.34]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Romero-Duarte et al. 2021	176	797	0.22	[0.19; 0.25]
Rosales-Castilo et a. 2021	23	74	0.31	[0.21; 0.43]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Sathyamurthy et al. 2021	25	279	0.09	[0.06; 0.13]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Seeßle et al. 2021	40	96	0.42	[0.32; 0.52]
Senjam et al. 2021	204	257	0.79	[0.74; 0.84]
Shang et al. 2021	201	796	0.25	[0.22; 0.28]
Silva et al. 2021	38	87	0.44	[0.33; 0.55]
Smet et al. 2021	90	137	0.66	[0.57; 0.74]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Staudt et al. 2021	50	101	0.50	[0.39; 0.60]
Steinbeis et al. 2022	44	72	0.61	[0.49; 0.72]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez-Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Taboada et al. 2021	34	91	0.37	[0.27; 0.48]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tleyjeh et al. 2021	66	222	0.30	[0.24; 0.36]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
Vanichkachorn et al. 2021	80	100	0.80	[0.71; 0.87]
van Veenendaal et al. 2021	16	50	0.32	[0.20; 0.47]
Wang et al. 2021	53	126	0.42	[0.33; 0.51]
Wong-Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Wu et al. 2021	13	54	0.24	[0.13; 0.38]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zayat et al. 2021	68	127	0.54	[0.44; 0.62]
Zhang et al. 2021	674	2433	0.28	[0.26; 0.30]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Zulu et al. 2020	4	27	0.15	[0.04; 0.34]
Random effects model		**39581**	**0.38**	**[0.33; 0.43]**

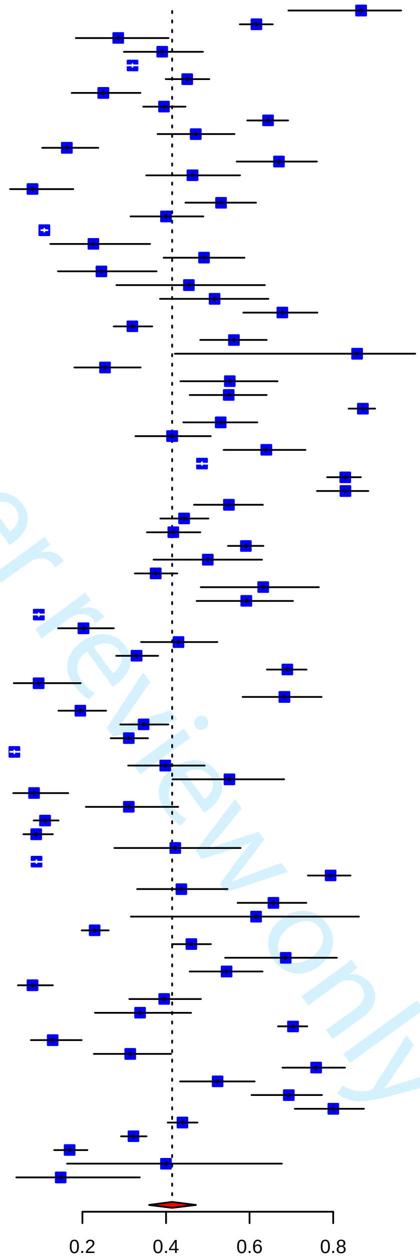
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.2087$, $p = 0$



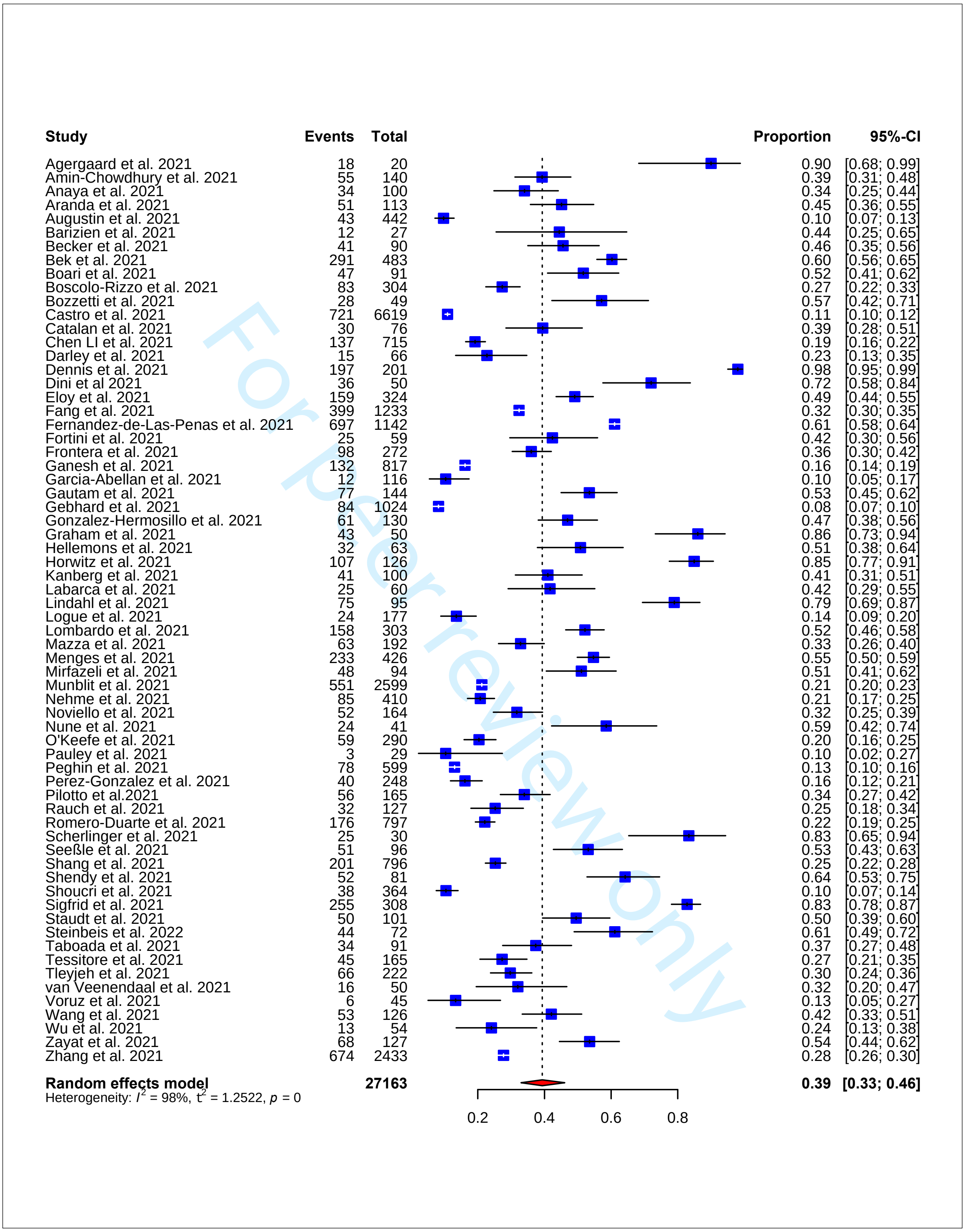
Supplementary file 8. Forest plot for fatigue proportions at 1-3 months

Study	Events	Total	Proportion	95%-CI
Albu et al. 2021	26	30	0.87	[0.69; 0.96]
Andrade Barreto et al. 2021	371	602	0.62	[0.58; 0.66]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi-Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Bek et al. 2021	248	385	0.64	[0.59; 0.69]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boesi et al. 2021	67	100	0.67	[0.57; 0.76]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carfi et al. 2020	76	143	0.53	[0.45; 0.62]
Carvalho-Schneider et al 2021	52	130	0.40	[0.32; 0.49]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Creamer et al. 2021	14	57	0.25	[0.14; 0.38]
Daher et al. 2020	15	33	0.45	[0.28; 0.64]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
D'Cruz et al. 2020	78	115	0.68	[0.58; 0.76]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Fatima et al. 2021	90	160	0.56	[0.48; 0.64]
Ferraro et al. 2020	6	7	0.86	[0.42; 1.00]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Garcia-Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Garrigues et al. 2020	66	120	0.55	[0.46; 0.64]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez-Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Heightman et al. 2021	644	1325	0.49	[0.46; 0.51]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Jacobs et al. 2021	82	149	0.55	[0.47; 0.63]
Karaarslan et al. 2021	133	300	0.44	[0.39; 0.50]
Kashif et al. 2021	101	242	0.42	[0.35; 0.48]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Liyanage-Don et al. 2021	31	153	0.20	[0.14; 0.28]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Miyazato et al. 2020	6	63	0.10	[0.04; 0.20]
Molnar et al. 2021	69	101	0.68	[0.58; 0.77]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno-Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Morin et al. 2021	134	431	0.31	[0.27; 0.36]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Raman et al. 2020	32	58	0.55	[0.42; 0.68]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Rosales-Castillo et a. 2021	23	74	0.31	[0.21; 0.43]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Sathyamurthy et al. 2021	25	279	0.09	[0.06; 0.13]
Savarraj et al. 2021	19	45	0.42	[0.28; 0.58]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Senjam et al. 2021	204	257	0.79	[0.74; 0.84]
Silva et al. 2021	38	87	0.44	[0.33; 0.55]
Smet et al. 2021	90	137	0.66	[0.57; 0.74]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Stavem et al. 2021	211	458	0.46	[0.41; 0.51]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez-Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Szekely et al. 2021	24	71	0.34	[0.23; 0.46]
Taylor et al. 2021	475	675	0.70	[0.67; 0.74]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
van den Borst et al. 2021	86	124	0.69	[0.60; 0.77]
Vanichkachorn et al. 2021	80	100	0.80	[0.71; 0.87]
Venturelli et al. 2021	337	767	0.44	[0.40; 0.48]
Wong-Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Zulu et al. 2020	4	27	0.15	[0.04; 0.34]
Random effects model		**29015**	**0.41**	**[0.36; 0.47]**

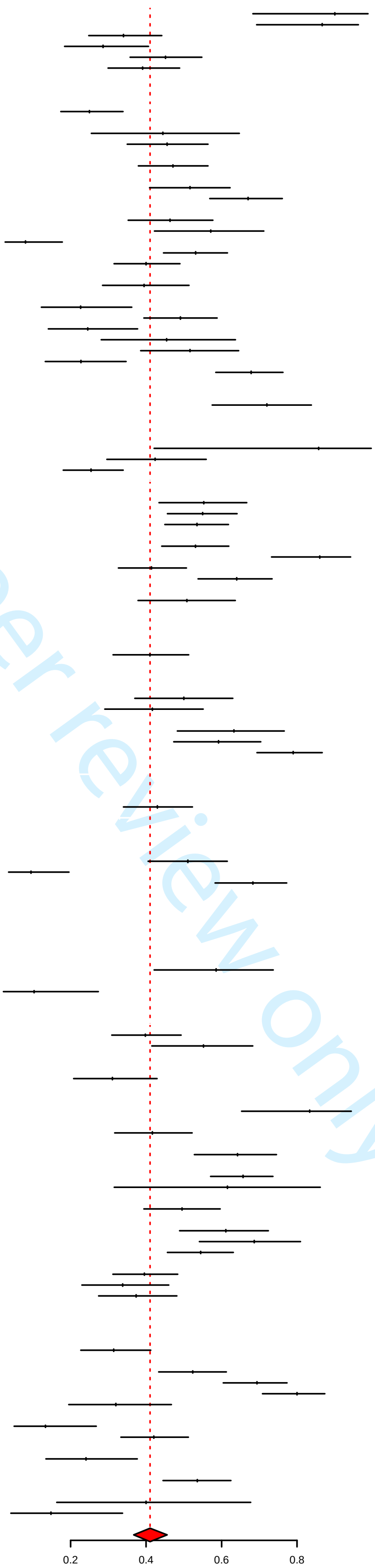
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.1465$, $p = 0$



Supplementary file 9. Forest plot for fatigue proportions >3 months



Supplementary file 10. Forest plot excluding unpublished articles



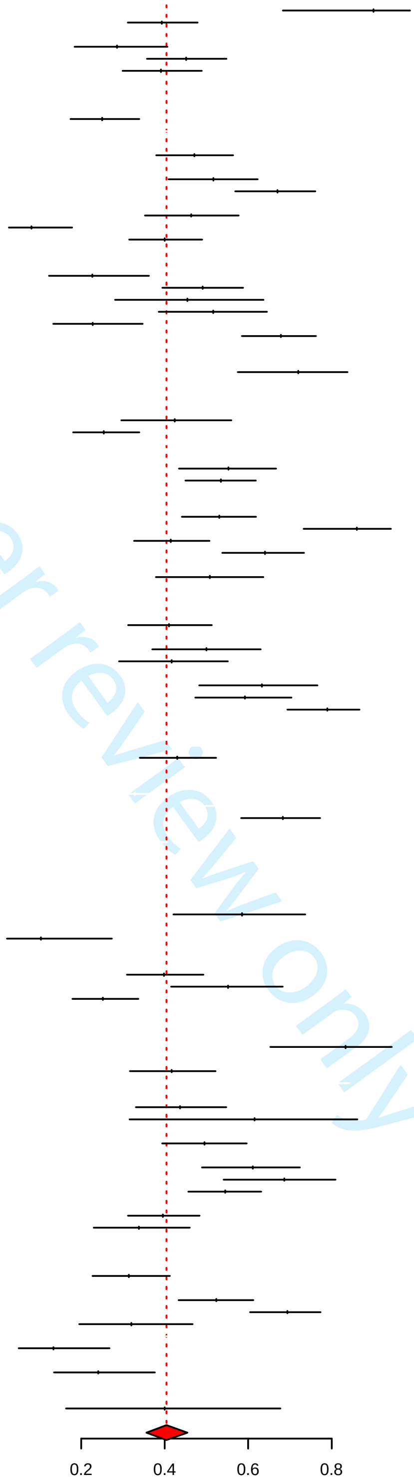
Study	Events	Total	Proportion	95%-CI
Agergaard et al. 2021	18	20	0.90	[0.68; 0.99]
Albu et al. 2021	26	30	0.87	[0.69; 0.96]
Anaya et al. 2021	34	100	0.34	[0.25; 0.44]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Aranda et al. 2021	51	113	0.45	[0.36; 0.55]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi-Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Augustin et al. 2021	43	442	0.10	[0.07; 0.13]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Barizien et al. 2021	12	27	0.44	[0.25; 0.65]
Becker et al. 2021	41	90	0.46	[0.35; 0.56]
Bek et al. 2021	248	385	0.64	[0.59; 0.69]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boari et al. 2021	47	91	0.52	[0.41; 0.62]
Boesi et al. 2021	67	100	0.67	[0.57; 0.76]
Boscolo-Rizzo et al. 2021	83	304	0.27	[0.22; 0.33]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Bozzetti et al. 2021	28	49	0.57	[0.42; 0.71]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carfi et al. 2020	76	143	0.53	[0.45; 0.62]
Carvalho-Schneider et al 2021	52	130	0.40	[0.32; 0.49]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Catalan et al. 2021	30	76	0.39	[0.28; 0.51]
Chen LI et al. 2021	137	715	0.19	[0.16; 0.22]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Creamer et al. 2021	14	57	0.25	[0.14; 0.38]
Daher et al. 2020	15	33	0.45	[0.28; 0.64]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
Darley et al. 2021	15	66	0.23	[0.13; 0.35]
D'Cruz et al. 2020	78	115	0.68	[0.58; 0.76]
Dennis et al. 2021	197	201	0.98	[0.95; 0.99]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Dini et al 2021	36	50	0.72	[0.58; 0.84]
Eloy et al. 2021	159	324	0.49	[0.44; 0.55]
Fang et al. 2021	399	1233	0.32	[0.30; 0.35]
Fernandez-de-Las-Penas et al. 2021	697	1142	0.61	[0.58; 0.64]
Ferraro et al. 2020	6	7	0.86	[0.42; 1.00]
Fortini et al. 2021	25	59	0.42	[0.30; 0.56]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Frontera et al. 2021	98	272	0.36	[0.30; 0.42]
Ganesh et al. 2021	132	817	0.16	[0.14; 0.19]
Garcia-Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Garrigues et al. 2020	66	120	0.55	[0.46; 0.64]
Gautam et al. 2021	77	144	0.53	[0.45; 0.62]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez-Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Graham et al. 2021	43	50	0.86	[0.73; 0.94]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Heightman et al. 2021	644	1325	0.49	[0.46; 0.51]
Hellemons et al. 2021	32	63	0.51	[0.38; 0.64]
Horwitz et al. 2021	107	126	0.85	[0.77; 0.91]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Jacobs et al. 2021	82	149	0.55	[0.47; 0.63]
Kanberg et al. 2021	41	100	0.41	[0.31; 0.51]
Karaarslan et al. 2021	133	300	0.44	[0.39; 0.50]
Kashif et al. 2021	101	242	0.42	[0.35; 0.48]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Labarca et al. 2021	25	60	0.42	[0.29; 0.55]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Lindahl et al. 2021	75	95	0.79	[0.69; 0.87]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Liyanage-Don et al. 2021	31	153	0.20	[0.14; 0.28]
Logue et al. 2021	24	177	0.14	[0.09; 0.20]
Lombardo et al. 2021	158	303	0.52	[0.46; 0.58]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Mazza et al. 2021	63	192	0.33	[0.26; 0.40]
Menges et al. 2021	233	426	0.55	[0.50; 0.59]
Mirfazeli et al. 2021	48	94	0.51	[0.41; 0.62]
Miyazato et al. 2020	6	63	0.10	[0.04; 0.20]
Molnar et al. 2021	69	101	0.68	[0.58; 0.77]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno-Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Morin et al. 2021	134	431	0.31	[0.27; 0.36]
Munblit et al. 2021	551	2599	0.21	[0.20; 0.23]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Nehme et al. 2021	85	410	0.21	[0.17; 0.25]
Noviello et al. 2021	52	164	0.32	[0.25; 0.39]
Nune et al. 2021	24	41	0.59	[0.42; 0.74]
O'Keefe et al. 2021	59	290	0.20	[0.16; 0.25]
Pauley et al. 2021	3	29	0.10	[0.02; 0.27]
Peghin et al. 2021	78	599	0.13	[0.10; 0.16]
Perez-Gonzalez et al. 2021	40	248	0.16	[0.12; 0.21]
Piotto et al.2021	56	165	0.34	[0.27; 0.42]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Raman et al. 2020	32	58	0.55	[0.42; 0.68]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Romero-Duarte et al. 2021	176	797	0.22	[0.19; 0.25]
Rosales-Castillo et a. 2021	23	74	0.31	[0.21; 0.43]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Sathyamurthy et al. 2021	25	279	0.09	[0.06; 0.13]
Scherlinger et al. 2021	25	30	0.83	[0.65; 0.94]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Seeßle et al. 2021	40	96	0.42	[0.32; 0.52]
Shang et al. 2021	201	796	0.25	[0.22; 0.28]
Shendy et al. 2021	52	81	0.64	[0.53; 0.75]
Sigfrid et al. 2021	255	308	0.83	[0.78; 0.87]
Smet et al. 2021	90	137	0.66	[0.57; 0.74]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Staudt et al. 2021	50	101	0.50	[0.39; 0.60]
Stavem et al. 2021	211	458	0.46	[0.41; 0.51]
Steinbeis et al. 2022	44	72	0.61	[0.49; 0.72]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez-Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Szekely et al. 2021	24	71	0.34	[0.23; 0.46]
Taboada et al. 2021	34	91	0.37	[0.27; 0.48]
Taylor et al. 2021	475	675	0.70	[0.67; 0.74]
Tessitore et al. 2021	45	165	0.27	[0.21; 0.35]
Tleyjeh et al. 2021	66	222	0.30	[0.24; 0.36]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
van den Borst et al. 2021	86	124	0.69	[0.60; 0.77]
Vanichkachorn et al. 2021	80	100	0.80	[0.71; 0.87]
van Veenendaal et al. 2021	16	50	0.32	[0.20; 0.47]
Venturelli et al. 2021	337	767	0.44	[0.40; 0.48]
Voruz et al. 2021	6	45	0.13	[0.05; 0.27]
Wang et al. 2021	53	126	0.42	[0.33; 0.51]
Wong-Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Wu et al. 2021	13	54	0.24	[0.13; 0.38]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zayat et al. 2021	68	127	0.54	[0.44; 0.62]
Zhang et al. 2021	674	2433	0.28	[0.26; 0.30]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Zulu et al. 2020	4	27	0.15	[0.04; 0.34]
Random effects model		**46024**	**0.41**	**[0.37; 0.46]**

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.1674$, $p = 0$

Supplementary file. 11 Forest plot for fatigue proportions with low grade studies removed

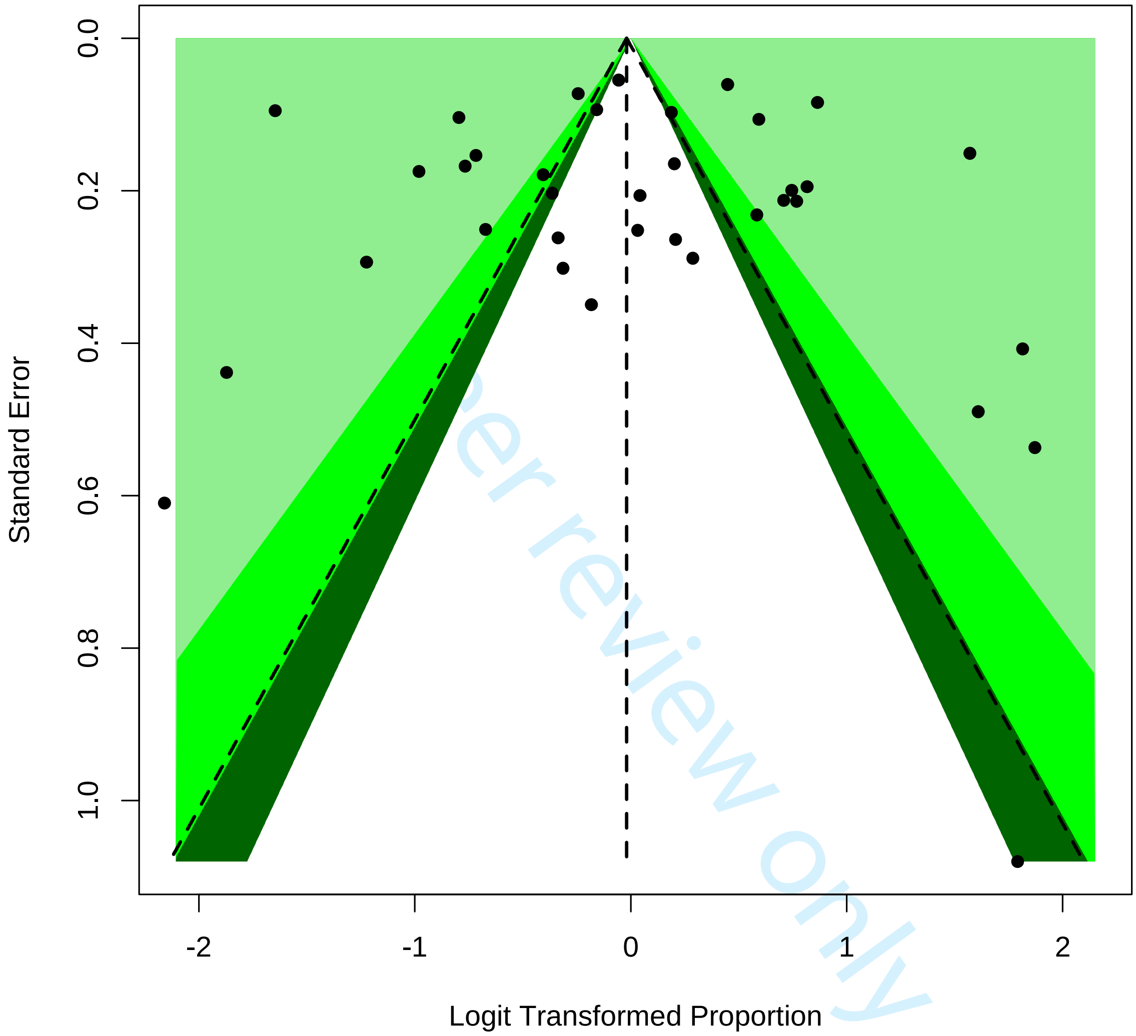
Study	Events	Total	Proportion	95%-CI
Agergaard et al. 2021	18	20	0.90	[0.68; 0.99]
Amin-Chowdhury et al. 2021	55	140	0.39	[0.31; 0.48]
Andrade Barreto et al. 2021	371	602	0.62	[0.58; 0.66]
Aparisi et al. 2021	20	70	0.29	[0.18; 0.41]
Aranda et al. 2021	51	113	0.45	[0.36; 0.55]
Arnold et al. 2020	43	110	0.39	[0.30; 0.49]
Asadi-Pooya et al. 2021	859	2685	0.32	[0.30; 0.34]
Augustin et al. 2021	43	442	0.10	[0.07; 0.13]
Aul et al. 2021	165	366	0.45	[0.40; 0.50]
Aydin et al. 2021	29	116	0.25	[0.17; 0.34]
Bai et al. 2021	149	377	0.40	[0.35; 0.45]
Bek et al. 2021	248	385	0.64	[0.59; 0.69]
Bell et al. 2021	57	121	0.47	[0.38; 0.56]
Bliddal et al. 2021	21	129	0.16	[0.10; 0.24]
Boari et al. 2021	47	91	0.52	[0.41; 0.62]
Boesi et al. 2021	67	100	0.67	[0.57; 0.76]
Boscolo-Rizzo et al. 2021	83	304	0.27	[0.22; 0.33]
Bottemanne et al. 2021	38	82	0.46	[0.35; 0.58]
Cao et al. 2021	5	62	0.08	[0.03; 0.18]
Carvalho-Schneider et al 2021	52	130	0.40	[0.32; 0.49]
Castro et al. 2021	721	6619	0.11	[0.10; 0.12]
Chen LI et al. 2021	137	715	0.19	[0.16; 0.22]
Chopra et al. 2021	12	53	0.23	[0.12; 0.36]
Clavario et al. 2020	54	110	0.49	[0.39; 0.59]
Daher et al. 2020	15	33	0.45	[0.28; 0.64]
Danesh et al. 2021	32	62	0.52	[0.39; 0.65]
Darley et al. 2021	15	66	0.23	[0.13; 0.35]
D'Cruz et al. 2020	78	115	0.68	[0.58; 0.76]
Dennis et al. 2021	197	201	0.98	[0.95; 0.99]
Desgranges et al. 2021	132	413	0.32	[0.27; 0.37]
Dini et al 2021	36	50	0.72	[0.58; 0.84]
Eloy et al. 2021	159	324	0.49	[0.44; 0.55]
Fang et al. 2021	399	1233	0.32	[0.30; 0.35]
Fernandez-de-Las-Penas et al. 2021	697	1142	0.61	[0.58; 0.64]
Fortini et al. 2021	25	59	0.42	[0.30; 0.56]
Froidure et al. 2021	32	126	0.25	[0.18; 0.34]
Frontera et al. 2021	98	272	0.36	[0.30; 0.42]
Ganesh et al. 2021	132	817	0.16	[0.14; 0.19]
Garcia-Abellan et al. 2021	42	76	0.55	[0.43; 0.67]
Gautam et al. 2021	77	144	0.53	[0.45; 0.62]
Gebhard et al. 2021	84	1024	0.08	[0.07; 0.10]
Goertz et al. 2020	398	457	0.87	[0.84; 0.90]
Gonzalez-Hermosillo et al. 2021	69	130	0.53	[0.44; 0.62]
Graham et al. 2021	43	50	0.86	[0.73; 0.94]
Gupta et al. 2021	51	123	0.41	[0.33; 0.51]
Halpin et al 2020	64	100	0.64	[0.54; 0.73]
Heightman et al. 2021	644	1325	0.49	[0.46; 0.51]
Hellemons et al. 2021	32	63	0.51	[0.38; 0.64]
Hossain et al. 2021	295	356	0.83	[0.79; 0.87]
Iqbal et al. 2021	131	158	0.83	[0.76; 0.88]
Jacobs et al. 2021	82	149	0.55	[0.47; 0.63]
Kanberg et al. 2021	41	100	0.41	[0.31; 0.51]
Khalaf et al. 2021	318	538	0.59	[0.55; 0.63]
Kozak et al. 2021	31	62	0.50	[0.37; 0.63]
Labarca et al. 2021	25	60	0.42	[0.29; 0.55]
Lemhofer et al. 2021	137	365	0.38	[0.33; 0.43]
Leth et al. 2021	31	49	0.63	[0.48; 0.77]
Liang et al. 2020	45	76	0.59	[0.47; 0.70]
Lindahl et al. 2021	75	95	0.79	[0.69; 0.87]
Liu et al. 2021	48	502	0.10	[0.07; 0.12]
Logue et al. 2021	24	177	0.14	[0.09; 0.20]
Lombardo et al. 2021	158	303	0.52	[0.46; 0.58]
Maamar et al. 2021	52	121	0.43	[0.34; 0.52]
Mahmud et al. 2021	117	355	0.33	[0.28; 0.38]
Mandal et al. 2020	265	384	0.69	[0.64; 0.74]
Mazza et al. 2021	63	192	0.33	[0.26; 0.40]
Menges et al. 2021	233	426	0.55	[0.50; 0.59]
Molnar et al. 2021	69	101	0.68	[0.58; 0.77]
Moradian et al. 2020	39	200	0.20	[0.14; 0.26]
Moreno-Perez et al. 2021	96	277	0.35	[0.29; 0.41]
Morin et al. 2021	134	431	0.31	[0.27; 0.36]
Munblit et al. 2021	551	2599	0.21	[0.20; 0.23]
Naik et al. 2021	46	1234	0.04	[0.03; 0.05]
Nehme et al. 2021	85	410	0.21	[0.17; 0.25]
Noviello et al. 2021	52	164	0.32	[0.25; 0.39]
Nune et al. 2021	24	41	0.59	[0.42; 0.74]
O'Keefe et al. 2021	59	290	0.20	[0.16; 0.25]
Pauley et al. 2021	3	29	0.10	[0.02; 0.27]
Peghin et al. 2021	78	599	0.13	[0.10; 0.16]
Perez-Gonzalez et al. 2021	40	248	0.16	[0.12; 0.21]
Poyraz et al. 2021	47	118	0.40	[0.31; 0.49]
Raman et al. 2020	32	58	0.55	[0.42; 0.68]
Rauch et al. 2021	32	127	0.25	[0.18; 0.34]
Righi et al. 2021	7	83	0.08	[0.03; 0.17]
Romero-Duarte et al. 2021	176	797	0.22	[0.19; 0.25]
Sami et al. 2021	50	452	0.11	[0.08; 0.14]
Scherlinger et al. 2021	25	30	0.83	[0.65; 0.94]
Shoucri et al. 2021	44	488	0.09	[0.07; 0.12]
Seeßle et al. 2021	40	96	0.42	[0.32; 0.52]
Senjam et al. 2021	204	257	0.79	[0.74; 0.84]
Sigfrid et al. 2021	255	308	0.83	[0.78; 0.87]
Silva et al. 2021	38	87	0.44	[0.33; 0.55]
Sollini et al. 2021	8	13	0.62	[0.32; 0.86]
Soraas et al. 2021	155	676	0.23	[0.20; 0.26]
Staudt et al. 2021	50	101	0.50	[0.39; 0.60]
Stavem et al. 2021	211	458	0.46	[0.41; 0.51]
Steinbeis et al. 2022	44	72	0.61	[0.49; 0.72]
Strumiliene et al. 2021	35	51	0.69	[0.54; 0.81]
Suarez-Robles et al. 2021	73	134	0.54	[0.46; 0.63]
Sultana et al. 2021	15	186	0.08	[0.05; 0.13]
Sykes et al. 2021	53	134	0.40	[0.31; 0.48]
Szekely et al. 2021	24	71	0.34	[0.23; 0.46]
Taylor et al. 2021	475	675	0.70	[0.67; 0.74]
Tessitore et al. 2021	45	165	0.27	[0.21; 0.35]
Tiwari et al. 2021	17	132	0.13	[0.08; 0.20]
Tomasoni et al. 2021	33	105	0.31	[0.23; 0.41]
Tosato et al. 2021	104	137	0.76	[0.68; 0.83]
Townsend et al 2020	67	128	0.52	[0.43; 0.61]
van den Borst et al. 2021	86	124	0.69	[0.60; 0.77]
van Veenendaal et al. 2021	16	50	0.32	[0.20; 0.47]
Venturelli et al. 2021	337	767	0.44	[0.40; 0.48]
Voruz et al. 2021	6	45	0.13	[0.05; 0.27]
Wong-Chew et al. 2022	299	928	0.32	[0.29; 0.35]
Wu et al. 2021	13	54	0.24	[0.13; 0.38]
Yomogida et al. 2021	62	366	0.17	[0.13; 0.21]
Zhang et al. 2021	674	2433	0.28	[0.26; 0.30]
Zhou et al. 2021	6	15	0.40	[0.16; 0.68]
Random effects model		**44359**	**0.40**	**[0.36; 0.45]**

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 1.2259$, $p = 0$

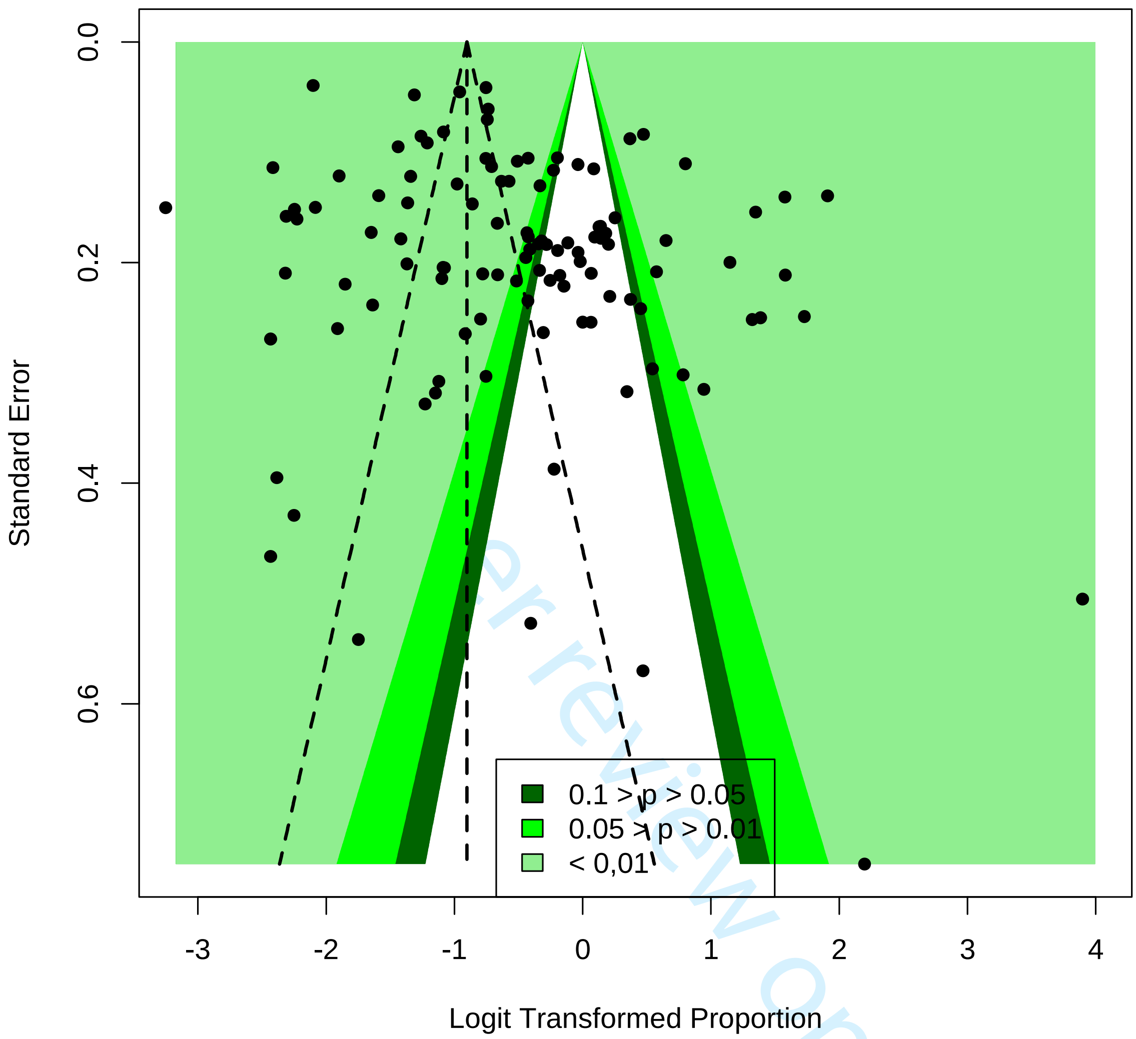


Supplementary file. 12 Funnel plots for fatigue proportions using a scale or no scale

Funnel plot for studies using a valid scale

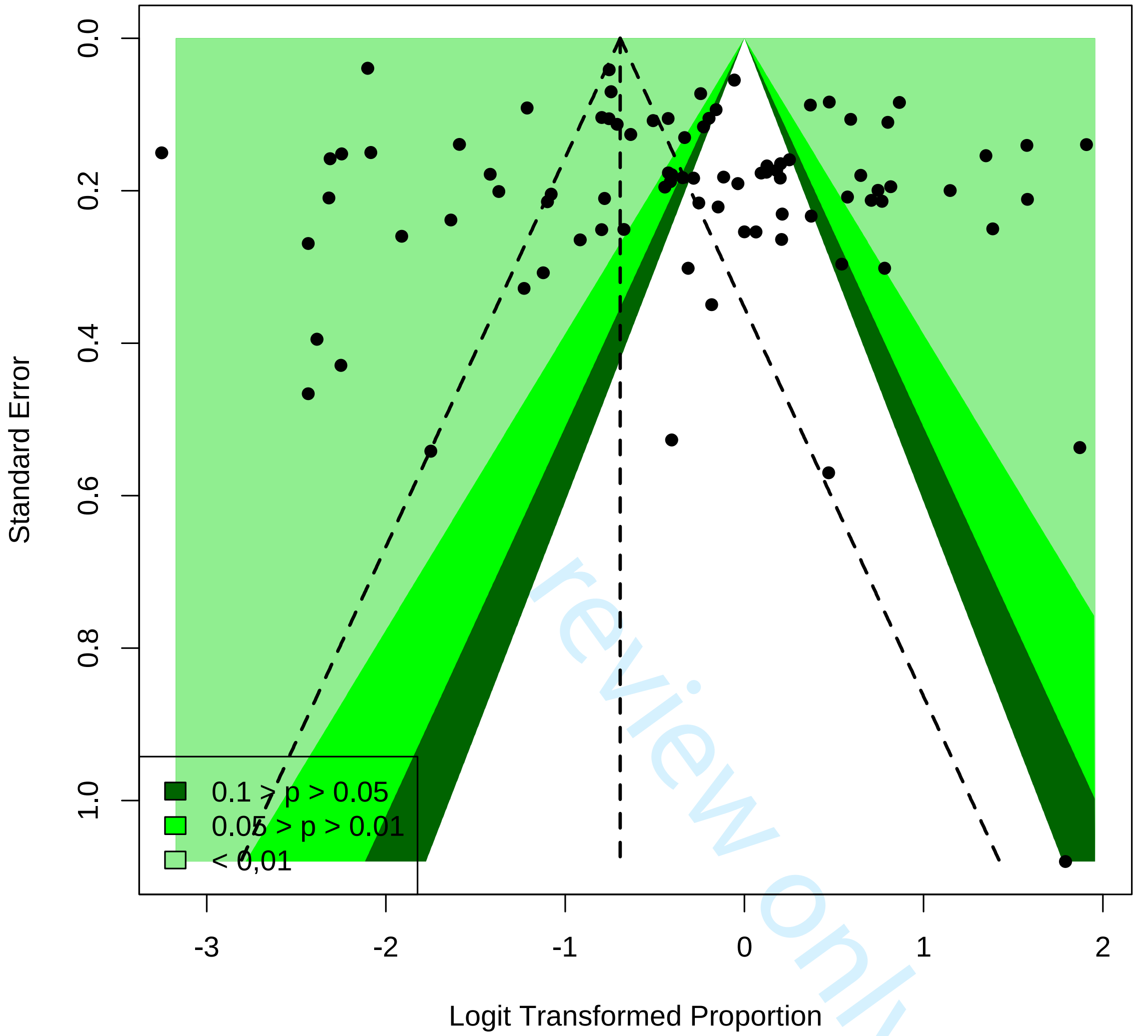


Funnel plot for studies not using a valid scale

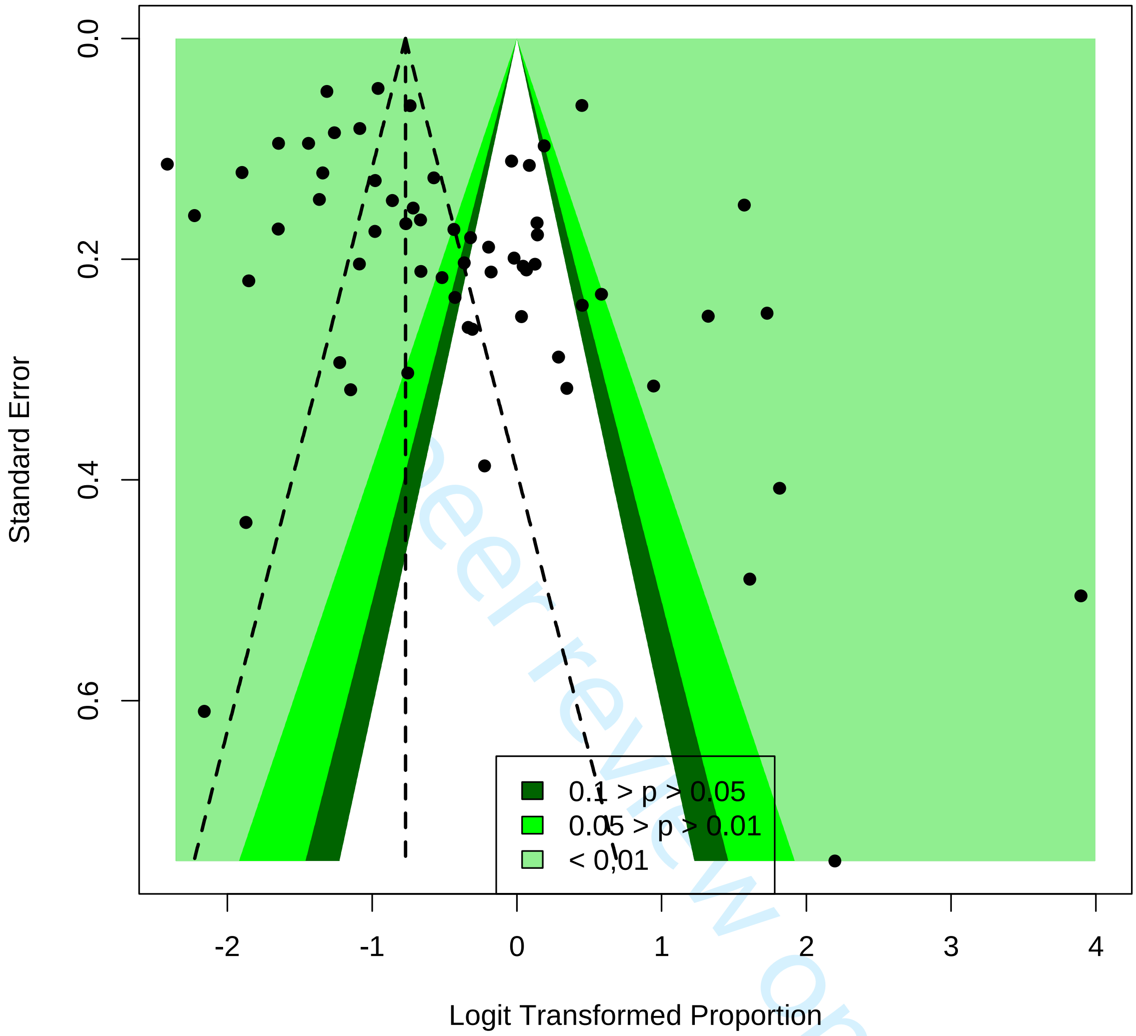


Supplementary file 13. Funnel plots for fatigue proportions 1-3 months & >3 months

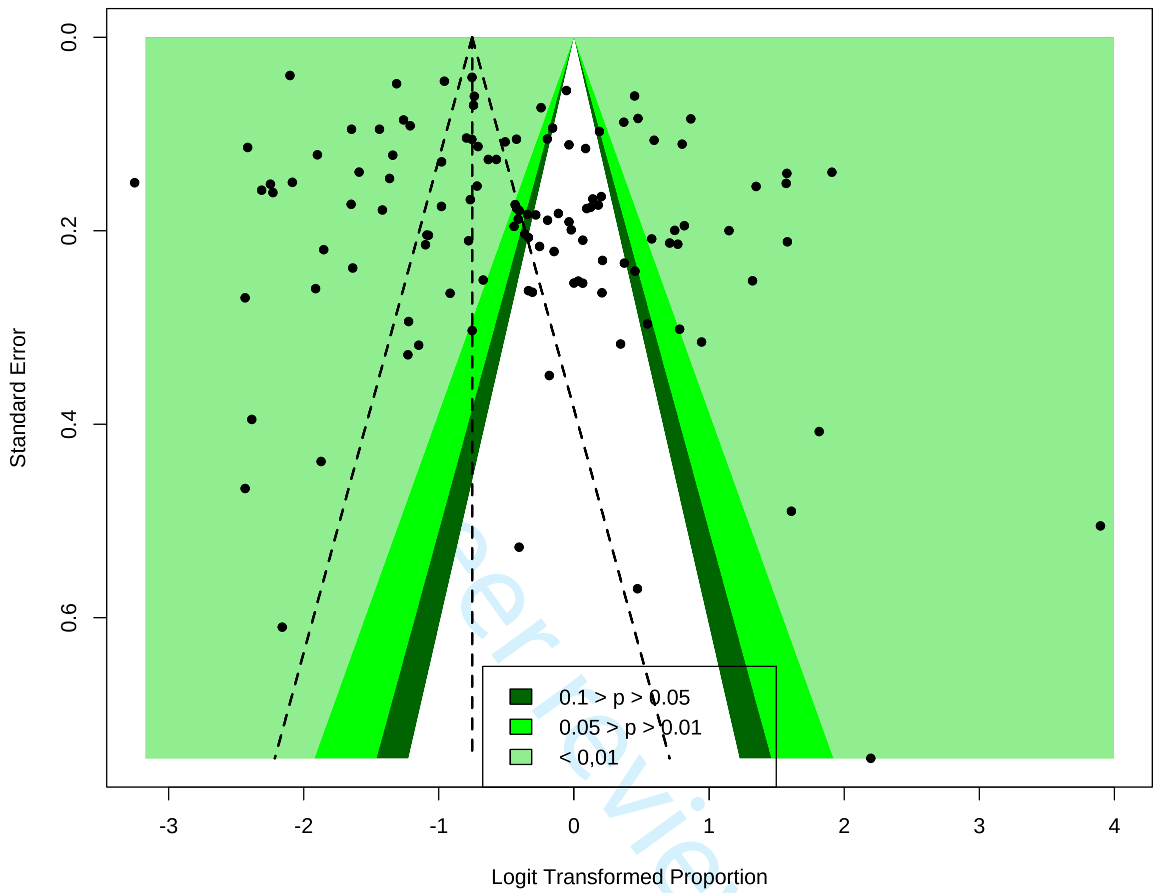
Funnel plot for 1-3 months



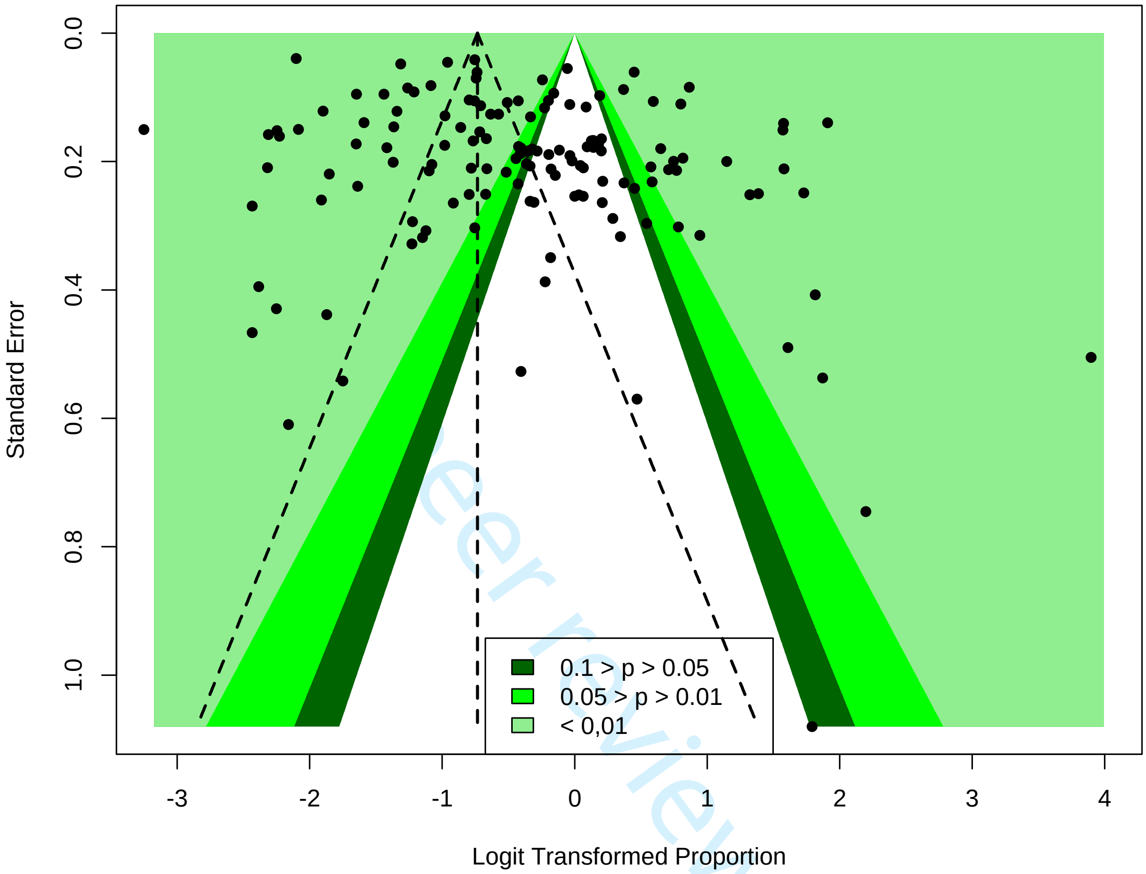
Funnel plot for >3 months



Supplementary file 14. Funnel plot for fatigue proportions excluding 'low grade' quality assessments



Supplementary file. 15 Funnel plot for fatigue proportions excluding unpublished articles



Supplementary File 16. Table of reported risk factors for fatigue

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Agergaard et al. (2021) Denmark	Outpatients	Case-control	20	77-255 days	Questionnaire	**Myopathy**	11 (100)	
						No myopathy	3 (33)	< .05
							RR 3.27	
Albu et al. (2021) Spain	Outpatients	Cross-sectional	30	≥ 3 months	MFIS	**ICU**		
						Overall Fatigue	13 (81.2)	
						Physical activities	80.55	*0.28*
						Cognitive activities	72.5	*0.28*
						Psychosocial activities	20	*0.40*
						No ICU		
						Overall Fatigue	13 (92.8)	
						Physical activities	81.9	
						Cognitive activities	73.75	
						Psychosocial activities	35	
						Depression		
						Physical fatigue	r = .490	*<.001*
						Cognitive fatigue	r = .490	*<.001*
						Social fatigue	r = .540	*<.001*
						Anxiety		
						Physical fatigue	r = .270	*NS*
						Cognitive fatigue	r = .270	*NS*
						Social fatigue	r = .340	*NS*
						Sleep quality		
						Physical fatigue	r = .640	*<.001*
						Cognitive fatigue	r = .640	*<.001*
						Social fatigue	r = .620	*<.001*
Amin-Chowdhury et al. (2021) UK	Survey	Prospective cohort	1,671	7 months	ADQ	**Gender (F)**	OR = 2.22	*<.001*
						Comorbidities	OR = 1.98	*<.001*
Anaya et al. (2021) Colombia	Survey	Case series	100	219 days	Questionnaire	**Disease severity**		
						Ambulatory	9 (25.7)	0.407
						Severe	15 (36.6)	
						Critical	10 (41.7)	
Andrade Barreto et al. (2021) Brazil	Outpatients	Cross-sectional	602	> 1 month	Questionnaire	**Mild disease**		
						Female	133 (73.5)	
						Male	33 (55.9)	*.011*
						Moderate disease		
						Female	59 (62.1)	
						Male	30 (41.1)	*.007*
						Severe disease		
						Female	53 (67.1)	*.086*
						Male	63 (54.8)	
						Quality of life (Total)	β = -8.28	*<.001*
Aparisi et al. (2021) Italy	Outpatients	Prospective cohort	70	3 months	Clinical assessment for symptom burden	**Persistent dyspnoea**	17 (41.5)	*0.005*
						Residual dyspnoea	3 (10.3)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Arnold et al. (2020) UK	Outpatients	Prospective cohort	110	8-12 weeks	ADQ	**Disease severity & excessive Fatigue**		
						Mild	7/27 (26%)	*NR*
						Moderate	26/65 (40%)	
						Severe	10/18 (56%)	
						Disease severity & vitality	**M (SD)**	
						Mild	43 (20)	
						Moderate	49 (22)	
						Severe	36 (24)	
Aul et al. (2021) UK	Survey	Cross-sectional	387	6 weeks	Questionnaire	**Age**		
						Fatigue	61 (49-72)	*0.12*
						No fatigue	64 (50-76)	
						Gender (M)		
						Fatigue	89 (42.8)	*0.40*
						No fatigue	119 (57.2)	
						BMI		
						Fatigue	26.5 (23.5-30)	*.035*
						No fatigue	28.9 (23.9-32.7)	
						ICU		
						Fatigue	49 (59)	*.003*
						No fatigue	34 (41)	
						Intubated		
						Fatigue	40 (67.8)	*<.001*
						No fatigue	19 (32.2)	
						Days intubated		
						Fatigue	22 (11-45)	*.097*
						No fatigue	17 (7-26)	
						Lymphocytes (10^9/L)		
						Fatigue	0.7 (0.5-1.0)	*0.64*
						No fatigue	0.7 (0.5-1.0)	
						Peak WBC (10^9/L)		
						Fatigue	10.1 (7.1-15.6)	*0.37*
						No fatigue	9.8 (7.2-13.7)	
						Peak CRP (mg/L)		
						Fatigue	147 (81-276)	*.081*
						No fatigue	133 (73-212)	
						Peak ferritin (μg/L)		
						Fatigue	999 (562-2053.5)	*.68*
						No fatigue	961.5 (559-1625)	
						Peak D-dimer (ng/ml)		
						Fatigue	1122 (326-3821)	*.138*
						No fatigue	657.5 (328-2473)	
						High risk inpatient CXR		
						Fatigue	83 (55.7)	*NS*
						No fatigue	78 (47.9)	
							OR 7.04	
						Post-COVID fibrosis		*.167*
						Ethnicity	-	*NS*
								.001

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Augustin et al. (2021) Germany	Outpatients	Prospective cohort	958	4, 7 months	ADQ	**IgG Levels**		
						Low ≤ 1.1	NR	*NR*
						Medium 1.2-4	NR	*NR*
						High > 4	NR	*NR*
						Gender		
						Male	13/353 (8.6%)	*NR*
						Female	37/353 (18.3%)	
Aydin et al. (2021) Turkey	Outpatients	Cohort	116	44 days	ADQ	**Gender (F)**	OR = 1.8	*.008*
Bai et al. (2021) Italy	Outpatients	Prospective cohort	377	102 days	Clinical interview	**Gender**		
						Females	75/137 (54.7)	.001
						Males	74/240 (30.8)	
						Long-Covid		
						No	20/117 (17.1)	.732
						Yes	39/260 (15)	
Barizien et al. (2021) France	Outpatients	Prospective cohort	39	7 months	Clinician assessment	**Fatigued v Not fatigued**		
						Age		*.085*
						Gender (F)		*.059*
						Physical comorbidities		*NS*
						Loss of taste & smell		*.951*
						Weight (before & current)		*NS*
						Height		*.499*
						BMI (before & current)		*NS*
						Loss of weight		*.632*
						Heart rate (BPM)		*.708*
						Blood pressure		*NS*
						NJIMEGEN Score		*.002*
						PTSD Score		*.001*
						30 s of up & down test		*.192*
						O^2 saturation (%)		*.663*
						Months since diagnosis		*.157*
						Systolic & diastolic BP		*NS*
Becker et al. (2021) Switzerland	Outpatients	Prospective cohort	90	12 months	ADQ VAS	**Psychological distress**	9 (23.1)	.288
						No psychological distress	30 (76.9)	
Bek et al. (2021) Netherlands	Outpatients	Prospective cohort	492	3, 6, 12 months	FAS	**Gender**	OR 2.76	<.001
						Comorbidity (Y)	OR 2.19	.007
						Employment (N)	OR 0.57	.009
						Employment Retired	OR 0.38	<.001
Bell et al. (2021) USA	Survey	Prospective cohort	303	> 30 days	ADQ	**Follow-up**		
						≥ 30 days	78 (37.5)	
						30-59 days	21 (24.1)	-
						≥ 60 days	57 (47.1)	
Boesl et al. (2021) Italy	Outpatients	Cross-sectional	100	≥ 12 weeks	FSS		**N (%)**	
						No impairment due to fatigue (1-3 on FSS)		
						Total	18 (19.8)	
						Female	13 (20.3)	*NR*
						Male	5 (18.5)	
						Impairment due to fatigue (4-7 on		

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						FSS) Total Female Male	 73 (80.2) 51 (79.7) 22 (81.5)	 *NR*
Bottemanne et al. 2021 France	Outpatients Telephone	Prospective cohort	84	1, 3 months	Clinical interview	**3-month outcomes** Anxiety @ 1 month Physical symptoms @ 1 month Depression	- aOR 0.81 aOR 4.00 aOR 0.84	 .250 .236 .307
Bozzetti et al. (2021) Italy	Outpatients	Prospective cohort	49	6 months	Questionnaire	**≥ 50% reduction of serum NfL levels** **< 50% reduction of serum NfL level**	4/14 (33) 4/15 (27)	 *.999*
Carvalho-Schneider et al. (2021) France	Survey	Prospective cohort	150	30-60 days	WHO Performance Status Classification	**Severe asthenia** Day 30 Day 60	 11 (7) 4 (3.1)	-
Castro et al. (2021) USA	EHR	Retrospective case-control	6,619	31-90 days 91-150 days	Reported symptoms	**Positive test v Negative test**	aOR = 0.98	*.761*
Catalan et al. (2021) Spain	Survey	Cohort	76	12 months	Questionnaire SF-36	**No Steroids** Asthenia Vitality **Steroids** Asthenia Vitality	 19 (43.2) 62.5 (IQR 40–85) 11 (34.4) 80 (56.2–85)	 *.440* *.120*
Chen, Li et al. (2021) China	Telephone	Longitudinal cohort	715	Median 225 days	Questionnaire	**Mechanical ventilation (ICU)** **Re-admission after discharge** **Hypertension**	OR 5.52 OR 3.41 OR 1.65	.001 .001 .0016
Chudzik et al. (2021) Poland	Outpatients	RCT	50	4 weeks	FAS	**Phase 0** 1-MNA supplementation No supplement **Phase 1** 1-MNA supplementation No supplement	**M (SD)** 4.23 4.53 4.42 4.94	 *.008*
Clavario et al. (2020) Italy	Outpatients	Prospective cohort	110	3 months	Questionnaire	**% predicted VO2 below 85%** **% predicted VO2 above 85%**	21/38 (55.3) 33/72 (45.8)	.459
Daugherty et al. (2021) USA	EHR	Retrospective cohort	27,074	1-6 months	ICD10	**Fatigue** **Age > 50**	HR = 2.20 -	 *<.001*
D'Cruz et al. (2020) UK	Outpatients	Prospective cohort	119	61 days	NRM	**Breathlessness** **Post-COVID-19 function** **Positive mental health** **Psychological impairment** **Age** **Pre-existing comorbidities**	OR = 3.19 OR = 4.66 OR = 3.58 NR NR NR	*.002* *.000* *.012* *NS* *NS* *NS*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Dennis et al. (2021 UK	Outpatients	Prospective cohort	201	Median 141 days	NR	**Not hospitalised** **Hospitalised** **Moderate PCS** **Severe PCS**	**159/163 (97.5)** **37 (100)** **73/77 (96.1)** **115/116 (99.1)**	 *1.0* *.302*
Desgranges et al. (2021) Switzerland	Survey	Cohort	418	3-10 months	Questionnaire	 **Overweight/Obese** **Female** **Age** **Smoker** **Physical comorbidities** **Time of phone survey**	 OR = 1.70 OR = 1.61 OR = 1.08 OR = 1.79 - -	 *.001* *.001* *NS* *NS* *NS* *NS*
Dini et al. (2021) Italy	Outpatients	Cross-sectional	50	5 months	Questionnaire	**Lower resilience**	-2.51	*.015*
Fang et al. 2021 China	Telephone	Prospective cohort	1233	12 months	Physician interview	**Severe disease** **Non-severe disease**	166/438 (37.9) 234/795 (29.4)	.002
Fatima et al. (2021) India	Survey	Cohort	160	40 days	ADQ	**Fatigue on 'daily routine'**	33 (20.6)	-
Fernandez-de-Las-Penas et al. (2021) Spain	Survey	Cohort	1142	7 months	FIC ADQ	**Gender** Male Female **Persistent fatigue (F)** **ICU Admission** **Medical comorbidity**	 329 (54.7) 367 (67.8) OR 1.80 OR 0.98 NR	 *.05* *.001* *.963* *NS*
Froidure et al. (2021) Italy	Outpatients	Cohort	126	3 months	Questionnaire	**Pulmonary functions** **Age** **Sex** **Dyspnoea** **Disease severity**	NR NR NR NR NR	*NS* *NS* *NS* *NS* *NS*
Frontera et al. (2021) USA	Survey	Prospective cohort	272	6 months	ADQ	 **Neurologic COVID v controls** **Return to work**	**Median (IQR)** 45.6 (38.2–54.4) r = .118	 *.760* *.160*
Garrigues et al. (2020) France	Outpatients	Cross-sectional	120	110.9 days	Questionnaire	**Ward Group** Fatigue **ICU Group** Fatigue	 52(54.2) 14(58.3)	 *NS*
Gebhard et al. (2021) Switzerland	Survey	Cohort	1024	6.5 months	ADQ	**Gender** Women Men	 44 (8) 40 (8)	 -
Gonzalez-Hermosillo et al. (2021) Mexico	Survey	Prospective cohort	130	3 months 6 months	Questionnaire	**Female** **BMI** **Age (>50 years)** **Longer LOS** **Fatigued v. Not fatigued** Anxiety Depression Pain	- - - - - - - -	*.07* *.03* *.09* *.04* *.001* *.004* *.05* *.007*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Stomach bloated post-meals	-	*.065*
						Abdominal pain	-	*.114*
						Diarrhoea	-	*.001*
						Constipation	-	*.003*
						Nausea	-	*.015*
						Urinary frequency	-	*.070*
						Difficulty emptying bladder	-	*.117*
						Sexual function	-	*.021*
						Postural dizziness	-	*.092*
						Light-headedness (prolonged standing)	-	*.004*
						Chest pain	-	*.001*
						Tachycardia	-	*.159*
						Change pattern of sweating	-	*.008*
						Intolerance to temperature	-	*<.05*
						Sleep	-	*.009*
						Concentration impairment	-	*.004*
						Short-term memory loss	-	*.017*
						Inability to focus vision	-	*.004*
						Light sensitivity	-	*.039*
						Anosmia	-	*.001*
						Ageusia	-	*.009*
						Tingling	-	*.001*
						Dyspnoea on effort	-	*.053*
						Resting dyspnoea		
						Chronic Fatigue	17 (17.2)	
						Prevalence	OR = 1.95	*.07*
						Female	OR = 2.5	*.03*
						Age >40	OR = 1.5	*.19*
						Age >50	OR = 0.68	*0.4*
						Smoking	-	*0.7*
						Comorbidities	OR = 1.6	*0.3*
						BMI	OR = 1.05	*0.8*
						LOS (+1 day)	OR 1.28	*0.5*
						Mechanical ventilation	-	*NS*
						Serology (All)		
Graham et al. (2021) USA	Survey	Cohort	100	7 months	PROMIS	**Processing speed**	r = .450	.02
						Executive function	r = .430	.02
						Working memory	r = .440	.02
						Attention		
						SARS-CoV+	r = −.070	.79
						SARS-CoV-	r = −.760	.02
Halpin et al. (2020) UK	Outpatients	Cross-sectional	100	4-8 weeks	Fatigue	**New fatigue**		
						Ward	41 (60.3)	-
						ICU	23 (72)	
						Fatigue severity severe (>4/10)		
						Ward	10 (14.7)	-
						ICU	4 (12.5)	
						Fatigue severity moderate		
						Ward	14 (20.6)	-
						ICU	13 (40.6)	
						Fatigue Severity mild		
						Ward	17 (25)	-

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						ICU	6 (18.8)	
						Gender		
						Moderate Severe fatigue		
						Women	46 (61)	-
						Men	54 (26.6)	
						PTSD		
						Moderate severe fatigue	(43.9)	-
						No fatigue	(18.6)	
						Cognitive problems		
						Moderate severe fatigue	(41.4)	-
						Less severe fatigue	(18.6)	
						Breathlessness		
						Moderate severe fatigue	(65.9)	-
						Less severe fatigue	(39)	
						Moderate severe fatigue	NR	-
						Younger age (ward)	-	-
						Age (ICU)	-	*NS*
						Ethnicity	-	*NS*
						BMI	-	*NS*
Heightman et al. (2021) UK	Outpatients	Cohort	1325	$\geq$ 6 weeks	FAS	**Total fatigue**		
						Post-Hospitalised	24 (16-34)	
						Non-Hospitalised	30 (24-38)	
						Post-Emergency	28 (23-36)	
						CFS	10 (0.8)	
						Return to full-time work		
						Hospitalised	OR = 0.29	
						Non-Hospitalised	OR = 0.67	
						Functional recovery		
						Hospitalised	OR = 0.47	
						Non-Hospitalised	OR = 0.49	
						Post-Emergency	OR = 0.40	
Hellemons et al. (2021) Netherlands	Outpatients Survey	Prospective cohort	92	3-6 months	FAS	**Post -Covid Time**		
						6 weeks to 3 months	-	*.863*
						3 months to 6 months	-	*.006*
						Gender (F)	β = 4.05	.027
						Physical functioning	β = -2.88	<.001
Hossain et al. 2021 Bangladesh	Outpatients	Prospective cohort	2198	12 weeks	ADQ	**Gender**		
						Female	96 (27)	*.763*
						Male	199 (55.9)	
						Age	X^2 5.59	*.241*
						Marital status	X^2 2.95	*.304*
						Education	X^2 2.59	*.659*
						Rural/Urban location	X^2 1.17	*.351*
						Occupation	X^2 1.48	*.928*
						Disease severity	X^2 0.51	*.540*
						Post-covid functional status score	B 0.094	*.001*
Iqbal et al. (2021) Pakistan	Survey	Cross-sectional	158	38 days	ADQ	**Female**	92 (58)	*.05*
						Days since recovery		
						Fatigued	33.98 (15.62)	*<.001*
						Not fatigued	58.07 (26.37)	
						Disease severity		

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Mild Moderate Severe	86 (65.6) 33 (25.2) 12 (9.2)	*.005*
Jacobs et al. (2020) USA	Survey	Cohort	149	35 days	PROMIS	**Physical health rating** Poor/fair **Quality of life rating** Moderate Mild to none	 OR = 0.128 OR = 0.785 OR = 0.104	 *<.001* *NS* *NS*
Kanberg et al. (2021) Sweden	Outpatients	Prospective cohort	100	6 months	KEDS	**Disease severity** Mild Moderate Severe	 9 (38) 11 (42) 20 (42)	 0.59
Karaarslan et al. (2021) Turkey	Survey	Cohort	300	1 month	ADQ	**Fatigue severity** Mild Moderate Severe Very severe None **Multivariate** Age Female BMI LOS	 93 (31.0) 30 (10.0) 9 (3.0) 1 (0.3) 167 (55.7) OR = 0.98 OR = 1.42 OR = 1.08 OR = 0.98	 *.060* *.145* *.003* *.468*
Kashif et al. 2021 Pakistan	Telephone	Cohort	242	3 months	Questionnaire	**Gender** Female Male **Comorbidities** With Without	 38 (51) 63 (38) 13/29 (44.8) 88/213 (41.3)	 .039 .647
Labarca et al. (2021) Chile	Outpatients	Cross-sectional	60	4 months	CFQ	**Disease severity** Mild Moderate Severe	 5 (11.1) 10 (47) 10 (36)	 *.05* *.05*
Liang et al. (2020) China	Outpatients	Prospective cohort	76	3 months	Questionnaire	**3 months fatigue** TN1 at acute phase	 r = . 782	 *.008*
Lindahl et al. (2021) Finland	Survey	Cohort	101	6 months	SF-36	 54.2 (23.6) **Gender** Women Men **Mild fatigue** Women Men **Severe fatigue** Women Men	**M (SD)** 36 (83.7) 39 (7) 26 (60.5) 32 (61) 17 (39.5) 7 (13)	 .033
Liu et al. (2021) China	Outpatients	Prospective cohort	594	3, 6, 12 months	Questionnaire	**3 months** Total	 48/502 (9.6)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Moderate Severe Critical **6 months** Total Moderate Severe Critical **12 months** Total Moderate Severe Critical	7/63 (11.1) 34/378 (9.0) 7/61 (11.5) 27/422 (6.4) 5/52 (9.6) 20/313 (6.4) 2/57 (3.5) 18/486 (3.7) 0 (0) 16/379 (4.2) 2/55 (3.6)	
Liyanage-Don et al. 2021 USA	Survey	Cross-sectional	153	3 months	ADQ	**Depression v No Depression** **Anxiety v. No Anxiety**	NR NR	*<.01* *<.01*
Lombardo et al. (2021) Italy	Telephone	Prospective cohort	303	12 months	ADQ	**Age** 18-47 47-58 59-90 **Gender (F)** **Hospitalised**	 OR =1.52 OR = 3.30 OR = 0.78 OR = 0.57 OR = −0.069	 *<.001* *<.001* *.044* *.022* *.801*
Maamar et al. (2021) Spain	Outpatients	Cross-sectional	121	3 months	Interview	**Post Covid Syndrome women** **Non-Post Covid Syndrome women** **Post Covid Syndrome men** **Non-Post Covid Syndrome men** **Neutrophil count (x103/µL)** Post-Covid fatigue No fatigue Post-Covid Men	17(70%) 20 (46.5) 4 (36.4) 12 (28.6) OR = 4.68 OR = 3.37 OR = 4.07	*.05* *.61* *.041* *.047*
Mazza et al. 2021 Italy	Outpatients Online	Prospective cohort	402	1, 6, 12 months	FSS	Age LOS Severity of Depression at 6 months Severity of PTSD at 6 months Severity of Anxiety at 6 months Severity of Depression at 12 months Severity of PTSD at 12 months Severity of Anxiety at 12 months **FSS M (SD)** Men Women Comorbid Psychiatric history No psychiatric history	r = .01 r = -.06 r = .47 r = .32 r = .37 r = .56 r = .52 r = .48 3.17 ± 1.42 3.88 ± 1.73 4.05 (1.62) 3.18 (1.48)	*NS* *NS* *NS* q = .05 q = .05 q = .05 q = .05 q = .05 q = .004 q =.001

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Menges et al. (2021) Switzerland	Survey	Prospective cohort	431	6-8 months	FAS	**Age**		
						18-39	105 (64.0)	
						40–64	104 (51.0)	
						65+	24 (41.4)	
						Gender		
						Female	125 (59.2)	*NS*
						Male	108 (50.2)	
						Not hospitalised	195 (55.9)	*NS*
						Hospitalised	38 (49.4)	
						Healthcare utilisation	OR = 1.61	
						Age 18-39	OR = 0.59	*NR*
						Female	OR = 1.38	*NR*
						Initial symptoms (v severe)	OR = 1.36	*NR*
						ICU admission	OR = 4.63	*NR*
						Ex-smoker	OR = 1.58	*NR*
						BMI	OR = 1.04	*NR*
						Comorbidities	OR = 1.27	*NR*
						Time since diagnosis	OR = 1.00	*NR*
								NR
Mirfazeli et al. (2021) Iran	Survey Interview	Prospective cohort	94	9 months	CDC Criteria for Fatigue Scale	**Chronic fatigue syndrome**		
						Total 21 (22.9)		
						Female	-	*.02*
						Age	-	*NS*
						Constitutional neuropsychiatric	-	
						symptoms in the acute phase		*.01*
						Initial Covid severity		
							-	*NS*
Molnar et al. (2021) Hungary	Outpatients	Prospective cohort	101	> 4 weeks	CFQ-11		**M (SD)**	
						Total fatigue score	15.7 (5.9)	
						4-12 weeks	15.8 (5.5)	*.951*
						> 12 weeks	5.6 (6.7)	
						Fatigue severity		
						Age	OR = 1.18	*.178*
						Antibody levels		
						Total CFQ-11 score	OR = 9.03	*.003*
Morin et al. (2021) France	Telephone	Prospective cohort	478	3-4 months	MFI		**M (IQR)**	
						MFI Score	4.5 (I3.0-5.0)	
						Mental fatigue score	3.7 (3.0-4.5	
							N (%)	
						Intubated	110 (29.9)	
						Non-intubated	24 (38.1)	
Munblit et al. (2021) Russia	Telephone	Longitudinal cohort	2599	218 days	Questionnaire	**Fatigue (chronic)**		
						Chronic pulmonary disease	OR = 1.68	*.05*
						Female	OR = 1.67	*.05*
						Hypertension	OR = 1.27	*.05*
						RT- PCR "+"	OR = 1.23	*.05*
Nehme et al. (2021)	Survey	Cohort	410	7-9 months	Questionnaire	**Female**	65 (23.6)	-

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Switzerland						**Male** **Age** 18-39 40-59 > 60	20 (14.8) 30 (17.3) 43 (21.7) 12 (30.8)	 -
Noviello et al. (2021) Italy	Survey	Case control	164 patients 184 controls	4.8 months	SAGIS	**Chronic fatigue** Patients **Disease severity** Mild Moderate Severe **Diarrhoea** **Somatisation** Fatigued Not fatigued	 RR = 2.24 (33.3) (25.9) (40.1) - **M (SD)** 61.7 (10.8) 50.9 10.9)	*<.001* *.41* *.05* *<.001*
Nune et al. (2021) UK	Telephone	Prospective cohort	271	3, 6, 9 months	ADQ VAS	**3 months** Evidence of pneumonia in CXR ITU/HDU admission	 OR = 3.22 OR = 5.58	 *.008* *.020*
O'Keefe et al. (2021) USA	Survey	Cross-sectional	290	1-6 months	ADQ	**Fatigue post-acute** Median 61 days Median 139 days **Worse physical health (than before Covid)** **Physical health affects daily activities** **Emotional health affects daily activities**	 17 (19.3) 42 (21.2) OR = 10.48 OR = 10.35 OR = 2.56	 *.710*
Pauley et al. (2021) UK	Telephone/ Outpatients	Prospective cohort	332	3 months 12 months	VAS	**Fatigue severity** **Age** Male 50-69 Male > 70 Female < 50 Female 50 - 69 **≥ 1 comorbidities** **Ventilated (ICU)**	β = 0.09 β = 1.33 β = 0.96 β = 2.56 β = 1.32 β = 1.20 OR = 0.50	*.242* *.101* *.295* *.037* *.101* *.037* *NR*
Peghin et al. 2021 Italy	Telephone	Prospective cohort	599	6 months	PRO	**Disease Severity @ Onset** Asymptomatic Mild Moderate Severe Critical	**N (%)** 1/55 (1.8) 45/409 (11.0) 21/93 (22.6) 5/24 (20.8) 6/15 (40.0)	 *<.001*
Pérez-González et al. (2021) Spain	Telephone	Prospective cohort	284	6 months	Questionnaire	**Hospitalised** **Not hospitalised** **Gender** Female Male **COPD v No COPD**	36 (20.9) 4 (5.3) 22 (22) 18 (12.2) -	 *.001* *.00* *NS*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Pilotto et al. (2021) Italy	Outpatients	Cohort	165	6 months	Questionnaire	**Disease severity**		
						Moderate/Severe	OR = 2.1	*NR*
Rass et al. (2021) Austria	Outpatients	Prospective cohort	90	3 months	NR SF-36	**Quality of life on SF-36**		
						MCS $\geq$ 40	13 (19.7)	*.009*
						MCS < 40	9 (40.9)	
						PCS $\geq$ 40	12 (15.8)	*.001*
						PCS < 40	9 (81.8)	
						Disease severity (VT)	NR	*NS*
Rauch et al. (2021) Germany	Survey	Prospective cohort	127	3, 6, 12 months	ADQ	**Disease severity**		
						Mild	3 (8)	
						Moderate	19 (31)	.004
						Severe	10 (39)	
						Age		
						18 - 19	8 (28)	*.471*
						40 - 59	13 (21)	
						> 60	11 (31)	
						Gender		
						Female	24 (28)	*.390*
						Male	8 (20)	
Righi et al. (2021) Italy	Outpatients Telephone	Prospective cohort	448	4-12 weeks	Questionnaire	**Duration of fatigue**		
						Inpatients	22 days	*<.001*
						Outpatients	14 days	
Romero-Duarte et al. (2021) Spain	EHR	Retrospective cohort	797	6 months	Reported symptoms	**Gender**		
						Men	81 (18.9)	*.021*
						Women	95 (25.7)	
Sami et al. (2020) Iran	Telephone	Cohort	452	4 weeks	Questionnaire	**Disease severity**		
						Non-Severe	43/400 (10.75)	*.320*
						Severe	7/52 (13.46)	
Sathyamurthy et al. (2021) India	Telephone	Prospective cohort	279	90 days	Questionnaire	**Gender**		
						Men	16/101 (9)	*.277*
						Women	9/178 (8.9)	
						Disease Severity		
						Mild/moderate	9/163 (5.5)	*.077*
						Severe/critical	16/116 (13.8)	
Scherlinger et al. (2021) France	Outpatients	Prospective cohort	30	152 days	VAS	**Immunised**	13 (86.7)	*NS*
						Not immunised	12 (80)	
Schandl et al. (2021) Sweden	Outpatients	Cohort	113	5 months	Rand 36	**Vitality**	M Scores	
						High-flow nasal O^2/Non-invasive ventilation	44	
						Invasive ventilation support	50	
Seeßle et al. (2021) Germany	Outpatients	Prospective cohort	96	5/12 months	Questionnaire			*.043*
Shang et al. (2021) China	Telephone	Cohort	796	6 months	Questionnaire	**Disease Severity**		
						Severe	183 (25.3)	*.902*
						Critical	18 (24.7)	
						Gender		
						Men	86 (21.3)	*.009*
						Women	115 (29.3)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
						Age		
						< 65	125 (26.1)	*.500*
						> 65	76 (24.0)	
Shendy et al. (2021) Egypt	Telephone	Cross-sectional	81	3-5 months	MFIS	**Fatigued v Not fatigued**		
						Gender	-	*.40*
						Age	-	*.80*
						BMI	-	*.44*
						Smoking status	-	*.89*
						O^2 supplementation	-	*.53*
						Hospitalised	-	*.52*
						NRS Dyspnoea	-	*.04*
						Physical MFIS	r = 0.44	*<.001*
						Cognitive MFIS	r = 0.31	*.005*
						Psychosocial MFIS	r = 0.27	*.01*
Sigfrid et al. (2021) UK	Outpatients Survey	Prospective cohort	308	222 days	VAS		**M (IQR)**	
						Gender		
						Men	4.0 (2.0 – 6)	*<.001*
						Women	6.0 (2.0 - 7.0)	
						Women		*.001*
						< 50 years	OR = 2.06	*.012*
						> 50 years	OR = 1.20	*.362*
						> 70 years	OR= 0.29	*.194*
						Males		
						< 70 years	OR = 0.44	*.194*
						> 70 years	OR = 0.38	*.272*
						≥ 1 comorbidity	OR = 0.95	*.001*
						Age	-	*NS*
						Disease severity	**VAS Score**	
						WHO Scale 4	OR = -0.26	*.266*
						WHO Scale 5	OR = -0.20	*.354*
						WHO Scale 6/7	OR = -0.18	*.354*
Silva et al. (2021) Brazil	Outpatients	Cross-sectional	87	54 days	Questionnaire CFQ-11	**CFQ-11 Score**	15 (0-32)	
						Sleep	r = .440	<.001
						Depression	r = .470	<.001

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Staudt et al. 2021 Germany	Outpatients	Prospective cohort	101	10 months	Questionnaire	**Age**	OR = 1.00	*NS*
						Gender	OR = 0.52	*NS*
						Smoking	OR = 0.80	*NS*
						SpO_2	OR = 0.99	*NS*
						BMI	OR = 1.02	*NS*
						FEV_1	OR = 0.97	*NS*
						TLC/RV	OR = 1.00	*NS*
						6MWT	OR = 1.02	*NS*
						Depression PHQ-9	OR = 1.27	*.05*
						Respiratory symptoms SGRQ	OR = 1.06	*.05*
						Haemoglobin levels (g/dL)	OR = 1.26	*NS*
						Somatization index SOMS-SAD	OR = 0.90	*NS*
Stavem et al. (2021) Norway	Survey	Cohort	458	1.5-6 months	CFQ-11 RAND-36		**M (SD)**	
						CFQ Physical	10.1 (3.8)	
						CFQ Mental	5.0 (1.8)	
						Vitality	56.8 (23.9)	
						CFQ-11		
						Age		
						Marital status	OR = 1.02	*.081*
						Female gender	OR = 0.56	*.022*
						Education (university)	OR = 0.49	*.002*
						No. comorbidities >2	OR = 1.17	*.070*
						Previous depression	OR = 1.52	*.230*
						Symptoms during COVID	OR = 1.10	*.840*
						No. covid symptoms (10-23)	OR = 3.66	*.001*
						Dyspnoea	OR = 1.56	*.069*
						Confusion	OR = 2.25	*.022*
						BMI	OR = 1.03	*.130*
						Smoking	OR = 1.34	*.210*
						Days since symptom onset (128-200)	OR = 0.55	*.034*
						RAND-36 (Vitality)		
						Age	β = 1.51	*.057*
						Gender (f)	β = 9.63	*<.001*
						Marital status	β = 3.53	*<.001*
						Education (university)	β = 4.42	*.230*
						Previous depression	β = -12.05	*.005*
						Covid symptoms (#10-23)	β = −15.59	*<.001*
						Confusion during covid	β = -7.35	*.018*
						BMI	β = -0.50	*.010*
						Days since symptom onset (128-200)	β = 6.09	*.015*

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Sykes et al. (2021) UK	Outpatients	Retrospective cohort	134	113 days	Questionnaire	**Gender**		
						Males	27 (30)	*.004*
						Females	26 (56.5)	
						ICU/Ward		
						Ward	44/107 (41.1)	NR
						ICU	9/27 (33.3)	
						Follow-up days		
						47-75	5 (71.4)	NR
						76-100	13 (50)	
						101-125	26(33.3)	
						126-167	9 (39.1)	
						BMI (>)	NR	*.046*
Taboada et al. (2021) Spain	NR	Prospective cohort	91	6 months	Questionnaire	**With a decrease in functional status v. no decrease**	OR = 12.321	*.01*
						With a decrease in QoL v. no decrease	OR = 15.448	*.01*
Taylor et al. (2021) UK	Telephone Survey	Cohort	675	> 12 weeks	Amplitude Questionnaire	**High risk for post-covid healthcare needs**	169 (50.3)	-
						Low risk for post-covid healthcare needs	376 (46.8)	
Tomasoni et al. (2021) Italy	Outpatients	Cross-sectional	105	1-3 months	Questionnaire	**HADS Anxiety Scores**		
						'Normal'	18/70 (25.7)	.044
						'Pathological'	15/30 (30)	
						Ongoing fatigue	-	.05
Townsend et al. (2020) Ireland	Outpatients	Cross-sectional	128	10 weeks	CFQ	**Physical fatigue**	11.38 (4.22)	
						Psychological fatigue	4.72 (1.99)	
						Severe fatigue group:		
						Female	45 (52.3)	*.002*
						Anxiety/Depression/anti-depressant history	-	*.002*
						Days since onset		*NS*
						Critical care		*NS*
						LOS		*NS*
						BMI		*NS*
						Lab tests (NLR, LDH, CRP)		*NS*
						COVID severity		*NS*
van den Borst et al. (2021) Netherlands	Outpatients	Prospective cohort	124	3 months	NCSI	**Disease severity**	NR	*.05*
Venturelli et al. (2021) Italy	Telephone	Cohort	767	49 days 81 days	BFI	**Male**	93 (18.1)	*NR*
						Female	93 (36.9)	

Author (year), country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors	Risk Factor n. (%), OR, RR, Median (IQR)	*p*
Voruz et al. (2021) Switzerland	Outpatients Survey	Cohort	75	6-9 months	FIS SF-36	**Disease Severity**		
						Mild	2/15 (13.3)	*.088*
						Moderate	3/15 (20)	
						Severe	1/15 (6.6)	
						Quality of Life	-	*.040*
						Vitality Score		
						Mild	38.66	*.039*
						Moderate	49.00	
						Severe	56.00	
Wu et al. (2021) China	Outpatients	Cohort	54	6 months	ADQ	**Disease Severity**	**N(%)**	
						Severe	6/23 (19.4)	*NR*
						Moderate	7/31 (30.4)	
Yomogida et al. (2021) USA	Telephone	Prospective cohort	366	1, 2, 6 months	Questionnaire	**Gender (F)**	aOR = 3.90	<.001
						≥ 1 comorbidity	aOR = 4.39	<.001
						Age ≥40	aOR = 2.25	0.01
Zhang et al. (2021) China	Telephone	Cohort	2433	1 year	ADQ	**Disease Severity**		
						Severe v. Not severe	OR = 1.36	.004
						Oder age	OR = 1.02	< .001
						Gender (F)	OR = 1.27	.008
						Severe disease during hospital-stay	OR = 1.43	< .001
Zhou et al. (2021) China	Outpatients	Case-control	15 patients 14 controls	3 months	NR	**Intestinibacter bartlettii**	r = 0.545	.036
						Escherichia unclassified	r = 0.567	.028

Table 1 continued - Continuous fatigue outcomes

Author (year), Country	**Setting**	**Study Design**	**Sample (n)**	**Follow-up Time**	**Fatigue Scale**	**Risk Factors for Fatigue**	**Risk Factors M (SD) Median (IQR)**	***P***
Bardakci et al. (2021) Turkey	Outpatients	Cohort	65	6-7 months	SF-36	**6MWT** **Pulmonary functions** FVC% FEV$_1$%	r = .526 r = .242 r = .290	*<.001* *.064* *.026*
Chen et al. (2020) China	Outpatients	Cross-sectional	361	1 month	SF-36	**Gender** Women Men **LOS** **Age**	 81.80 (16.32) 83.25 (16.13) β .113 β .128	 <.001 .040 .04
Dalbosco-Salas et al. (2021) Chile	Outpatients	Prospective cohort	115	30 days	SF-36 VAS Fatigue	**Pre-rehabilitation (VT)** Total Hospitalised Not hospitalised **Post-rehabilitation (VT)** Total Hospitalised Not hospitalised **Non-ICU** Pre-rehabilitation Post-rehabilitation **ICU** Pre-rehabilitation Post-rehabilitation	 40.7 38.3 42.9 58.5 58.3 58.7 44.3 62.4 37.6 55.9	 *.001* *.001* *.001* - - - *.001* *.001*
Elanwar et al. (2021) Egypt	Outpatients	Case control	46 fatigue 46 no fatigue	6 months	CFQ	**Fatigue** Physical Mental **Fatigued v. no fatigue** Duration of acute illness Increased ferritin (ng/mL Mean consecutive difference for ECD Decremental response in ADM (Y/N) Decremental response in trapezius (Y/N)	 4 (2-7) 2 (0-3) β = 0.099 R = .425 40.7 (36.7,44.8) 9 (13%) 20 (43%)	 .05 .003 <.001 .011 <.001

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Elkan et al. (2021) Israel	Survey	Case control	42 cases 42 controls	9 months	SF-36	**Age**	-	.914
						Gender		
						Males	55 (27.5-87.5)	.720
						Females	60 (30-70)	
						Smoking		
						Never	55 (30-75)	.992
						Ever	60 (10.0-87.5)	
						Physical comorbidities	-	NS
						Obesity		
						No	60 (30-81.2)	.197
						Yes	50 (27.5-63.7)	
						BMI	r = -0.13	.310
						LOS	r = 0.03	.798
						Disease Severity		
						Mild	55 (30-75)	.440
						Moderate	60 (50-78.7)	
						Severe	45 (25-85)	
						O^2 support		
						Yes	47.5 (21.2-81.2)	.435
						No	60 (33.7-76.2)	
						Follow-up (months)	r = 0.138	.270
Evans et al. (2021) UK	Outpatients	Prospective cohort	1077	5 months	FACIT	**Disease severity**		
						WHO Class 3-4	18·5 (14·3)	NR
						WHO Class 5	14·6 (12·1)	
						WHO Class 6	16·4 (13·1)	
						WHO Class 7-9	18·5 (13·4)	
Gamberini et al. (2021) Italy	Telephone	Prospective cohort	205	3, 12 months	15D	**Full Recovery**	0.931(0.125)	
						Partial Recovery Mental	0.718 (0.160)	
						Partial Recovery Physical	0.806 (0.227)	<.001
						Bad Recovery	0.499 (0.185)	
Guo et al. (2020) China	Outpatients	Prospective cohort	259	1 month	SF-36	**Positive nucleic-acid duration > 14 days (Age 46-69)**		*.047*
						Gender	NR	*NS*
						Age	NR	*NS*
						Smoking	NR	*NS*
						Corticosteroids	NR	*NS*
Henneghan et al. (2021) USA	Survey	Cross-sectional	52	4 months	PROMIS	**Younger age**	r = .280	*<.05*
						Total symptoms (n.)	r = .300	*<.05*

Author (year), Country	Setting	Study Design	Sample (n)	Follow-up Time	Fatigue Scale	Risk Factors for Fatigue	Risk Factors M (SD) Median (IQR)	*P*
Kedor et al. (2021) Germany	Outpatients	Prospective cohort	42	6 months	CFQ	**Covid-19 Syndrome**	7 (2-10)	*.687*
						CFS v. CCS		
						Stress intolerance	-	*.042*
						Post-exertional malaise	-	*.007*
						Temperature sensitivity	-	*.024*
						Sensitivity to light	-	*.014*
						Sensitivity to noise	-	*.029*
						Autonomic dysfunction	-	*NS*
Liu et al. (2020) China	Outpatients	RCT	72	6 weeks	SF-36	**Intervention Group**		
						Pre-rehab	60.6 (6.9)	*< .05*
						Post-rehab	75.6 (7.1)	
						Control Group		
						Pre-rehab	60.5 (7.1)	*NS*
						Post-rehab	61.2 (6.3)	
Mantovani et al. (2021) Italy	Outpatients	Cohort	37	6 months	Clinical interview BORG	**MFI - FG - General fatigue**		
						All	**9**.5 (4.8)	.002
						CFS	13.6 (4.6)	
						No CFS	7.9 (3.9)	
						MFI-FF Physical Fatigue		
						All	8.7 (4.7)	.001
						CFS	13.1 (5.0)	
						No CFS	7.0 (3.4)	
						MFI-RA Reduced Activity		
						All	8.7 (4.8)	<.001
						CFS	13.6 (4.7)	
						No CFS	6.9 (3.4)	
						MFI-RM Reduced Motivation		
						All	7.5 (3.8)	.001
						CFS	10.9 (4.1)	
						No CFS	6.3 (2.9)	
						MFI-FM Mental Fatigue		
						All	8.0 (4.3)	<.001
						CFS	13.2 (3.5)	
						No CFS	6.0 (2.7)	
						Between CFS +Ve and CFS -Ve		
						Lung functions (all)	-	NS
						6MWT	-	NS
						BORG dyspnoea (baseline)	-	.014
						Subjective neuropsychological complaints (Y/N)	-	<.001
						Anxiety	-	.11
						Depression	-	.002
						SARS-CoV-2 Inflammatory markers	-	NS
						Hospitalisation	-	NS
						Sleep	-	.05
						Pain	-	.05

Author (year), Country	**Setting**	**Study Design**	**Sample (n)**	**Follow-up Time**	**Fatigue Scale**	**Risk Factors for Fatigue**	**Risk Factors M (SD) Median (IQR)**	***P***
Qin et al. (2021) USA	Telephone	Cross-sectional	55	30 days	PROMIS 7a	 **Gender (F)** **Anxiety** **Depression** **No. initial symptoms** **Age ≥ 65 vs age <65** **Frail Score** **BMI** **Baseline ADLs** **Initial symptoms (n.)** **Each day of hospitalisation** **Longer LOS** **Hypertension** **ICU admission** **ICU length of stay**	**Univariate** β = 5.4 β = 1.47 β = 0.89 OR 1.33 OR = 0.36 OR = 0.63 β = 0.05 OR = 0.29 **Multivariate** OR = 1.43 OR = 1.2 OR = 1.2 OR = 5.0 OR = 5.18 OR = 1.24	 *≤.05* *≤.05* *≤.1* *.05* *≤.1* *≤.1* *NS* *<.05* *<.01* *.08* *≤.1* *≤.1* *.03* *.02*
Strumiliene et al. (2021) Lithuania	Outpatients	Prospective cohort	51	2 months	SF-36	**Disease severity**	NR	*NS*
van der Sar -van der Brugge (2021) Netherlands	Outpatients	Prospective cohort	101	6 weeks	SF-36	**Disease severity v. Pop Norms** Moderate (lowest VT)	 NR	 *.001*
Yildirim et al. (2021) Turkey	Outpatients	Prospective cohort	70	6 months	SF-36	**Vitality Score** ICU Non-ICU	**Median (IQR)** 65 (40-80) 60 (45-80)	 *.680*
Zhao et al. (2021) China	Outpatients	Prospective cohort	94	1 year	SF-36 Questionnaire	**Disease severity (VT)** Mild/moderate Severe/critical	 80 (65, 90) 70 (60, 85)	 *.108*

NA = Not analysed; NR = Not reported; NS = not significant; r = Pearson's correlation; OR = Odds Ratio; CFS = chronic fatigue syndrome; 6MWT = 6-minute walking test; FEV_1 = forced expiratory volume; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for CO^2; KCO = carbon monoxide transfer coefficient; TLco = gas transfer capacity; ECLA = extracorporeal lung assist; ARDS = acute respiratory distress syndrome; FMA = fibromyalgia; BFHX = Bufei Huoxue supplement, PTSD = post-traumatic stress disorder; CXR = chest X-ray; WBC – white blood cell; CRP = c-reactive protein; ADL = activities of daily living; ADQ = author designed questionnaire; BFI = Brief Fatigue Inventory; BORG = Borg rating of perceived exertion scale; BRAF-NRS, V2 Revised = Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale-Revised; CFQ = Chalder Fatigue Scale; ECOG = Eastern Cooperative Oncology Group performance scale; EHR = electronic health records; FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue; FAI = Fatigue Assessment Inventory; FIC = Functional Impairment Checklist; FSS = Fatigue Severity Scale; FAS = Fatigue Assessment Scale; FIS = Fatigue Impact Scale; FRS = Fatigue Rating Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; KEDS = Karolinska Exhaustion Disorder Scale; NCSI = Nijmegen Clinical Screening Instrument; NRS = Numeric Rating Score; PCL-5 = Post-Traumatic Stress Disorder Checklist; PRO = Patient reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS-7a = short-form Fatigue; SAGIS = Structured Assessment of Gastrointestinal Symptoms Scale; SF-36 = 36-Item Short-Form Survey; SPHERE-34 = Somatic & Psychological Health Report; VAS-F = Visual Analogue Scale- Fatigue.

Supplementary Table 1. Summary of included studies with fatigue and vitality outcomes

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Agergaard et al. (2021) Denmark	Outpatients	Case-control	20	77-255 days	ADQ	NR	18 (90)	
Albu et al. (2021) Spain	Outpatients	Cross-sectional	30	≥ 3 months	MFIS	Range = 0 - 84 Higher score = severe impact	26 (86)	
Amin-Chowdhury et al. (2021) UK	Survey	Prospective cohort	1671	7 months	ADQ	NR	**+Ve cases** 55 (39.3) **-Ve controls** 203 (17.5)	<.001
Anaya et al. (2021) Colombia	Survey	Case series	100	219 days	ADQ	NR	34 (34)	
Andrade Barreto et al. (2021) Brazil	Outpatients	Cross-sectional	602	> 1 month	ADQ	NR	371 (61.6)	
Aparisi et al. (2021) Italy	Outpatients	Prospective cohort	70	3 months	NR	NR	20 (28.6)	
Aranda et al. (2021) Spain	Outpatients	Prospective cohort	113	240 days	ADQ	Range 0 - 10	51 (45)	
Arnold et al. (2020) UK	Outpatients	Prospective cohort	110	8-12 weeks	ADQ	NR	32/81 (39)	
Asadi-Pooya et al. (2021) Iran	Telephone	Retrospective cohort	4681	3-6 months 6-12 months	ADQ	NR	**3 months** 859/2685 (32) **6 months** 499/1996 (25)	.001
Augustin et al. (2021) Germany	Outpatients	Prospective cohort	958	4 months 7 months	ADQ	NR	**4 months** 43/442 (9.7) **7 months** 50/353 (14.2)	
Aul et al. (2021) UK	Telephone	Cross-sectional	387	6 weeks	ADQ	NR	165/366 (45.1)	
Aydin et al. (2021) Turkey	Outpatients	Cross-sectional	116	44 days	ADQ	NR	29 (25)	
Bai et al. 2021 Italy	Outpatients	Prospective cohort	377	102 days	Clinical interview	NR	149 (39.5)	
Barizien et al. (2021) France	Outpatients	Prospective cohort	39	7 months	Clinician assessment	NR	-	
Becker et al. 2021 Switzerland	Outpatients	Prospective cohort	90	12 months	ADQ VAS for severity	NR Range 0-10	41/90 (46%) M 5.54 (SD 2.34)	
Bek et al. (2021) Netherlands	Outpatients	Prospective cohort	492	3, 6, 12 months	FAS	≥ 36 = caseness	**3 months** 248/385 (64.5) **6 months** 277/483 (63.1) **12 months** 156/271 (60.2)	.932
Bell et al. (2021) USA	Survey	Prospective cohort	303	> 30 days	ADQ	NR	**>30 days** 78/208 (37.5) **30-59 days** 21/87 (24.1) **> 60 days** 57/121 (47.1)	
Bliddal et al. (2021) Denmark	Survey	Cohort	445	> 4 weeks	ADQ	NR	**4 weeks** 32/198 (16) **12 weeks** 21/129 (16)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Boari et al. (2021) Italy	Outpatients	Prospective cohort	91	4 months	ADQ	NR	47 (52)	
Boesl et al. (2021) Italy	Outpatients	Cross-sectional cohort	100	> 12 weeks	FSS	4-7 impairment due to fatigue > 36 = caseness	**N (%)** 67 (67)	
Boscolo-Rizzo et20 al. (2021) Italy	Outpatients	Cohort	304	12 months	ADQ	NR	83 (27.3)	
Bottemanne et al. (2021) France	Outpatients Telephone	Prospective cohort	84	1, 3 months	Clinical interview	NR	**1 month** 50/84 (59.5) **3 months** 38/82 (46.3)	
Bozzetti et al. (2021) Italy	Outpatients	Prospective cohort	49	6 months	Modified BORG Scale	6 = No exertion 20 = Maximal exertion	28 (57.1)	
Cao et al. (2021) China	Survey	Cohort	81	1-3 months	ADQ	NR	**1 month** 7 (11) **3 months** 5 (8)	
Carfi et al. (2020) Italy	Outpatients	Cohort	143	60 days	ADQ	NR	76 (53.1)	
Carvalho-Schneider et al. (2021) France	Survey	Prospective cohort	150	30-60 days	WHO Performance Status Classification	Grade 3 Grade 4	**Day 30** 74 (49.3) **Day 60** 52 (40)	
Castro et al. (2021) USA	EHR	Retrospective case-control	6619	> 30 days	EHR	NR	**31-90 days** 887 (13.4) **91-150 days** 721 (10.9)	
Catalan et al. (2021) Spain	Telephone	Cohort	76	12 months	ADQ SF-36 Vitality	NR	**No steroids** 19/44 (43.2) **Steroids** 11/32 (34.4)	
Chen, Li et al. (2021) China	Telephone	Longitudinal cohort	715	M 225 days	ADQ	NR	137 (19.2%)	
Chopra et al. (2021) India	Survey	Cohort	53	30 days	ADQ	NR	12 (22.6)	
Chudzik et al. (2021) Poland	Outpatients	RCT	50	4 weeks	FAS	Score ≥4 = severe	-	
Clavario et al. (2020) Italy	Outpatients	Prospective cohort	110	3 months	ADQ	NR	54 (49.1)	
Creamer et al. (2021) UK	Outpatients Telephone	Cohort	57	6, 9 weeks	NR	NR	14 (25)	
Daher et al. (2020) Germany	Outpatients	Prospective cohort	33	6 weeks	BORG	Range 6 - 20	15 (45)	
Danesh et al. (2021) USA	Telephone	Cross-sectional	200	2-10 months	ADQ	NR	32/62 (52)	
Darley et al. (2021) Australia	Outpatients	Longitudinal cohort	66	8 months	SPHERE-34 VAS-F	NR Range 0 – 10 > 7 = severe	15 (23) 2.0 (0.38-5.0)	
D'Cruz et al. (2020) UK	Outpatients	Prospective cohort	119	61 days	NRS	NR	78/115 (67.8)	
Daugherty et al. (2021) USA	EHR	Retrospective cohort	27074	1-6 months	ICD10	-	-	
Dennis et al. (2021) UK	Outpatients	Prospective cohort	201	Median 141 days	NR	-	197 (98)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Desgranges et al. (2021) Switzerland	Telephone	Cohort	413	3-10 months	ADQ	NR	**Cases** 132 (32) **Controls** 15 (17)	.006
Dini et al. (2021) Italy	Outpatients	Cross-sectional	50	5 months	ADQ	0 = None 1 = Mild 2 = Moderate 3 = Severe 4 = Very Severe	36 (71)	
Eloy et al. (2021) France	Survey	Prospective cohort	324	3-6 months	ADQ	NR	**3 months** 159 (49) **6 months** 152 (47)	.05
Fang et al. (2021) China	Telephone	Prospective cohort	1233	12 months	Physician interview	NR	400 (32.4)	
Fatima et al. (2021) India	Survey	Cohort	160	40 days	ADQ	NR	90 (56.2)	
Fernandez-de-Las-Penas et al. (2021) Spain	Survey	Cohort	1142	7 months	FIC ADQ	Mild = 25% Moderate = 50% Severe = 75%%	695 (61)	
Ferraro et al. (2020) Italy	Outpatients	Case-series	7	Post-discharge	BORG Scale	Range 6 - 20	6 (85.7)	
Fortini et al. (2021) Italy	Outpatients	Prospective cohort	59	4 months	ADQ	NR	25 (42.4)	
Froidure et al. (2021) Italy	Outpatients	Cohort	126	3 months	ADQ	NR	32 (25)	
Frontera et al. (2021) USA	Survey	Prospective cohort	272	6 months	ADQ	NR	98 (36)	
Ganesh et al. (2021) USA	Survey	Cross-sectional	817	6 months	PROMIS-Fatigue	NR	132 (16.2)	
Garcia-Abellan et al. (2021) Spain	Outpatients	Prospective cohort	116	1-6 months	ADQ	NR	**6 months** 12 (10.3)	
Garrigues et al. (2020) France	Outpatients	Cohort	120	110.9 days	ADQ	NR	66 (55)	
Gautam et al. (2021) UK	Outpatients	Case series	200	4-7 months	ADQ	NR	77/144 (53.5)	
Gebhard et al. (2021) Switzerland	Survey	Cohort	1024	6.5 months	ADQ	NR	84 (8.2)	
Goertz et al. (2020) Belgium Netherlands	Survey	Cohort	457	3 months	ADQ	NR	398 (87)	
Gonzalez-Hermosillo et al. (2021) Mexico	Survey	Prospective cohort	130	3 months 6 months	ADQ	NR	**3 months** 69 (53) **6 months** 61 (46.9)	.019
Graham et al. (2021) USA	Survey	Cohort	50	7 months	PROMIS	$\geq$ 50 = average	43 (85)	
Gupta et al. (2021) Pakistan	Outpatients	Case series	371	30 days	ADQ	NR	51/123 (41.4)	
Halpin et al. (2020) UK	Telephone	Cross-sectional	100	4-8 weeks	ADQ	Mild = 0-3 Moderate = 4-6 Severe = 7-10	64(64)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Heightman et al. (2021) UK	Outpatients	Cohort	1325	≥ 6 weeks	FAS	< 22 = no fatigue ≥ 22 = fatigue	644 (48.6)	
Hellemons et al. (2021) Netherlands	Outpatients Survey	Prospective cohort	92	3-6 months	FAS	≥ 22 = fatigue	**6 months** 32/63 (50.8)	
Horwitz et al. (2021) USA	Survey	Prospective cohort	126	6 months	PROMIS-10	≥ 50 = average > 0 = fatigued	107 (85)	
Hossain et al.(2021) Bangladesh	Outpatients	Prospective cohort	2198	12 weeks	ADQ	NR	295/356 (82.9)	
Iqbal et al. (2021) Pakistan	Survey	Cross-sectional	158	38 days	ADQ	NR	131 (82.9)	
Jacobs et al. (2020) USA	Survey	Cohort	149	35 days	PROMIS	NR	82 (55)	
Kanberg et al. (2021) Sweden	Outpatients	Prospective cohort	100	6 months	KEDS	19 points	40 (41)	
Karaarslan et al. (2021) Turkey	Survey	Cohort	300	1 month	ADQ	NR	133 (44.3)	
Kashif et al. 2021 Pakistan	Telephone	Cross-sectional	242	3 months	ADQ	NR	101 (41.7)	
Khalaf et al. (2021) Egypt	Survey	Cross-sectional	538	83 days	ADQ	NR	318 (59.1)	
Kozak et al. (2021) Canada	EHR	Retrospective cohort	223	3 months	ADQ	NR	31/62 (50)	
Labarca et al. (2021) Chile	Outpatients	Cross-sectional	60	4 months	CFQ	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	25 (41.7)	
Lemhofer et al. 2021 Germany	Survey	Cross-sectional	365	3 months	ADQ SF-36 Vitlity	NR Range 0 – 100 100 = max vitality	137 (37.5) M 54.6	
Leth et al. (2021) Denmark	Outpatients Telephone	Prospective cohort	49	6 weeks 12 weeks	ADQ	NR	**6 weeks** 32 (65) **12 weeks** 31 (63)	
Liang et al. (2020) China	Outpatients	Prospective cohort	76	3 months	ADQ	NR	45 (59)	
Lindahl et al. (2021) Finland	Survey	Cohort	101	6 months	ADQ SF-36 Vitality	Range 0 – 100 100 = max vitality	75 (79) **M (SD)** 54.2 (23.6)	
Liu et al. (2021) China	Outpatients	Prospective cohort	594	3, 6, 12 months	ADQ	NR	-	
Liyanage-Don et al. (2021) USA	Survey	Cross-sectional	153	3 months	ADQ	NR	31 (20.3)	
Logue et al. (2021) USA	Survey	Prospective cohort	177	3 months 9 months	ADQ	NR	24 (13.6)	
Lombardo et al. (2021) Italy	Telephone	Cohort	303	12 months	ADQ	NR	158 (52)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Maamar et al. (2021) Spain	Outpatients	Cross-sectional	121	3 months	Interview	NR	52 (42.8)	
Mahmud et al. (2021)	Telephone	Prospective cohort	355	30 days	ADQ	NR	117 (33)	
Mandal et al. (2020) UK	Outpatients Telephone	Cross-sectional	384	54 days	ADQ	NR	265 (69)	
Mazza et al. (2021) Italy	Outpatients Online	Prospective cohort	402	1, 6, 12 months	FSS	Range 0 – 63 > 36 = caseness	**12 months** 63/192 (33)	
Menges et al. (2021) Switzerland	Survey	Prospective cohort	431	6-8 months	FAS	> 22 = fatigue	233/426 (54.7)	
Mirfazeli et al. (2021) Iran	Survey Interview	Prospective cohort	94	9 months	CDC Criteria for Fatigue Scale	> 25 = fatigue	48 (51.0)	
Miyazato et al.(2020) Japan	Telephone	Retrospective cohort	63	1-4 months	ADQ	NR	10 (16) 6 (9.5)	
Molnar et al. (2021) Hungary	Outpatients	Prospective cohort	101	> 4 weeks	CFQ-11	Range 0 – 33 > 29 = caseness 0 – 11 > 4 = caseness	69 (68.3) 4-12 weeks 15.8 (5.5) >12 weeks 5.6 (6.7)	.951
Moradian et al. (2020) Iran	Telephone	Cross-sectional	300	6 weeks	ADQ	NR	39 (19.5)	
Moreno-Perez et al. (2021) Spain	Outpatients	Prospective cohort	277	8 – 12 weeks	ADQ	NR	96 (34.8)	
Morin et al. (2021) France	Telephone	Prospective cohort	478	3-4 months	MFI	Range 4 – 20 > 15 severe	134/431 (31)	
Munblit et al. (2021) Russia	Telephone	Prospective cohort	2599	218 days	ADQ	NR	551 (21.2)	
Naik et al. (2021) India	Outpatients	Prospective cohort	1234	3-6 months	ADQ	NR	45 (3.7)	
Nehme et al. (2021) Switzerland	Survey	Cohort	410	7-9 months	ADQ ECOG	NR 0 no limitations – 4 disabled	85 (20)	
Noviello et al. (2021) Italy	Survey	Case-control	164 cases 184 controls	4.8 months	SAGIS	NR	**Cases v. Controls** 52 (31.7) v. 25 (13.7) = <.001	
Nune et al. (2021) UK	Telephone	Prospective cohort	271	3, 6, 9 months	ADQ VAS	NR Range 0 – 10 > 7 = severe	**9 months** 24/41 (58) M 5.8	
O'Keefe et al. (2021) USA	Survey	Cross-sectional	290	1-6 months	ADQ	NR	59 (20.3)	
Pauley et al. (2021) UK	Telephone/ Outpatients	Prospective cohort	332	3 months 12 months	VAS	Range 0 – 10 > 7 = severe	**3 months (Cases v. Controls)** 7 (8.9) v. 51 (27.1) **6 months** 3 (10.3) v. 54 (32.5)	.809 .001
Peghin et al. (2021) Italy	Telephone	Prospective cohort	599	6 months	PRO	NA	78 (13.1)	
Pérez-González et al. (2021) Spain	Telephone	Prospective cohort	248	6 months	ADQ	NR	40 (16.1)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Pilotto et al. (2021) Italy	Outpatients	Cohort	165	6 months	ADQ	NR	56 (33.9)	
Poyraz et al. (2021) Turkey	Survey	Cross-sectional cohort	118	50 days	ADQ	Range 0 - 8	47 (40)	
Raman et al. (2020) UK	Outpatients	Cohort	58	2-3 months	FSS	Range 0 – 63 ≥ 36 = caseness	33 (55)	
Rass et al. (2021) Austria	Outpatients	Prospective cohort	90	3 months	SF-36 Vitality	< 40 = low energy/vitality	-	
Rauch et al. (2021) Germany	Survey	Prospective cohort	127	3, 6, 12 months	ADQ	NR	**6 months** 32 (25)	
Righi et al. (2021) Italy	Outpatients Telephone	Prospective cohort	448	6 - 12 weeks	ADQ	NR	**T1** = 45/175 (26) **T2** = 7/83 (9)	
Romero-Duarte et al. (2021) Spain	EHR	Retrospective cohort	797	6 months	EHR	NR	176 (22.1)	
Rosales- Castillo et al. (2021) Spain	Outpatients	Retrospective cohort	118	50 days	Question	NR	22/74 (30.5)	
Sami et al. (2020) Iran	Telephone	Cohort	452	4 weeks	ADQ	NR	50 (11)	
Sathyamurthy et al. (2021) India	Telephone	Prospective cohort	279	90 days	ADQ	NR	25 (8.9)	
Savarraj et al. (2021) USA	Telephone	Prospective cohort	48	3 months	FSS	Range 0 – 63 ≥ 36 = caseness	20 (42)	
Scherlinger et al. (2021) France	Outpatients	Prospective cohort	30	152 days	VAS	Range 0 – 10 ≥ 7 = severe	T1 28 (93) T2 25 (82)	
Seeßle et al. (2021) Germany	Outpatients	Prospective cohort	96	5, 12 months	ADQ	NR	**5 months** 40 (41.7) **12 months** 51 (53.1)	.043
Senjam et al. (2021) India	Online	Cross-sectional	773	1 month	ADQ	NR	204/257 (79·3)	
Shang et al. (2021) China	Telephone	Cohort	796	6 months	ADQ	NR	201 (25.3)	
Shendy et al. (2021) Egypt	Telephone	Cross-sectional	81	3-5 months	MFIS	Range 0 – 84 ≥ 38 caseness	52 (64.2)	
Shoucri et al. (2021) USA	EHR	Case series	929	3, 6 months	EHR	NA	**3 months** 44/488 (9.0) **6 months** 38/364 (10.4)	
Sigfrid et al. (2021) UK	Outpatients Survey	Prospective cohort	308	90, 200 M 222 days	VAS	Range 0 – 10 ≥ 7 = severe	255 (82.8)	
Silva et al. (2021) Brazil	Outpatients	Cross-sectional	87	54 days	ADQ CFQ-11	NR Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	38 (43.7)	
Smet et al. (2021) Belgium	Outpatients	Cross-sectional	220	10 weeks	ADQ	NR	90/137 (66)	
Sollini et al. (2021) Italy	Outpatients	Case control	39	98 days	NR	NR	Cases 8/18 (62)	
Soraas et al. (2021) Norway	Survey	Cohort	794	3-8 months	ADQ	NR	157/597 (23)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Staudt et al. (2021) Germany	Outpatients	Prospective cohort	101	10 months	ADQ	NR	50 (49.5)	
Stavem et al.(2021) Norway	Survey	Cross-sectional	458	1.5-6 months	CFQ-11 RAND-36	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	211 (46)	
Steinbeis et al. (2021) Germany	Outpatients	Prospective cohort	72	3, 6, 12 months	ADQ	NR	44 (60.8)	
Strumiliene et al. (2021) Lithuania	Outpatients	Cohort	51	2 months	ADQ	NR	35 (68.6)	
Suarez-Robles et a. (2021) Spain	Telephone	Cross-sectional	134	90 days	ADQ	NR	73 (54.5)	
Sultana et al. (2021) Bangladesh	Telephone	Cross-sectional	186	30-60 days	ADQ	NR	**≥ 60 days** 15 (8.1)	
Sykes et al. (2021) UK	Outpatients	Retrospective cohort	134	113 days	ADQ	NR	53 (39.6) 47-75 days 5 (71.4) 76-100 days 13(50) 101-125 days 26 (33.3) 126-167 days 9 (39.1)	
Szekely et al. (2021) Israel	Outpatients	Prospective cohort	71	90 days	Modified BORG Scale	6 - 20 17 = very hard exertion	COVID 24 (34) Control 9/35 (26)	
Taboada et al. (2021) Spain	NR	Prospective cohort	91	6 months	ADQ	NR	34 (37.4)	
Taylor et al. (2021) UK	Telephone Survey	Cohort	675	> 12 weeks	Amplitude Questionnaire	NR	-	
Tessitore et al. (2021) Switzerland	Telephone	Prospective cohort	184	1, 12 months	PROMIS	NR	**1 month** 113 (61) **12 months** 45/165 (27)	
Tiwari et al. (2021) Nepal	Outpatients	Cross-sectional	132	2 months	ADQ	NR	17 (13)	
Tleyjeh et al. (2021) Saudi Arabia	Telephone	Prospective cohort	222	122 days	ADQ	NR	T1 48 (21.6) T2 66 (29.7)	
Tomasoni et al. (2021) Italy	Outpatients	Cross-sectional	105	1-3 months	ADQ	NR	33 (31.4)	
Tosato et al. (2021) Italy	Outpatients	Cross-sectional	165	76 days	ADQ	NR	104/137 (75.9)	
Townsend et al. (2020) Ireland	Outpatients	Cross-sectional cohort	128	Median 10 weeks <8, 8-10, 10-12, >12 weeks	CFQ-11	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	67 (52.3)	
van den Borst et al. (2021) Netherlands	Outpatients	Prospective cohort	124	3 months	NCSI	Range 0 - 64	86 (69)	
Vanichkachom et al. (2021) USA	Outpatients	Case series	100	3 months	NR	NR	80 (80)	
van Veenendaal et al. (2021) Netherlands	Survey	Prospective cohort	50	3, 6 months	ADQ	NR	17 (33)	
Venturelli et al. (2021) Italy	Telephone	Cohort	767	49 days 81 days	BFI	Range 1 - 10 8-10 = Severe	334 (44.1)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Voruz et al. (2021) Switzerland	Outpatients Survey	Cohort	75	6-9 months	FIS SF-36 Vitality	Range 0 - 84	6 (8)	
Wang et al. (2021) USA	Outpatients	Cohort	126	5 months	NR	-	53 (42)	
Wong-Chew et al. (2021) Mexico	Telephone	Prospective cohort	1303	1, 3 months	ADQ	NR	**30 days** 449/1303 (34.5) **90 days** 299/928 (32.2)	.001
Wu et al. (2021) China	Outpatients	Cohort	54	6 months	ADQ	NR	13 (24.1)	
Yomogida et al. (2021) USA	Telephone	Prospective cohort	366	1, 2, 6 months	ADQ	NR	**1 month** 88 (24.0) **2 months** 62 (16.9) **6 months** 50 (13.7)	
Zayet et al. (2021) France	Telephone	Retrospective cohort	354	289 days	ADQ	NR	68 (53.5)	
Zhang et al. (2021) China	Telephone	Cohort	2433	1 year	ADQ	NR	673 (27.7)	
Zhou et al. (2021) China	Outpatients	Case-control	15 patients 14 controls	3 months	NR	-	6 (40)	
Zulu et al. (2020) Zambia	Telephone	Cohort	302	54 days	ADQ	NR	4/27 (14.8)	
CONTINUOUS FATIGUE OUTCOMES								
Bardakci et al. (2021) Turkey	Outpatients	Cohort	65	6-7 months	SF-36 Vitality	Range 0 – 100 100 = max vitality	**M (SD)** 70.8 (NR)	
Chen, Li et al. 2020 China	Outpatients	Cross-sectional	361	1 month	SF-36 Vitality	Range 0 – 100 100 = max vitality	**Male** 83.25 **Female** 81.80	
Chen, Liu et al. (2021) China	Outpatients	RCT	129	94 days	FAI	> 4 = severe fatigue	**BFHX group (n. 64)** 85.5 ± 27.6 **Placebo group (n. 65)** 100.4 ± 25.7	.0019
Dalbosco-Salas et al. (2021) Chile	Outpatients	Prospective cohort	115	30 days	SF-36 Vitality VAS Fatigue	Range 0 – 10 ≥ 7 = severe	- **VAS Fatigue** Pre-rehab = 3 (0-5) Post-rehab = 1 (0-3)	
Daynes et al. (2021) UK	Outpatients	Cohort	30		FACIT	Range 0 - 52 < 30 = severe	**Pre rehabilitation** 29 (14) **Post rehabilitation** 34 (13)	
Donaghy et al. (2021) N. Ireland	Outpatients/ Telephone	Prospective cohort	113	3 months	FIS	Range 0-160	**M** =65	
Elanwar et al. (2021) Egypt	Outpatients	Case-control	46 fatigue 46 no fatigue	6 months	CFQ	Range 0 – 33 > 29 = caseness 0 – 11 ≥ 4 = caseness	**Fatigued** 6 (3-9)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Elkan et al. (2021) Israel	Survey	Case-control	66 Cases 42 Controls	9 months	SF-36 Vitality	"	**Cases v Controls** 57.5 (30–76.2) v. 50 (23.7-80)	NS
Evans et al. (2021) UK	Outpatients	Prospective cohort	1077	5 months	FACIT	Range 0 - 52 < 30 = severe	16·8 (13·2)	
Gamberini et al. (2021) Italy	Telephone	Prospective cohort	205	3, 12 months	15D	5 = worst 1 = best	**12 months** M 0.816 (0.196)	
Guo et al. (2020) China	Outpatients	Prospective cohort	259	1 month	SF-36	"	-	
Henneghan et al. (2021) USA	Survey	Cross-sectional	52	4 months	PROMIS	NR	51.14 (7.61)	
Kayaaslan et al. (2021) Turkey	Outpatients Survey	Prospective cohort	1007	3 months	ADQ	4 (3–5) (Range 0-10)	24 (24.3)	
Kedor et al. (2021) Germany	Outpatients	Prospective cohort	42	6 months	CFQ	0 – 11 ≥ 4 = caseness	**Chronic Covid Syndrome** 7 (2-10) **CFS** 8 (5-10)	
Latronico et al. (2021) Italy	Survey	Prospective cohort	114	3-12 months	SF-36	Range 0 – 100 100 = max vitality	**M (IQR)** **3 months** 53 (46–59) **6 months** 77 (44–59) **12 months** 54 (47–59)	.600
Liu et al. (2020) China	Outpatients	RCT	72	6 weeks	SF-36	"	**Post-pulmonary rehabilitation** 75.6 (7.1) **Controls** 61.2 (6.3)	
Mancini et al. (2021) USA	Outpatients	Prospective cohort	41	3 months	BORG	Range 6 - 20	**M (SD)** 15 (NR)	
Mantovani et al. (2021) Italy	Outpatients	Cohort	37	6 months	Clinical interview BORG	NR Range 6 - 20	**M (SD)** 42.5 (20.0-36.0) 0.16 (0.45-0.0	
Novak et al. (2021) USA	Outpatients	Retrospective cohort	24	> 4 weeks	BRAF-NRS, V2 Revised	Range 0-70 > 3 (0-10)	**PASC** 9/9 (100) **Controls** 0/5 (0) **POTS** 10/10 (100)	.001
Ortelli et al (2021) Italy	Outpatients	Case-control	12 cases 12 controls	11 weeks	FRS FSS	≥ 6 = casenes Range 0 – 10 ≥ 36 = caseness Range 0–63	**M (SD)** **Cases** 8.1 (1.7) 31.6 (10.8) **Controls** 0.7 (0.5) 9.5 (0.5)	<.001
Qin et al. (2021) USA	Telephone	Cross-sectional	55	1 month	PROMIS-7a	Standard T-score = 50 (SD 10)	**Before hospitalisation** 44.2 (7.4) **After hospitalisation** 54.5 (9.8)	

Author (year), country	Setting	Study Design	Sample	Follow-up Time	Fatigue Scale	Cut-off scores for fatigue Score Range	Total Fatigue prevalence no. (%) M (SD) M (IQR)	*p*
Schandl et al. (2021) Sweden	Outpatients	Prospective cohort	113	5 months	SF-36	Range 0 – 100 100 = max vitality	**M (95% CI)** **High-flow nasal O^2/ Non-Invasive ventilation** 44 (32- 56) **Invasive mechanical ventilation** 50 (44- 57)	
Valent et al. (2020) France	Outpatients	Retrospective cohort	19	3 months	SF-36	Range 0 – 100 100 = max vitality	60 (IQR - 50-65)	
van der Sar -van der Brugge (2021) Netherlands	Outpatients	Prospective cohort	101	6 weeks	SF-36	"	NR	
Weerahandi et al. (2020) USA	Telephone	Prospective cohort	152	37 days	PROMIS	NR	**Before Covid** 4 (IQR 4-5) **After Covid** 3 (3-4)	
Yildirim et al. (2021) Turkey	Outpatients	Prospective cohort	70	6 months	SF-36	Range 0 – 100 100 = max vitality	NR	
Zhao et al. (2021) China	Outpatients	Prospective cohort	94	1 year	SF-36	"	75 (63.75, 90)	

NA = Not analysed; NR = Not reported; NS = not significant; r = Pearson's correlation; OR = Odds Ratio; CFS = chronic fatigue syndrome; 6MWT = 6-minute walking test; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for CO^2; KCO = carbon monoxide transfer coefficient; TLco = gas transfer capacity; ECLA = extracorporeal lung assist; ARDS = acute respiratory distress syndrome; FMA = fibromyalgia; BFHX = Bufei Huoxue supplement, PTSD = post-traumatic stress disorder; CXR = chest X-ray; WBC – white blood cell; CRP = c-reactive protein; ADQ = author designed ADQ; BFI = Brief Fatigue Inventory; BORG = Borg rating of perceived exertion scale; BRAF-NRS, V2 Revised = Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale-Revised; CFQ = Chalder Fatigue Scale; ECOG = Eastern Cooperative Oncology Group performance scale; EHR = electronic health records; FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue; FAI = Fatigue Assessment Inventory; FIC = Functional Impairment Checklist; FSS = Fatigue Severity Scale; FAS = Fatigue Assessment Scale; FIS = Fatigue Impact Scale; FRS = Fatigue Rating Scale; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; KEDS = Karolinska Exhaustion Disorder Scale; NCSI = Nijmegen Clinical Screening Instrument; NRS = Numeric Rating Score; PCL-5 = Post-Traumatic Stress Disorder Checklist; PRO = Patient reported outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS-7a = short-form Fatigue; SAGIS = Structured Assessment of Gastrointestinal Symptoms Scale; SF-36 = 36-Item Short-Form Survey; SPHERE-34 = Somatic & Psychological Health Report; VAS-F = Visual Analogue Scale- Fatigue.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4-5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplemental 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5-6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6,7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6,7,8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5,7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	7 & Supplemental
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplemental 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7 & Supplemental
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	na
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	13-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplemental 1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	15
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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