BMJ Open

Incidence and associated in-hospital mortality of myocardial injury characterised by elevated cardiac troponin in adult patients with traumatic brain injury: protocol for a systematic review and meta-analysis

Jiuning Tang, Jinhui Yu, Xinhai Zhang, Jun He, Minruo Chen, Maoyuan Tang, Qifu Ren, Zhi Liu, Huaqiang Ding

To cite: Tang J, Yu J, Zhang X, *et al*. Incidence and associated in-hospital mortality of myocardial injury characterised by elevated cardiac troponin in adult patients with traumatic brain injury: protocol for a systematic review and meta-analysis. *BMJ Open* 2024;**14**:e079370. doi:10.1136/bmjopen-2023-079370

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-079370).

JT and JY are joint first authors.

Received 30 August 2023
Accepted 09 April 2024

Department of Neurosurgery, People's Hospital of Yubei District of Chongqing City, Chongqing, China

Correspondence to
Dr Huaqiang Ding;
dinghuaqiang512@qq.com

ABSTRACT

Introduction Myocardial injury is a relatively common complication of traumatic brain injury (TBI). However, the incidence and clinical impact of myocardial injury characterised by elevated cardiac troponin (cTn) levels after TBI are still poorly known. The objective of our study is to assess the global incidence of myocardial injury characterised by elevated cTn in adult patients with TBI and its association with in-hospital mortality.

Methods and analysis The protocol of our systematic review and meta-analysis is performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines. We will search the Medline, Embase, Cochrane Library, Scopus and Web of Science databases from inception to 1 January 2024, for observational studies in any language that reported the incidence of elevated cTn and/or in-hospital mortality associated with elevated cTn among adult patients with TBI. Two reviewers will independently assess study eligibility, extract the data and assess the risk of bias. ORs and 95% CIs will be used with a random-effects or fixed-effects model according to the estimated heterogeneity among studies assessed by the I^2 index. We will perform a quantitative synthesis for the incidence of elevated cTn and in-hospital mortality data. If sufficient data are available, we will perform subgroup analysis and meta-regression to address the heterogeneity. In addition, we will perform a narrative analysis if quantitative synthesis is not appropriate.

Ethics and dissemination Ethics approval was not required for this study. We intend to publish our findings in a high-quality, peer-reviewed journal.

PROSPERO registration number CRD42023454686.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A broad search strategy without language or geographical limitations should help ensure that all available literature is included.
⇒ Quality, risk of bias and evidence grading will be performed.
⇒ A potential limitation can be high heterogeneity in the study quality and study population. However, subgroup analysis and meta-regression will be performed to find the exact source of heterogeneity.

INTRODUCTION

Background

Traumatic brain injury (TBI) is the leading cause of death and disability worldwide among all trauma-related injuries, with an estimated 69 million people suffering a TBI each year.[1 2] Significant morbidity and mortality are commonly caused by the neurological consequences of brain injury in patients with TBI. Nevertheless, different non-neurological complications also may occur frequently following TBI and are associated with worse outcomes. These post-traumatic non-neurological complications involve the respiratory system, cardiovascular system, coagulation, liver and/or kidney.[3 4]

Various types of cardiovascular disturbances were found in patients with TBI, including myocardial injury, left and/or right ventricular dysfunction, electrocardiography abnormalities and cardiac arrhythmias.[5] Among them, ischaemic or non-ischaemic myocardial injury, defined by cardiac troponin (cTn) elevation >99th percentile, is a relatively common cardiovascular complication, with a reported prevalence of nearly 30% in moderate to severe patients with TBI.[6] However, within the current literature, there is no uniform reflection of the incidence of myocardial injury characterised by cTn elevation after TBI. The proposed mechanisms behind cTn elevation following TBI involve

massive catecholamine release, overstimulation of sympathetic nerve activity and activation of the adrenal glands, resulting in myocardial injury and cardiac dysfunction.[5] In recent studies, elevated cTn levels have been reported as an independent risk factor for in-hospital mortality of TBI.[7 8] In addition, Krishnamoorthy *et al* have found that early myocardial injury characterised by elevated high-sensitivity cTn was associated with poor 6-month clinical outcomes following moderate to severe TBI.[6] Because cTn levels are widely used and the assays are relatively inexpensive, these levels are a promising marker for the risk stratification of TBI. However, many of the relevant published studies to date have varied in the severity and type of TBI among included patients as well as in their design (prospective vs retrospective), risk of bias and characteristics of patients (with cardiovascular comorbidities vs without cardiovascular comorbidities). Thus, their reported results vary considerably. Therefore, the purpose of this systematic review and meta-analysis is to estimate the cumulative incidence of early myocardial injury detected by cTn within the first 72 hours of admission among patients hospitalised after acute TBI. We also aim to synthesise the impact of myocardial injury on in-hospital mortality after acute TBI.

A previous meta-analysis has indicated that elevated cTn is significantly associated with high mortality in patients with TBI.[9] However, it included only four studies with relatively small sample sizes and did not assess the incidence of elevated cTn after TBI. Furthermore, this meta-analysis did not introduce relevant analysis methods, such as subgroup analysis and meta-regression, to address the heterogeneity. Against this backdrop, we outline a protocol for conducting an updated systematic review and meta-analysis to comprehensively investigate the incidence of myocardial injury characterised by elevated cTn and the association of myocardial injury with in-hospital mortality after TBI in adults. A better understanding of the incidence and clinical impact of early myocardial injury after TBI may provide important evidence to guide future healthcare design for patients with TBI and may improve the early management of TBI.

Objectives

This study has the following objectives:

1. To determine the incidence of myocardial injury characterised by early cTn elevation (>99th percentile) in adult patients with acute TBI.
2. To identify the association between myocardial injury and in-hospital mortality in patients with acute TBI.

METHODS AND ANALYSIS

Study registration

The protocol is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines (online supplemental appendix 1).[10] This protocol was registered on the PROSPERO database (CRD42023454686) on 26 August 2023.

This systematic review was planned for April 2023 and is expected to be completed in September 2024. In the final systematic review, we will describe any deviation from the protocol.

Eligibility criteria

Studies will be selected according to the criteria outlined below.

Study designs

All cross-sectional, case-control and cohort studies will be included. Cross-sectional studies will be used to extract incidence rate data. Case-control and cohort studies will be used to extract incidence rate and/or in-hospital mortality data.

Population

The population of interest is adult patients who have sustained mild, moderate or severe TBI. Considering teenagers aged 16 and 17 years are at the legal age for consent in many countries and are often treated in adult trauma units, adults are defined as 16 years and older in our review. Due to possible variations in the diagnosis of TBI, the definitions of TBI will be extracted from source studies. If the source study definition of TBI is covered by the CDC definition,[11] it will be included. Based on the initial Glasgow coma scale (GCS) score, TBI is classified as mild (GCS score, 13–15), moderate (GCS score, 9–12) and severe (GCS score, 3–8).

Exposure

The exposure will be early myocardial injury, defined as elevated serum/plasma cTn of any type (cTnI or cTnT) and assay (high-sensitive cTnI or high-sensitive cTnT) measured within the first 72 hours of admission after TBI.

According to the fourth Universal Definition of Myocardial Infarction (fourth UDMI),[12] myocardial injury is defined as the presence of an elevated cTn value above the 99th percentile URL. Previous studies analysed the role of elevated cTn in TBI in general but did not differentiate between acute or chronic myocardial injury, according to the fourth UDMI. Therefore, for our study aim, the exposure will be the presence of both acute and chronic myocardial injury after TBI in our systematic review.

To detect early myocardial injury after acute TBI and improve early management of TBI, we will choose within 72 hours of admission as the time point for measuring cTn.

Outcomes

The primary outcome will be the incidence rate of myocardial injury, defined by the presence of an elevated cTn value above the 99th percentile URL within 72 hours of admission in patients with TBI. The secondary outcome will be the in-hospital mortality of patients with TBI, with or without myocardial injury.

Search strategies

A comprehensive search without language restrictions will be conducted in the Medline via Ovid, Embase via Embase.com, Cochrane Library, Scopus and Web of Science databases from inception to 1 January 2024. We will include two search terms: 'troponin' and 'traumatic brain injury'. Search strategies are shown in online supplemental appendix 2. The search will be performed by two independent investigators (QR and ZL). To identify further eligible articles, references to the included studies will also be reviewed.

Inclusion criteria

Studies will be included in the review if they examine the incidence of early elevated cTn (measured within the first 72 hours of admission), the association between elevated cTn and in-hospital mortality in patients with TBI or both. In order to avoid publication bias, we will include grey literature (eg, conference abstracts, dissertations, policy documents and book chapters) and unpublished studies. Studies of mixed populations will be eligible if it is possible to extract data on patients with TBI.

Exclusion criteria

Studies will be excluded from the review if they are not original research studies with unique observational data (eg, reviews and meta-analyses). Additionally, studies will be excluded if they have a sample size smaller than 25 or if they are judged to be from the same study sample as another study included in the analysis. For studies that are identifiably from the same study sample, we will include the study with the largest sample size in the meta-analysis.

The PRISMA flow chart (see online supplemental appendix 3) will be used to present the selection process.

Data extraction

Two reviewers (JT and JH) will independently extract the relevant data from eligible studies. A data extraction spreadsheet will be used to extract data from the included studies (see online supplemental appendix 4). Consensus between the two reviewers was achieved through discussion. If no agreement can be reached, a third reviewer (XZ) will intervene. Data will be extracted from the following: study title, first author, year of publication, country of origin, study design (cohort, case control and so on), sample size, demographic data, type of cTn, outcome data and primary results for each study. We will contact study authors for clarification when the population characteristics, method of study or outcome data are unclear or not reported.

Risk of bias and quality assessment

The risk of bias will be independently assessed by two reviewers (JY and MC), with disagreements resolved by consensus and third-party (MT) adjudication if required.

The Newcastle-Ottawa Scale (NOS)[13] will be used to assess the quality of case-control and cohort studies, and studies were rated as good, fair or poor (see online supplemental appendix 5). The NOS includes the following three categorical criteria with a maximum score of nine stars: 'selection', which accounts for a maximum of four stars; 'comparability', which accounts for a maximum of two stars and 'exposure' (case-control studies) or 'outcome' (cohort studies), which accounts for a maximum of three stars. The National Institutes of Health (NIH) quality assessment tool[14] (see online supplemental appendix 6) will be used to assess the quality of cross-sectional studies. We will present a risk-of-bias graph and summary.

Strategy for data synthesis

Stata/MP V.14.0 (StataCorp, College Station, Texas, USA) will be used to conduct the meta-analysis. Pooled estimates of the incidence rate of elevated cTn will be determined using the 'metaprop' programme after Freeman-Tukey double arcsine transformation to stabilise the variances and will be calculated with 95% CIs. ORs with the corresponding 95% CIs will be used for pooled estimates of in-hospital mortality. Random-effects or fixed-effects models will be used according to the estimated heterogeneity. Heterogeneity will be investigated using the χ^2 test and quantified using the I^2 statistic. Low, moderate and high levels of heterogeneity are defined by I^2 values of 25%, 50% and 75%, respectively. Forest plots will be used to graphically display the effect size in each study and the pooled estimates. Funnel plots and Egger's test will be used to evaluate potential publication bias when at least 10 studies are included to synthesise the outcomes of interest.

Sensitivity analysis will be applied to identify studies responsible for heterogeneity where necessary. High heterogeneity among the available studies may be observed, including in TBI severity, presence of associated injury, prior cardiovascular comorbidity, method and timing of the cTn evaluations and management of TBI. If sufficient data are available, we will perform a comprehensive subgroup analysis based on study level (publication year, country, study design, study quality and types or assays of cTn) and patient level (associated injury, prior cardiovascular comorbidity and severity of TBI) variables to find a trend of heterogeneity. In addition, univariate and multivariate logistic meta-regression analysis will be used to find the potential source of heterogeneity. Variables with a $p<0.1$ in the univariate meta-regression will be included in the multivariate meta-regression. For all other analyses, a $p<0.05$ will be considered significant. The amount of heterogeneity in the outcome explained by risk factors will be evaluated using the R^2 index.

A narrative synthesis of studies will be undertaken if the included studies are too diverse (either clinically or methodologically) to combine in a meta-analysis.

Quality of the evidence

The quality of the evidence for each outcome will be determined with the Grading of Recommendations Assessment, Development and Evaluation working group methodology in this systematic review.

Patient and public involvement

No patient is involved.

DISCUSSION

Myocardial injury following TBI, which may negatively influence cardiac function, has been reported in observational studies. However, a robust estimate of the incidence of myocardial injury and associated in-hospital mortality after TBI is limited. With the results of our systematic review and meta-analysis, we will better understand the current situation and the unique challenges of myocardial injury after TBI, which is necessary for better management of TBI. Additionally, in our meta-analysis, identifying potential factors of heterogeneity across studies will contribute to the design of further studies.

The main strength of our study is the comprehensive analysis of outcomes and our well-recognised methodology approaches.[15 16] In the first part of our work, we will examine the pooled incidence of myocardial injury characterised by elevated cTn after TBI, which has not been conducted by any other meta-analysis. Understanding the epidemiology of myocardial injury after TBI may provide useful evidence to monitor cardiac biomarkers and echocardiograms in patients with TBI for more timely and accurate treatment.[5 17] In another part of our work, we will reexamine the relationship between myocardial injury and in-hospital mortality after TBI, which may provide evidence or direction for developing a prognosis model for TBI. As an update and expansion to the previous meta-analysis[9], many more studies published recently will be included through our comprehensive search, and new analysis methods such as subgroup analysis and meta-regression will be introduced in our systematic review and meta-analysis.

Our study has several potential limitations. First, though we will perform our systematic review according to high methodological standards, the results of our meta-analysis may be limited by the quality of the studies and the clinical and statistical heterogeneity in the reporting of the severity of TBI, different types and assays of cTn, timing of sampling and threshold of cTn. To address such concerns, we plan to conduct subgroup analysis and meta-regressions. Second, outcomes in the studies included may not be adjusted for significant extracranial injury, a significant history of pre-existing cardiovascular disease or management of TBI, which may introduce biases. Third, our results could be biased by a small sample size due to the scarcity of studies and data on our interest outcomes.

Despite some limitations, we hope that our study can answer some important clinical questions about myocardial injury after TBI, provide useful information for clinicians, researchers and policymakers, and eventually promote better understanding and management of TBI.

Contributors HD, JT and JY conceived and designed the study. HD, JT, JY, XZ, JH, MT and MC conceived the search strategy, study selection, data extraction, risk of bias/quality and statistical analysis plans. QR and ZL performed the preliminary search. JT, XZ, JH, MT and MC drafted the manuscript. HD and JY revised the manuscript. All authors approved the final version. HD is the guarantor of the review.

Funding This work was supported by the Scientific Research Project of People's Hospital of Yubei District of Chongqing City (ybyk2023-08).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Huaqiang Ding http://orcid.org/0000-0001-9101-4632

REFERENCES

1 Dewan MC, Rattani A, Gupta S, *et al*. Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2019;130:1080–97.
2 Rubiano AM, Carney N, Chesnut R, *et al*. Global neurotrauma research challenges and opportunities. *Nature* 2015;527:S193–7.
3 Astarabadi M, Khurrum M, Asmar S, *et al*. The impact of non-neurological organ dysfunction on outcomes in severe isolated traumatic brain injury. *J Trauma Acute Care Surg* 2020;89:405–10.
4 Corral L, Javierre CF, Ventura JL, *et al*. Impact of non-neurological complications in severe traumatic brain injury outcome. *Crit Care* 2012;16:R44.
5 Coppalini G, Salvagno M, Peluso L, *et al*. Cardiac injury after traumatic brain injury: clinical consequences and management. *Neurocrit Care* 2024;40:477–85.
6 Krishnamoorthy V, Manley GT, Jain S, *et al*. Incidence and clinical impact of myocardial injury following traumatic brain injury: a pilot TRACK-TBI study. *J Neurosurg Anesthesiol* 2022;34:233–7.
7 El-Menyar A, Ramzee AF, Asim M, *et al*. Comparative analysis for the implication of serum cardiac troponin measurements by conventional versus high-sensitivity assays in patients with traumatic brain injury. *Minerva Cardioangiol* 2020;68:27–33.
8 Wang R, He M, Xu J. The prognostic value of cardiac troponin T in different age groups of traumatic brain injury patients. *Acta Neurol Belg* 2022;122:709–19.

9 El-Menyar A, Sathian B, Wahlen BM, *et al*. Serum cardiac troponins as prognostic markers in patients with traumatic and non-traumatic brain injuries: a meta-analysis. *Am J Emerg Med* 2019;37:133–42.
10 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;350:g7647.
11 CDC. Traumatic brain injury and concussion. 2023. Available: https://www.cdc.gov/traumaticbraininjury/index.html [Accessed 12 May 2023].
12 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231–64.
13 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of Nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
14 National Heart, Lung, and Blood Institute, National Institutes of health. Study quality assessment tools. 2021. Available: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
15 Page MJ, Moher D, Bossuyt PM, *et al*. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;372:n160.
16 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
17 Chen F, Komisarow JM, Mills B, *et al*. Echocardiogram utilization patterns and association with mortality following severe traumatic brain injury. *Anesth Analg* 2021;132:1060–6.

Appendix 1: PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☒	☐	3
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	1
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	8
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☐	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☐	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	2,3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	3
METHODS					

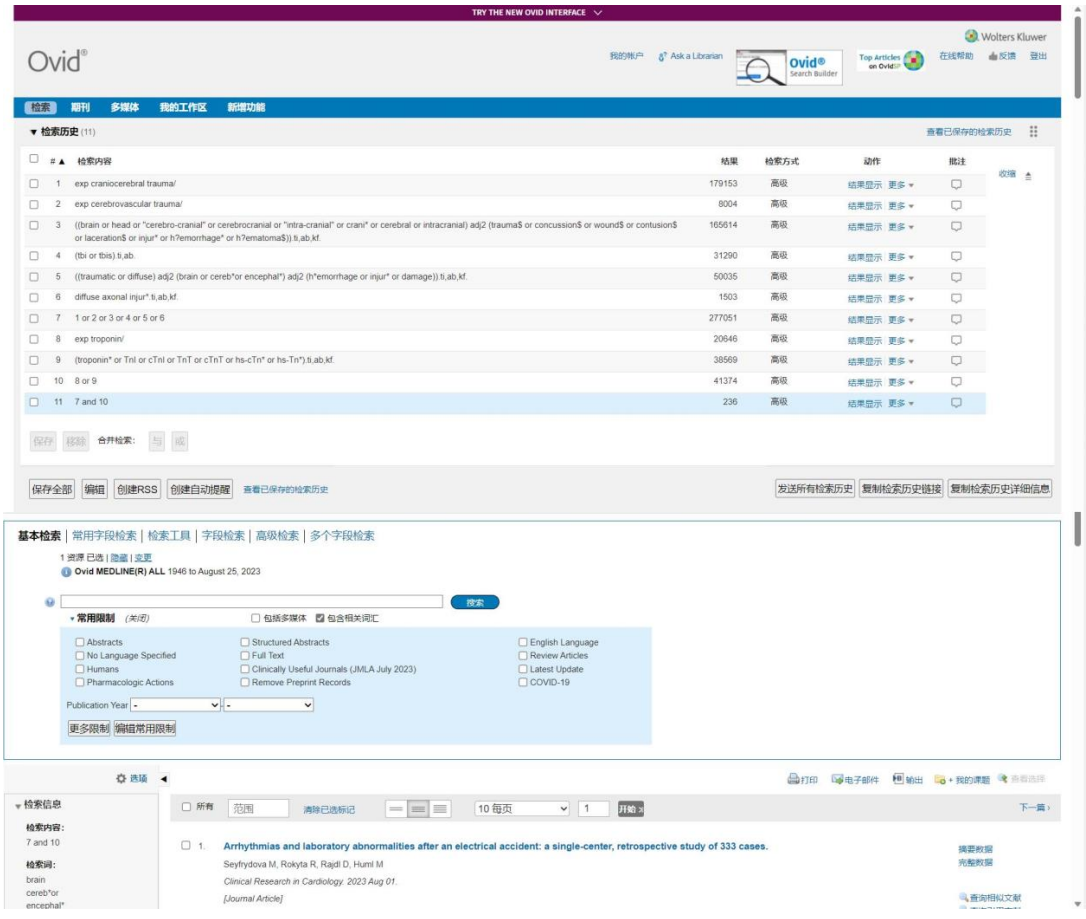
Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	3,4
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	4
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	4
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	4
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	4,5
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	4,5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	5,6
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	5,6
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	5,6
Confidence in	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	6

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
cumulative evidence					

Appendix 2: Search strategies

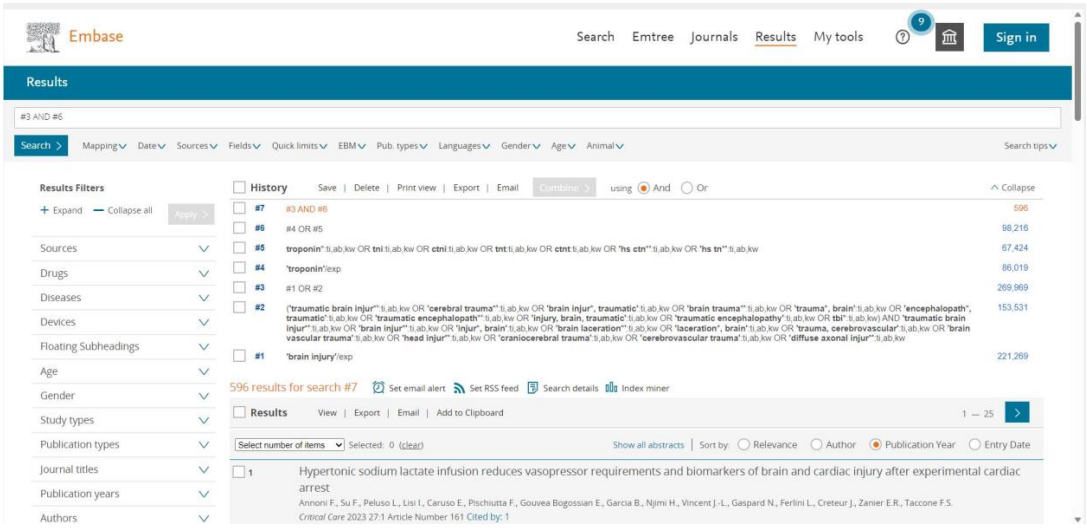
1. Medline via Ovid: Ovid MEDLINE(R) ALL 1946 to August 25, 2023

#	Search Strategy	Results
1	exp craniocerebral trauma/	179153
2	exp cerebrovascular trauma/	8004
3	((brain or head or "cerebro-cranial" or cerebrocranial or "intra-cranial" or crani* or cerebral or intracranial) adj2 (trauma$ or concussion$ or wound$ or contusion$ or laceration$ or injur* or h?emorrhage* or h?ematoma$)).ti,ab,kf.	165614
4	(tbi or tbis).ti,ab.	31290
5	((traumatic or diffuse) adj2 (brain or cereb*or encephal*) adj2 (h*emorrhage or injur* or damage)).ti,ab,kf.	50035
6	(diffuse axonal injur*).ti,ab,kf.	1503
7	1 or 2 or 3 or 4 or 5 or 6	277051
8	exp troponin/	20646
9	(troponin* or TnI or cTnI or TnT or cTnT or hs-cTn* or hs-Tn*).ti,ab,kf.	38569
10	8 or 9	41374
11	7 and 10	236



2. Embase: to 28 August 2023

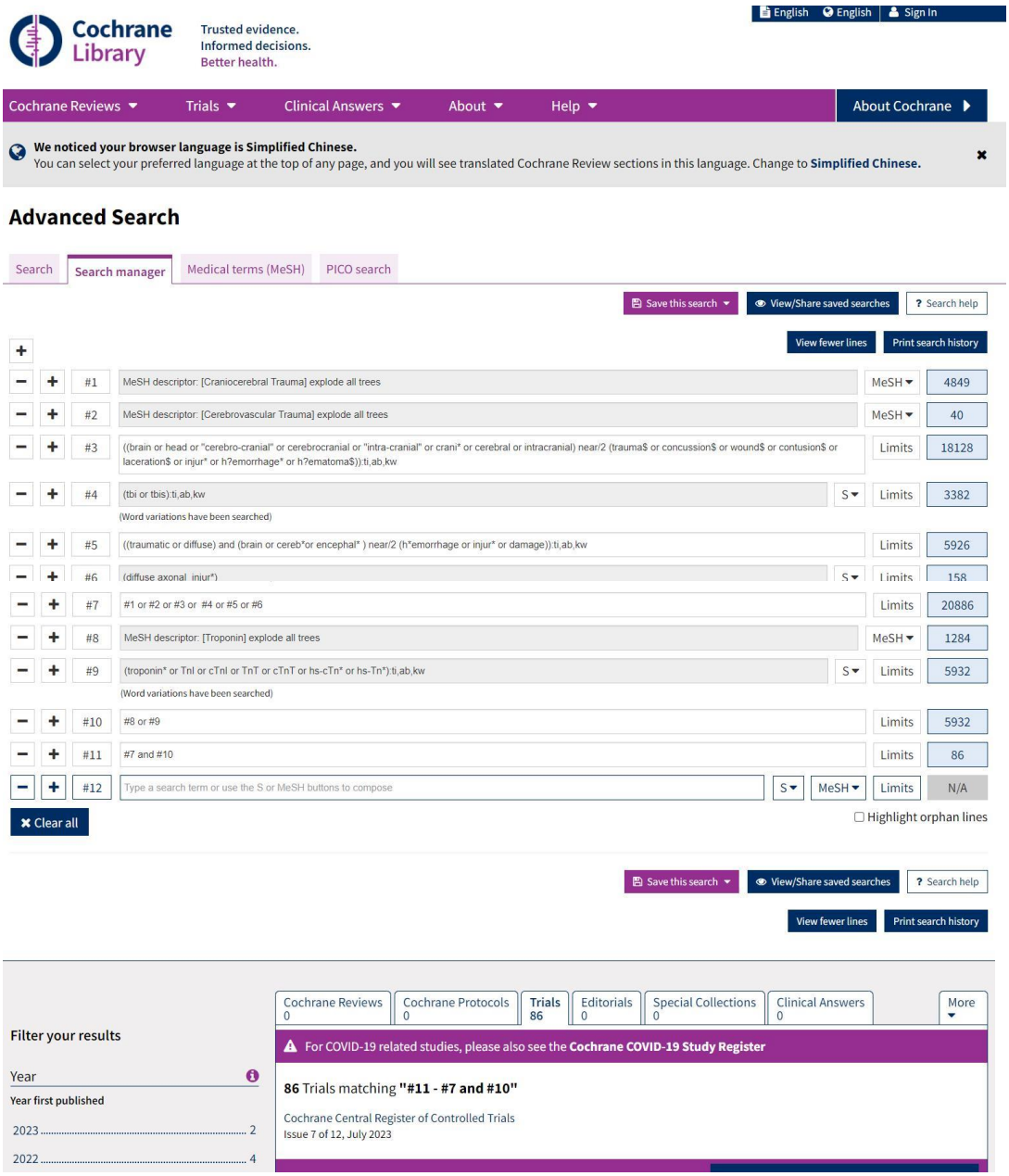
#	Search Strategy	Results
1	'brain injury'/exp	221269
2	('traumatic brain injur*' or 'cerebral trauma*' or 'brain injur*, traumatic' or 'brain trauma*' or 'trauma*, brain' or 'encephalopath*, traumatic' or 'traumatic encephalopath*' or 'injury, brain, traumatic' or 'traumatic encephalopathy' or tbi* ('traumatic brain injur*') or 'brain injur*' or 'injur*, brain' or 'brain laceration*' or 'laceration*, brain' or 'trauma, cerebrovascular' or 'brain vascular trauma' or 'head injur*' or 'craniocerebral trauma' or 'cerebrovascular trauma' or 'diffuse axonal injur*'):ti,ab,kw	153531
3	1 or 2	269969
4	'troponin'/exp	86019
5	(troponin* or TnI or cTnI or TnT or cTnT or hs-cTn* or hs-Tn*):ti,ab,kw	67424
6	4 or 5	98216
7	3 and 6	596



3.Cochrane CENTRAL advanced search (Issue 7 of 12, July 2023)

#	Search Strategy	Results
1	MeSH descriptor: [craniocerebral trauma] explode all trees	4849
2	MeSH descriptor: [cerebrovascular trauma] explode all trees	40
3	((brain or head or "cerebro-cranial" or cerebrocranial or "intra-cranial" or crani* or cerebral or intracranial) near/2 (trauma$ or concussion$ or wound$ or contusion$ or laceration$ or injur* or h?emorrhage* or h?ematoma$)).ti,ab,kw	18128
4	(tbi or tbis).ti,ab,kw	3382
5	((traumatic or diffuse) and (brain or cereb*or encephal*) near/2 (h*emorrhage or injur* or damage)).ti,ab,kw	5926
6	diffuse axonal injur*	158
7	1 or 2 or 3 or 4 or 5 or 6	20886

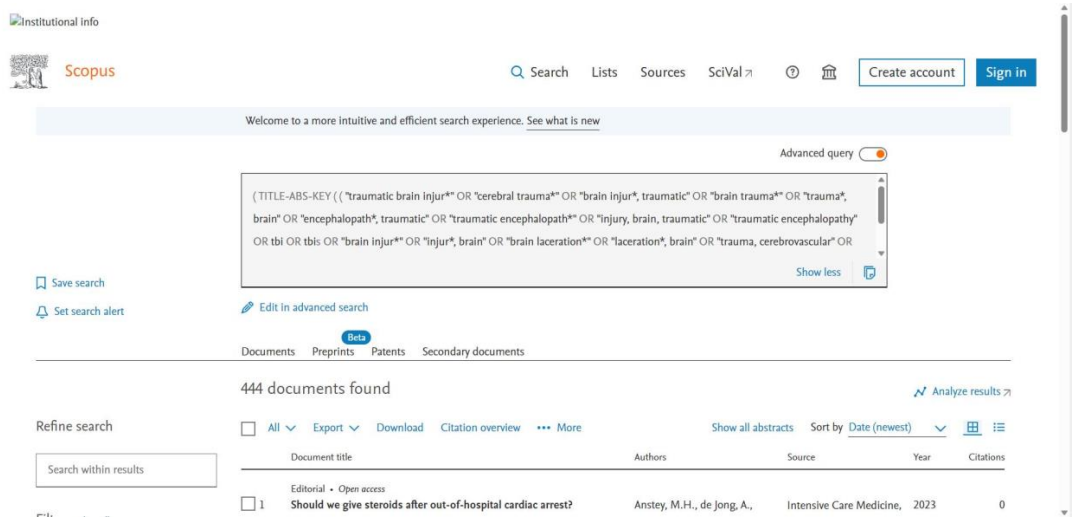
8	MeSH descriptor: [troponin] explode all trees	1284
9	(troponin* or TnI or cTnI or TnT or cTnT or hs-cTn* or hs-Tn*).ti,ab,kw	5932
10	8 or 9	5932
11	7 and 10	86



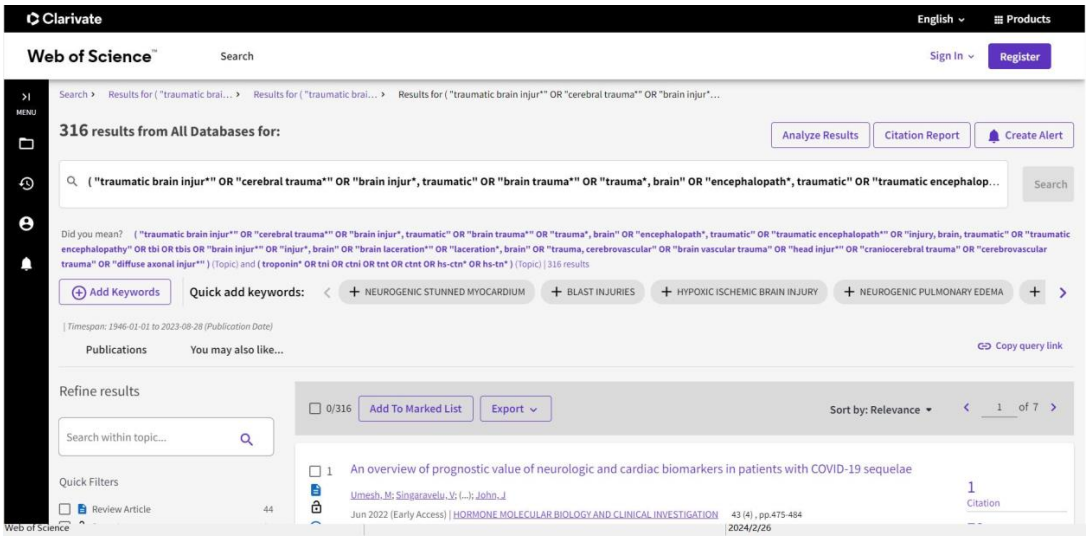
4. Scopus

TITLE-ABS-KEY ("traumatic brain injur*" OR "cerebral trauma*" OR "brain injur*, traumatic" OR "brain trauma*" OR "trauma*, brain" OR "encephalopath*, traumatic" OR "traumatic encephalopath*" OR "injury, brain, traumatic" OR "traumatic encephalopathy" OR tbi OR tbis OR "brain injur*" OR "injur*, brain" OR "brain laceration*" OR "laceration*,

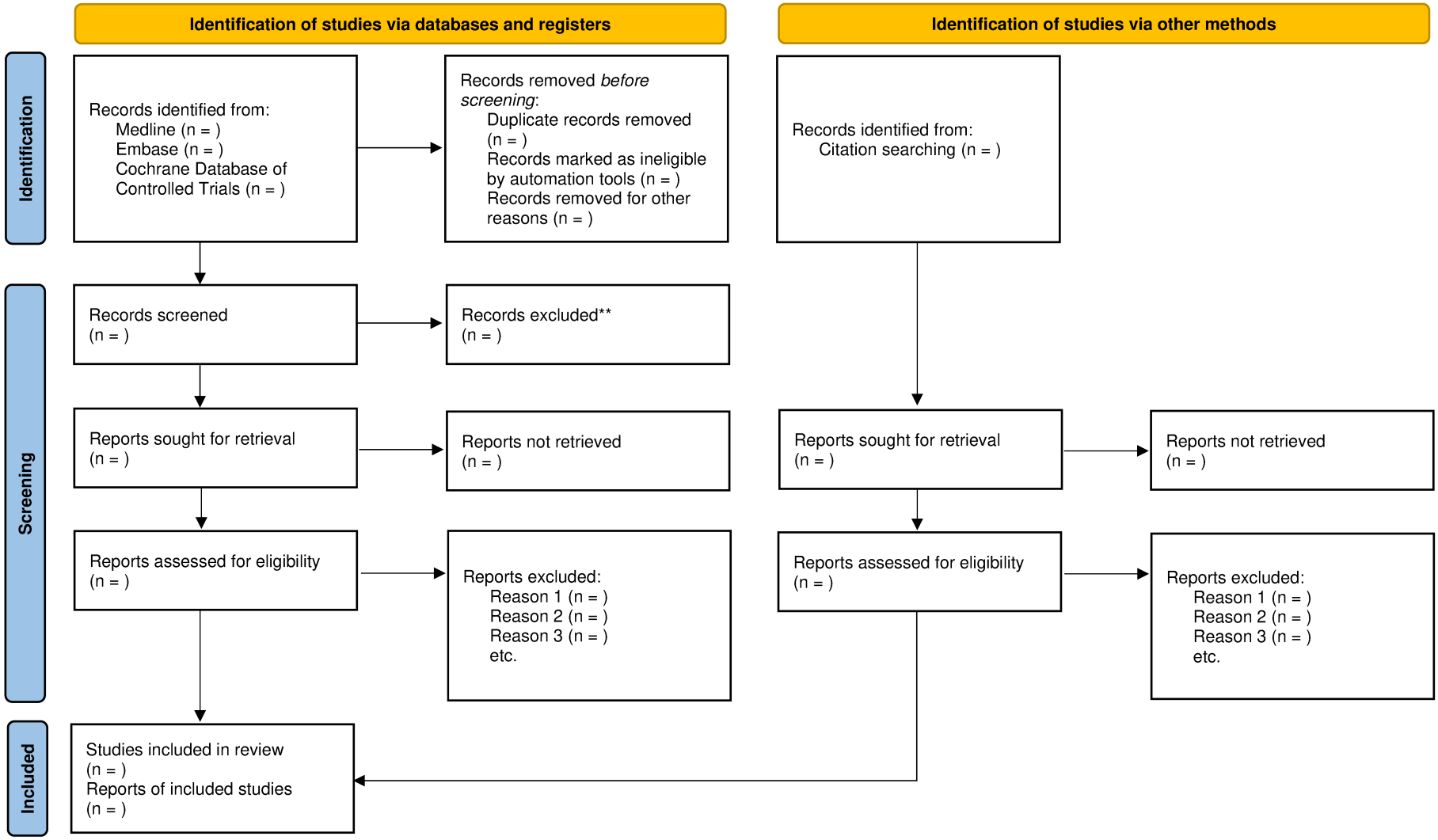
brain" OR "trauma, cerebrovascular" OR "brain vascular trauma" OR "head injur*" OR "craniocerebral trauma" OR "cerebrovascular trauma" OR "diffuse axonal injur*")
AND
TITLE-ABS-KEY ((troponin* OR tni OR ctni OR tnt OR ctnt OR hs-ctn* OR hs-tn*))
AND
PUBYEAR < 2024
444 citations



4. Web of Science
TOPIC: ("traumatic brain injur*" OR "cerebral trauma*" OR "brain injur*, traumatic" OR "brain trauma*" OR "trauma*, brain" OR "encephalopath*, traumatic" OR "traumatic encephalopath*" OR "injury, brain, traumatic" OR "traumatic encephalopathy" OR tbi OR tbbs OR "brain injur*" OR "injur*, brain" OR "brain laceration*" OR "laceration*, brain" OR "trauma, cerebrovascular" OR "brain vascular trauma" OR "head injur*" OR "craniocerebral trauma" OR "cerebrovascular trauma" OR "diffuse axonal injur*")
TOPIC: (troponin* OR tni OR ctni OR tnt OR ctnt OR hs-ctn* OR hs-tn*)
Timespan: 1946-01-01 to 2023-08-28
316 citations



Appendix 3: PRISMA flow diagram



Appendix 4: Summary of the Studies Reporting Myocardial Injury after Traumatic Brain Injury

Author and publication year	Country	Study design	Sample size	Age (years)	Men (%)	Severity of TBI	Pre-existing cardiac disease excluded	Extracranial injury excluded	β-blockers Used	Type of cTn	Time of evaluation	Definitions of myocardial injury	Prevalence n (%)	Primary outcome	Findings

Appendix 5: NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

1. Newcastle-Ottawa Quality Assessment Form for Case-Control Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition (non survivors with traumatic brain injury during hospitalization) adequate?
   a) yes, with independent validation ✸
   b) yes, e.g. record linkage or based on self report
   c) no description

2) Representativeness of the cases with traumatic brain injury
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls (survivors with traumatic brain injury during hospitalization)
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ severity of traumatic brain injury _____ (Select the most important factor.) ✸
   b) study controls for any additional factor: age, gender, injury mechanism, extracranial injury or cardiovascular history ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure (myocardial injury)
   a) secure record (e.g. surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

2. Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be awarded a maximum of one star (✸)for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
a) truly representative of the average _population with myocardial injury after traumatic brain injury_____ (describe) in the community ✸
b) somewhat representative of the average ___ population with myocardial injury after traumatic brain injury _____ in the community ✸
c) selected group of users e.g. nurses, volunteers
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort ✸
b) drawn from a different source
c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure (myocardial injury after traumatic brain injury)
a) secure record (e.g. surgical records) ✸
b) structured interview ✸
c) written self report
d) no description

4) Demonstration that outcome (incidence or in-hospital mortality of myocardial injury after traumatic brain injury) of interest was not present at start of study
a) yes ✸
b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
a) study controls for ___ severity of traumatic brain injury _____ (select the most important factor) ✸
b) study controls for any additional factor: age, gender, injury mechanism, extracranial injury or cardiovascular history ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome (incidence or in-hospital mortality of myocardial injury after traumatic brain injury)
a) independent blind assessment ✸
b) record linkage ✸
c) self report
d) no description

2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) ✸
b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✹
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > __80__ % (select an adequate %) follow up, or description provided of those lost) ✹
   c) follow up rate < __80__% (select an adequate %) and no description of those lost
   d) no statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 6: National Institutes of Health (NIH) quality assessment tool for cross-sectional studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?		√	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?		√	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			

11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Reviewers used the study rating tools on the range of items included in each tool to judge each study to be of "good," "fair," or "poor" quality.

Note: For cross-sectional analyses, the answer to Question 6 and Question7 should be "no."