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Diagnostic performance of food consumption for bacteraemia in patients admitted with suspected infection: a prospective diagnostic study

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Abstract

Objectives

A previous study reported that food consumption assessed by nursing staff is useful to rule out bacteraemia in hospitalized patients. The aims of this study were to validate the diagnostic performance of i) food consumption, and ii) a previously reported algorithm using food consumption and shaking chills for bacteraemia in patients admitted to hospital with suspected infection.

Design

Prospective cohort study.

Setting

Department of General Medicine in two acute care hospitals in Japan.

Participants

A total of 2009 adult patients who underwent at least two blood cultures upon admission.

Primary outcome measures

The reference standard for bacteraemia was judgement by two independent specialists of infectious diseases. Food consumption was rated by patients themselves or their caregivers. Diagnostic performance of food consumption and the algorithm using food consumption and shaking chills were evaluated.

Results

Among 2009 patients, 326 patients were diagnosed with bacteraemia (16.2%). Diagnostic performance of food consumption for bacteraemia was sensitivity of 84.4% (95% confidence interval [CI] 80.1 – 88.0) and negative predictive value of 86.8% (95% CI 83.1 – 89.8). The discriminative performance was close to the line of no discrimination with an area under the curve of 0.53 (95% CI 0.50 – 0.56). The performance of the algorithm using food

consumption and shaking chills was also poor, missing 36 patients (10.2% [95% CI 7.5 – 13.9]) with bacteraemia among 352 patients categorized in the low risk group.

Conclusion

Contrary to previous findings, our results did not show the usefulness of food consumption for the diagnosis of bacteraemia in patients admitted to hospital with suspected infection.

Article Summary

Strengths and limitations of this study

This was the first study to evaluate the external validity of the diagnostic performance of food consumption and an algorithm using food consumption and shaking chills for bacteraemia in patients admitted to hospital with suspected infection.

For the assessment of food consumption in patients admitted for work-up/management of suspected infection that occurred outside the hospital, food consumption was rated by patients themselves or their caregivers as 24-hour food intake in proportion to the usual intake.

Rather than the inclusion criterion of those who underwent blood cultures based on physicians' judgment, more objective criteria (e.g., based on patient's signs and symptoms) would be more appropriate.

Introduction

Blood cultures are essential for correct identification and management of bacteraemia.[1] Positive blood cultures provide information about the causative organism of the infection and its susceptibility to antibiotics.[2] Since the sensitivity of the cultures is diminished by antibiotics, blood cultures should be obtained before antibiotics are administered.[3] Consequently, physicians are likely to perform blood cultures in patients with suspected infection even when the suspicion of bacteraemia is low, resulting in positive results in only about 10% of patients.[4] This low yield of blood cultures leads to an unnecessary increase in medical costs, burden on both patients and healthcare workers, and risk of contamination.[5-7] Thus, it is crucial to identify patients who truly need assessment by blood cultures.

Among several clinical and laboratory items reported as useful predictors for bacteraemia, Komatsu et al. found that food consumption assessed by nursing staff is useful to rule out bacteraemia in hospitalized patients, with a negative predictive value of 98.3% for patients with a normal amount of food consumption.[8 9] They also developed a simple algorithm consisting of two items: food consumption and shaking chills. This simple algorithm was reported as useful for the risk estimation of bacteraemia. However, the assessment of food consumption by nursing staff is possible only in patients who have an episode of suspected infection during hospitalization. Thus, it is not applicable to patients admitted for work-up/management of suspected infection that occurs outside the hospital. Still, in these patients, food consumption can be assessed by the patients themselves or their caregivers.

Accordingly, the aims of this study were to validate the diagnostic performance of i) food consumption, and ii) the algorithm using food consumption and shaking chills for bacteraemia in patients admitted to hospital with suspected infection.

Materials and methods

This study was a prospective observational study at two acute care hospitals: Shirakawa Kosei General Hospital (471-bed capacity, Fukushima, Japan) and Iizuka Hospital (1048-bed

capacity, Fukuoka, Japan). The ethics committee of each hospital granted ethical approval. We followed the Standards for Reporting of Diagnostic accuracy (STARD) guideline.[10]

Patients

Between April 2017 and January 2019, we consecutively included patients using the following inclusion criteria: i) patients who underwent at least two sets of blood culture within 24 hours of admission to the Department of General Medicine and ii) aged 18 years or older. As in previous studies,[6 7 9] we used the physicians' decision to obtain blood cultures as a surrogate indicator of suspected infection. The exclusion criteria were as follows: i) patients under tube-feeding (because the amount of food consumption is not affected by the patients' status) and ii) use of glucocorticoid or immunosuppressants (because blood cultures should be taken for these high-risk patients).

Food consumption

In the previous study by Komatsu et al., food consumption was defined as the amount of meal intake during hospitalization just before blood cultures as rated by nursing staff.[9] However, this assessment by nursing staff was not applicable to patients who underwent blood cultures upon admission. Therefore, food consumption needed to be assessed by the patients themselves or by their caregivers in this study. From a previous study that evaluated the diagnostic performance of food consumption for the diagnosis of community-acquired pneumonia, we used a definition of food consumption based on self-assessment of 24-hour food intake in proportion to the usual intake.[11] In cases where patients could not assess food consumption by themselves (e.g., those with dementia), we asked their caregivers to rate it. Although the cut-off point for food consumption in the study by Komatsu et al. was 80% (i.e., normal: >80% intake of a meal, low: ≤80% intake), this cut-off was not defined to optimize its diagnostic performance (i.e., it was clinically defined).[8 9] Therefore, we evaluated its diagnostic performance with various cut-off points. Further details of the evaluation are given in the *Statistical analyses* section below.

Algorithm using food consumption and shaking chills

In the algorithm developed by Komatsu et al., shaking chills was used in addition to food consumption.[9] According to a previous study,[12] shaking chills was defined as "feeling extremely cold with rigors and generalized bodily shaking, even under a thick blanket". Based on these two dichotomized variables of food consumption and shaking chills, patients were categorized into four groups: normal food consumption without shaking chills (group 1), normal food consumption with shaking chills (group 2), low food consumption without shaking chills (group 3), and low food consumption with shaking chills (group 4). In the original study by Komatsu et al., the prevalence of bacteraemia in each group was 2.4%, 4.0%, 14.4%, and 47.7%, respectively.[9] Group 1 and 4 were classified as low and high risk of true bacteraemia, respectively, while group 2 and 3 were classified as "further assessment is required".

Definition of bacteraemia

At least two sets of blood cultures (one aerobic and one anaerobic bottle) were collected in all patients within 24 hours of admission. For blood cultures, BacT/Alert (bioMérieux, Marcy-l'Etoile, France) was used in Shirakawa Kosei General Hospital, while BACTEC (Becton Dickinson, Sparks, USA) was used in Iizuka Hospital. In both hospitals, the minimum incubation period was 7 days. Positive blood cultures do not always indicate true bacteraemia as it is sometimes caused by contamination of common skin pathogens.[13] In this study, cases with two or more positive blood cultures of a certain, unique pathogen were judged as true bacteraemia. In addition, in cases with only one positive blood culture (including cases with two or more positive blood cultures of different pathogens), they were independently judged by two infectious disease specialists (YT and HI), who were blinded from the information on food consumption and shaking chills to avoid incorporation bias.[14] Those specialists made their judgement based on other clinical information including the clinical course and the type of bacteria. Conflicts between two specialists were resolved by discussion between them.

Statistical analyses

In our dataset, there were some missing values. To avoid biased results by excluding patients with missing values, we imputed them using chained equations with all available information including the outcome.[15 16] Ten imputed datasets were separately analyzed and the results were pooled using Rubin's rules.[17]

The agreement in the judgement of the presence of bacteraemia between the two infectious disease specialists was assessed using Cohen's kappa coefficient (κ).[18]

Between those with and without bacteraemia, food consumption and the proportion of patients with shaking chills were compared using the Mann-Whitney-Wilcoxon test and the chi-square test, respectively. The diagnostic performance of food consumption was evaluated in terms of sensitivity (Sn), specificity (Sp), positive and negative predictive values (PPV and NPV, respectively), positive and negative likelihood ratio (LR+ and LR-, respectively), and diagnostic odds ratio (DOR). DOR was calculated by dividing LR+ by LR-. Higher DOR indicates better performance of discrimination, while a DOR of 1 indicates that the information does not contribute to the diagnosis at all.[19] These indexes were assessed using various cut-off points. In addition, we drew a receiver operating characteristic (ROC) curve to evaluate discriminative performance using the area under the curve (AUC). AUC ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination).[20] The diagnostic performance of shaking chills was also evaluated.

Next, we applied Komatsu et al.'s algorithm to our patients. The prevalence of bacteraemia in each of the four groups was calculated. Also, the diagnostic performance of the algorithm was calculated in a conservative scenario in which all patients in group 2 and group 3 were categorized as the high-risk group (i.e., blood cultures should be performed).

Because self-reported food consumption could be unreliable, especially in elderly patients, we performed a subgroup analysis based on age with the cut-offs of 65, 75, and 85 years old. In this subgroup analysis, the diagnostic performance of food consumption was evaluated with the cut-off of 80%.

All values above were reported as point estimates with 95% confidence intervals (CI). The Wilson Score method was used to estimate 95% CI for Sn, Sp, PPV, and NPV.[21] We

used R statistical software (version 3.6.0; R foundation for Statistical Computing, www.R-project.org) for all analyses.

Patient and public involvement

No patients were involved in the development of the research question, the outcome measures, or in the design and implementation of the study.

Results

Patients characteristics

Among the 2226 eligible patients, 12 patients under tube-feeding, 205 patients with the use of glucocorticoid or immunosuppressants were excluded. A total of 2009 patients were analyzed. Patient characteristics are shown in Table 1. Median age was 81.0 years (interquartile range [IQR] 69.0 – 88.0). Bacteraemia was diagnosed in 326 patients (16.2%). Among patients with bacteraemia, common clinical diagnoses were urinary tract infection (n = 153 [46.9%]), hepatobiliary tract infection (n = 24 [7.4%]), and skin and soft tissue infection (n = 18 [5.5%]). On the other hand, among those without bacteraemia, respiratory infection (n = 514 [30.5%]), urinary tract infection (n = 204 [12.1%]), and viral infection (n = 82 [4.9%]) were common diagnoses. Food consumption was not significantly different between patients with and without bacteraemia (30.0% [IQR 10.0 – 60.0] vs. 40.0% [IQR 10.0 – 70.0]; p = 0.194). The proportion of patients with shaking chills was significantly higher in those with bacteraemia than in those without (22.7% vs. 5.2%; p < 0.001).

Agreement in the judgement of bacteraemia

There were 156 patients with one positive blood culture. Among them, 102 patients were judged as true bacteraemia by the two infectious disease specialists. By adding 102 to 224 patients with two or more positive blood cultures, there were 326 patients with "true" bacteraemia. *Escherichia coli* was the most frequent pathogen (n = 157, 48.2%). The agreement in the judgement between the two specialists was κ of 0.83 (almost perfect agreement).[18]

Diagnostic performance of food consumption and shaking chills

In Table 2, the diagnostic performance of food consumption and shaking chills are summarized. With the cut-off of 80%, the diagnostic performance of food consumption was Sn of 84.4% (95% CI 80.1 – 88.0), NPV of 86.8% (95% CI 83.1 – 89.8), and DOR of 1.3 (95% CI 1.0 – 1.9). With the cut-off between 60% and 90%, the diagnostic performance of food consumption did not change dramatically with Sn around 80%, NPV less than 90%, and DOR around 1.3. The ROC curve is shown in Figure 1. The curve is very close to the line of no discrimination (diagonal line) with an AUC of 0.53 (95% CI 0.50 – 0.56). Shaking chills showed Sp of 94.7 (95% CI 93.6 – 95.7), PPV of 45.4 (95% CI 37.9 – 53.1), and DOR of 5.3 (95% CI 3.7 – 7.4).

Diagnostic performance of the algorithm

In Figure 2, the prevalence of bacteraemia in each group categorized based on the algorithm is shown. Among 352 patients categorized as low risk of bacteraemia (with normal food consumption without shaking chills), 36 (10.2%) patients were diagnosed with bacteraemia. The prevalence of bacteraemia was 10.2% (95% CI 7.5 – 13.9) in group 1, 46.9% (95% CI 30.9 – 63.6) in group 2, 14.5% (95% CI 12.8 – 16.4) in group 3, and 44.6% (95% CI 36.3 – 53.2) in group 4. In a conservative scenario assuming that all patients in group 2 and 3 underwent blood cultures, the diagnostic performance of the algorithm was Sn of 89.0% (95% CI 85.1 – 91.9), Sp of 18.8% (95% CI 17.0 – 20.7), PPV of 17.5% (95% CI 15.7 – 19.4), NPV of 89.8% (95% CI 86.2 – 92.5), LR of 1.1 (95% CI 1.1 – 1.1), LR- of 0.6 (95% CI 0.6 – 0.6), and DOR of 1.9 (1.7 – 2.0).

Subgroup analysis

The results of the subgroup analysis based on age are summarized in Table 3. The diagnostic performance was not different among the subgroups with Sn around 80% and NPV around 86%.

Discussion

Diagnostic performance of self-reported food consumption for bacteraemia was poor in patients admitted to hospital with suspected infection, with Sn of 84.4% (95% CI 80.1 – 88.0), NPV of 86.8% (95% CI 83.1 – 89.8), and DOR of 1.3 (95% CI 1.0 – 1.9) at the previously reported cut-off point of 80%. This poor performance of food consumption was consistent with various cut-off points between 60% and 90%. The performance of the algorithm using food consumption and shaking chills was also poor, missing 36 patients (10.2% [95% CI 7.5 – 13.9]) with bacteraemia among 352 patients categorized in the low risk of bacteraemia group.

Comparison with previous findings

In the study by Komatsu et al., the performance of food consumption was reported as Sn of 93.7%, Sp of 34.6%, LR+ of 1.43, LR- of 0.18, and DOR of 7.9,[9] which was much better than our findings. Also, only 2.4% of patients were diagnosed with bacteraemia in the low-risk group categorized by the algorithm using food consumption and shaking chills.[9]

There were several possible explanations for these dissociated findings. First, food consumption was rated by nursing staff in the study by Komatsu et al., while it was self-reported in this study. Compared to the food consumption rated by nursing staff who received instruction on how to evaluate food consumption, self-reporting by patients themselves or their caregivers could be much less reliable. We hypothesized that self-reported food consumption was imprecise because there might be many patients with memory disturbance in this super-aged population (median age 81.0 [IQR 69.0 – 88.0]). Thus, we conducted a subgroup analysis comparing the performance of self-reported food consumption between younger and older patients. However, performance did not differ among age groups, which implies that the poor diagnostic performance of self-reported food consumption was not due to the high proportion of older patients in the present study. Also, food consumption in the study by Komatsu et al. was based on the meal just before the blood cultures were taken, while it was based on 24-hour food intake before presentation in proportion to the usual intake in this study. The food consumption of the last meal latest before presentation may

reflect patients' status better than that of meals during the 24 hours before presentation. Second, the study population was different between the two studies. We included patients who were admitted for work-up/management of suspected infection (i.e., community-acquired infection), while Komatsu et al. included hospitalized patients (i.e., infection could have been acquired either in the community or in the hospital). While the prevalence of bacteraemia was similar in the two studies (16.2% in this study and 13.6% in Komatsu et al.), patients with bacteraemia in the study by Komatsu et al. could be more severe than our study patients as the former included severe hospital-acquired conditions like catheter-related blood stream infection. A larger difference in severity between patients with and without bacteraemia might lead to better discriminative performance of food consumption. However, vital sign parameters in patients with bacteraemia (e.g., body temperature, heart rate, systolic blood pressure, and respiratory rate) showed almost similar values in both studies, implying this hypothesis for the difference between the findings of the two studies is not very convincing.

Furthermore, our findings were not in line with our previous study which suggested the usefulness of self-rated food consumption (using the same definition as the present study) for the diagnosis of community-acquired pneumonia in older patients who presented with upper respiratory symptoms.[11] In this previous study, food consumption with the cut-off of 50% showed Sn of 66.7%, Sp of 79.3%, LR+ of 3.2, LR- of 0.4, and DOR of 7.7 for the diagnosis of community-acquired pneumonia.[11] The previous study aimed to differentiate pneumonia from other viral infection (i.e., upper respiratory infection), while we aimed to differentiate bacteraemia from other bacterial infection in the present study. Thus, the severity between the two conditions was less prominent in the present study than in the previous one, which might have led to the poorer performance of food consumption.

Clinical implications

Our findings suggest that self-reported food consumption is not useful for the diagnosis of bacteraemia in patients admitted for work-up of suspected infection. In a questionnaire survey, Lautenbach et al. asked physicians about the acceptability of the performance of a

clinical prediction rule for the diagnosis of bacteraemia.[22] They revealed that physicians required a very high Sn of 95% and infectious disease specialists required an even higher Sn of 98% for the clinical implementation of a prediction rule for the diagnosis of bacteraemia. This high expectation hampered the use of existing prediction rules for the diagnosis of bacteraemia. Considering the diagnostic performance of Sn of less than 90% when applied to patients admitted with suspected infection, food consumption alone and its algorithm in combination with shaking chills seemed unacceptable in clinical practice, at least with the current definition of self-reported food consumption. The performance of the algorithm in the original paper by Komatsu et al. (Sn of 93.7%) also did not satisfy this expected high Sn. Physicians may use the prediction model developed by Shapiro et al., which has been well validated in emergency and in-hospital settings with Sn of around 95%,[7 23 24] although it is less simple than the algorithm using only the two items of food consumption and shaking chills.

Strength and limitations

To the best of our knowledge, this is the first study to evaluate the external validity of the diagnostic performance of food consumption for bacteraemia. Some limitations should be noted. First, we included those who underwent at least two sets of blood culture. This criterion has been frequently used as a surrogate indicator of suspected infection in previous studies reporting prediction rules/algorithms for the diagnosis of bacteraemia.[6 7 9] Whether to order blood culture was based on physicians' judgement, therefore, it could be subjective. To improve the reproducibility of our findings, more objective criteria (e.g., based on patient's signs and symptoms) would be more appropriate. However, it is unethical and unfeasible to obtain blood cultures in patients who do not have clinical indication. Second, we performed the subgroup analysis based on age to investigate the effect of memory disturbance on the performance of food consumption. However, this should be assessed by subgroup analysis based on the presence/absence of memory disturbance and whether the judgement was rated by patients themselves or their caregivers. Unfortunately, since we did not collect these variables, we could not conduct such subgroup analysis.

Conclusions

Contrary to previous findings, our results did not show the usefulness of food consumption and the algorithm using food consumption and shaking chills for the diagnosis of bacteraemia in patients admitted to hospital with suspected infection.

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Contributors:

Toshihiko Takada: Conceptualization, Methodology, Formal analysis, Writing – Original Draft, Kotaro Fujii: Conceptualization, Methodology, Data Curation, Writing – Review & Editing, Masataka Kudo: Data Curation, Writing – Review & Editing, Sho Sasaki: Data Curation, Writing – Review & Editing, Tetsuhiro Yano: Data Curation, Writing – Review & Editing, Yu Yagi: Data Curation, Writing – Review & Editing, Yasuhiro Tsuchido: Data Curation, Writing – Review & Editing, Hideyuki Itoh: Data Curation, Writing – Review & Editing, Shunichi Fukuhara: Conceptualization, Supervision, Project administration

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Competing interests:

The authors report no conflict of interest.

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Not required.

Ethics approval:

The ethics committee of Shirakawa Kosei General Hospital (HAKURIN 17-003) and Iizuka Hospital (R-17135) granted ethical approval.

Data availability statement:

Data are available upon reasonable request to the corresponding author.

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Tables

Table 1. Patient characteristics

	Missing proportion	All patients N = 2009	Patients without bacteraemia n = 1683	Patients with bacteraemia n = 326
Age, years, median (IQR)	0.0	81.0 (69.0, 88.0)	81.0 (68.0, 88.0)	82.0 (70.0, 88.0)
Male sex, n (%)	0.0	1007 (50.1)	866 (51.5)	141 (43.3)
Diabetes mellitus, n (%)	0.0	439 (21.9)	346 (20.6)	93 (28.5)
Food consumption, proportion, median (IQR)	3.3	30.0 (10.0, 70.0)	40.0 (10.0, 70.0)	30.0 (10.0, 60.0)
Shaking chills, n (%)	2.0	162 (8.1)	88 (5.2)	74 (22.7)
Systolic blood pressure, mmHg, median (IQR)	0.9	126.0 (107.0, 147.0)	127.0 (108.0, 147.0)	122.0 (102.0, 143.0)
Diastolic blood pressure, mmHg, median (IQR)	1.6	72.0 (62.0, 85.0)	73.0 (62.0, 86.0)	69.0 (58.0, 81.0)
Pulse rate, /min, median (IQR)	0.3	93.0 (80.0, 108.0)	92.0 (80.0, 107.0)	97.5 (83.0, 110.0)
Respiratory rate, /min, median (IQR)	11.5	20.0 (18.0, 24.0)	20.00 (18.00, 24.00)	22.0 (18.0, 25.0)
Body temperature, °C, median (IQR)	0.6	37.4 (36.7, 38.3)	37.3 (36.6, 38.1)	38.0 (37.2, 39.1)
White blood cell, /μL, median (IQR)	0.0	10000.0 (7000.0, 13960)	9800.0 (6940.0, 13600.0)	10885.0 (760.0, 15487.5)
C-reactive protein, mg/dL, median (IQR)	0.0	6.8 (1.8, 13.6)	6.4 (1.7, 13.2)	8.8 (3.1, 15.9)
Death, n (%)	0.0	153 (7.6)	120 (7.1)	33 (10.1)

IQR = interquartile range.

Table 2. Diagnostic performance of food consumption and shaking chills

	Sn	Sp	PPV	NPV	LR+	LR-	DOR
Food consumption with cut-off of 60%	77.6 (72.7-81.8)	29.0 (26.9-31.2)	17.5 (15.6-19.5)	87.0 (83.9-89.5)	1.1 (1.0-1.2)	0.8 (0.6-1.0)	1.4 (1.1-1.9)
Food consumption with cut-off of 70%	79.4 (74.7-83.5)	24.5 (22.5-26.6)	16.9 (15.1-18.9)	86.0 (82.6-88.8)	1.1 (1.0-1.1)	0.8 (0.7-1.1)	1.3 (0.9-1.7)
Food consumption with cut-off of 80%	84.4 (80.1-88.0)	19.8 (18.0-21.8)	16.9 (15.2-18.9)	86.8 (83.1-89.8)	1.1 (1.0-1.1)	0.8 (0.6-1.0)	1.3 (1.0-1.9)
Food consumption with cut-off of 90%	86.0 (81.8-89.3)	17.8 (16.1-19.7)	16.9 (15.1-18.7)	86.8 (82.8-90.0)	1.1 (1.0-1.1)	0.8 (0.6-1.1)	1.3 (1.0-1.9)
Shaking chills	22.5 (18.3-27.4)	94.7 (93.6-95.7)	45.4 (37.9-53.1)	86.3 (84.7-87.8)	4.3 (3.2-5.7)	0.8 (0.8-0.9)	5.3 (3.7-7.4)

Values in parentheses are 95% confidence intervals.

Sn = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, DOR = diagnostic odds ratio

Table 3. Diagnostic performance of food consumption in subgroups based on age

	Sn	Sp	PPV	NPV	LR+	LR-	DOR
Age <65 years n = 371	80.9 (62.3-95.9)	20.2 (11.7-29.4)	16.1 (10.7-22.3)	86.3 (75.1-93.5)	1.0 (0.8-1.4)	0.8 (0.3-2.4)	1.2 (0.3-4.5)
Age 65-75 years n = 334	80.0 (60.7-95.4)	20.6 (12.0-30.0)	15.9 (10.3-22.5)	86.7 (75.3-93.6)	1.0 (0.8-1.3)	0.8 (0.3-2.6)	1.2 (0.3-4.9)
Age 75-85 years n = 523	81.1 (64.7-94.9)	20.5 (13.0-28.5)	16.1 (11.3-21.6)	86.8 (77.8-93.0)	1.0 (0.8-1.3)	0.8 (0.3-2.4)	1.3 (0.4-4.8)
Age ≥85 years n = 781	82.8 (71.0-92.8)	19.9 (13.4-26.7)	16.6 (12.6-20.9)	86.6 (79.5-91.7)	1.0 (0.9-1.2)	0.8 (0.4-1.6)	1.3 (0.6-2.9)

Values in parentheses are 95% confidence intervals.

Sn = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, DOR = diagnostic odds ratio

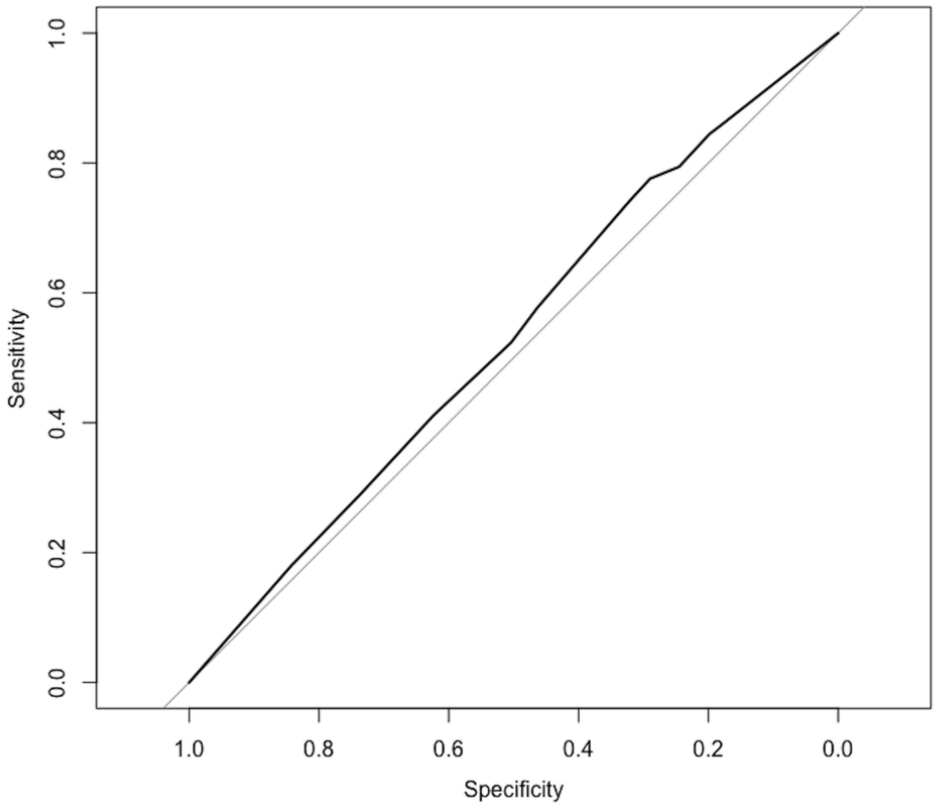
Figure legends

Figure 1. Receiver operating characteristic curve of food consumption for the diagnosis of bacteraemia

The ROC curve (black line) is close to the diagonal line (gray line), which indicates the "line of no discrimination". The area under the curve was 0.53 (95% CI 0.50 – 0.56).

Figure 2. Categorization of patients based on the algorithm using food consumption and shaking chills

Among 352 patients categorized as low risk of bacteraemia (with normal food consumption without shaking chills), 36 (10.2%) patients were diagnosed with bacteraemia.



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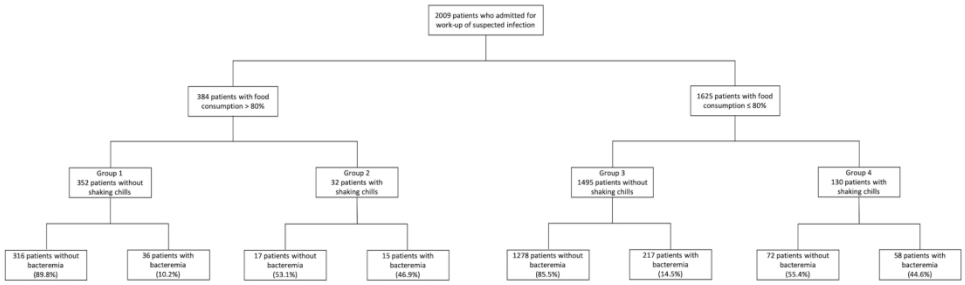

173x61mm (300 x 300 DPI)

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STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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Diagnostic performance of food consumption for bacteraemia in patients admitted with suspected infection: a prospective cohort study

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Abstract

Objectives

A previous study reported that food consumption is useful to rule out bacteraemia in hospitalized patients. We aimed to validate the diagnostic performance of i) food consumption, and ii) a previously reported algorithm using food consumption and shaking chills for bacteraemia in patients admitted to hospital with suspected infection.

Design

Prospective cohort study.

Setting

Department of General Medicine in two acute care hospitals in Japan.

Participants

A total of 2009 adult patients who underwent at least two blood cultures upon admission.

Primary outcome measures

The reference standard for bacteraemia was judgement by two independent specialists of infectious diseases. Food consumption was evaluated by the physician in charge asking the patient or their caregivers the following question upon admission: "What percentage of usual food intake were you able to eat during the past 24 hours?"

Results

Among 2009 patients, 326 patients were diagnosed with bacteraemia (16.2%). Diagnostic performance of food consumption was sensitivity of 84.4% (95% confidence interval [CI] 80.1 – 88.0), specificity of 19.8% (95% CI 18.0 – 21.8), positive predictive value (PPV) of 16.9% (95% CI 15.2 – 18.9) and negative predictive value (NPV) of 86.8% (95% CI 83.1 – 89.8). The discriminative performance was an area under the curve of 0.53 (95% CI 0.50 – 0.56). The performance of the algorithm using food consumption and shaking chills was

sensitivity of 89.0% (95% CI 85.1 – 91.9), specificity of 18.8% (95% CI 17.0 – 20.7), PPV of 17.5% (95% CI 15.7 – 19.4), and NPV of 89.8% (95% CI 86.2 – 92.5).

Conclusion

Our results did not show the usefulness of food consumption and the algorithm using food consumption and shaking chills for the diagnosis of bacteraemia in patients admitted to hospital with suspected infection.

Strengths and limitations of this study

This was the first study to evaluate the external validity of the diagnostic performance of food consumption and an algorithm using food consumption and shaking chills for bacteraemia in patients admitted to hospital with suspected infection.

The value of adding food consumption to previously reported predictors for the diagnosis of bacteraemia was also assessed.

Food consumption was evaluated by the physician in charge asking the patient or their caregivers the following question upon admission: "What percentage of usual food intake were you able to eat during the past 24 hours?"

Rather than the inclusion criterion of those who underwent blood cultures based on physicians' judgment, more objective criteria (e.g., based on patient's signs and symptoms) would be more appropriate.

Keywords:

clinical decision-making; bacteraemia; blood culture; appetite

Introduction

Blood cultures are essential for correct identification and management of bacteraemia.[1] Positive blood cultures provide information about the causative organism of the infection and its susceptibility to antibiotics.[2] Since the sensitivity of the cultures is diminished by antibiotics, blood cultures should be obtained before antibiotics are administered.[3] Consequently, physicians are likely to perform blood cultures in patients with suspected infection even when the suspicion of bacteraemia is low, resulting in positive results in only about 10% of patients.[4] This low yield of blood cultures leads to an unnecessary increase in medical costs, burden on both patients and healthcare workers, and risk of contamination.[5-7] Thus, it is crucial to identify patients who truly need assessment by blood cultures.

Among several clinical and laboratory items reported as useful predictors for bacteraemia, Komatsu et al. found that food consumption assessed by nursing staff is useful to rule out bacteraemia in hospitalized patients, with a negative predictive value of 98.3% for patients with a normal amount of food consumption.[8] They also developed a simple algorithm consisting of two items: food consumption and shaking chills.[9] This simple algorithm was reported as useful for the risk estimation of bacteraemia. However, the assessment of food consumption by nursing staff is possible only in patients who have an episode of suspected infection during hospitalization. Thus, it is not applicable to patients admitted for work-up/management of suspected infection that occurs outside the hospital. Still, in these patients, food consumption can be assessed by the patients themselves or their caregivers.

Accordingly, the aims of this study were to validate the diagnostic performance of i) food consumption, and ii) the algorithm using food consumption and shaking chills for bacteraemia in patients admitted to hospital with suspected infection.

Materials and methods

This study was a prospective observational study at two acute care hospitals: Shirakawa Kosei General Hospital (471-bed capacity, Fukushima, Japan) and Iizuka Hospital (1048-bed capacity, Fukuoka, Japan). The ethics committee of each hospital granted ethical approval.

All patients provided written informed consent. We followed the Standards for Reporting of Diagnostic accuracy (STARD) guideline.[10]

Patients

Between April 2017 and January 2019, we consecutively included patients using the following inclusion criteria: i) patients who underwent at least two sets of blood culture within 24 hours of admission to the Department of General Medicine and ii) aged 18 years or older. As in previous studies,[6 7 9] we used the physicians' decision to obtain blood cultures as a surrogate indicator of suspected infection. The exclusion criteria were as follows: i) patients under tube-feeding (because the amount of food consumption is not affected by the patients' status) and ii) use of glucocorticoid or immunosuppressants (because blood cultures should be taken for these high-risk patients).

Food consumption

In the previous study by Komatsu et al., food consumption was defined as the amount of meal intake during hospitalization just before blood cultures as rated by nursing staff.[9] However, this assessment by nursing staff was not applicable to patients who underwent blood cultures upon admission. Therefore, food consumption needed to be assessed by the patients themselves or by their caregivers in this study. From a previous study that evaluated the diagnostic performance of food consumption for the diagnosis of community-acquired pneumonia, we used a definition of food consumption based on self-assessment of 24-hour food intake in proportion to the usual intake.[11] Upon admission, the physician in charge of the management of a patient during hospitalization asked the patient "What percentage of usual food intake were you able to eat during the past 24 hours?" and recorded the responses. In cases where patients could not assess food consumption by themselves (e.g., those with dementia), we asked their caregivers to rate it. Although the cut-off point for food consumption in the study by Komatsu et al. was 80% (i.e., normal: >80% intake of a meal, low: ≤80% intake), this cut-off was not defined to optimize its diagnostic performance (i.e., it was clinically defined).[8 9] Therefore, we evaluated its diagnostic performance with various

cut-off points. Further details of the evaluation are given in the *Statistical analyses* section below.

Algorithm using food consumption and shaking chills

In the algorithm developed by Komatsu et al., shaking chills was used in addition to food consumption.[9] According to a previous study,[12] shaking chills was defined as "feeling extremely cold with rigors and generalized bodily shaking, even under a thick blanket". Based on these two dichotomized variables of food consumption and shaking chills, patients were categorized into four groups: normal food consumption without shaking chills (group 1), normal food consumption with shaking chills (group 2), low food consumption without shaking chills (group 3), and low food consumption with shaking chills (group 4). In the original study by Komatsu et al., the prevalence of bacteraemia in each group was 2.4%, 4.0%, 14.4%, and 47.7%, respectively.[9] Group 1 and 4 were classified as low and high risk of true bacteraemia, respectively, while group 2 and 3 were classified as "further assessment is required".

Definition of bacteraemia

At least two sets of blood cultures (one aerobic and one anaerobic bottle) were collected in all patients within 24 hours of admission. For blood cultures, BacT/Alert (bioMérieux, Marcy-l'Etoile, France) was used in Shirakawa Kosei General Hospital, while BACTEC (Becton Dickinson, Sparks, USA) was used in Iizuka Hospital. In both hospitals, the minimum incubation period was 7 days. Positive blood cultures do not always indicate true bacteraemia as it is sometimes caused by contamination of common skin pathogens.[13] In this study, cases with two or more positive blood cultures of a certain, unique pathogen were judged as true bacteraemia. In addition, in cases with only one positive blood culture (including cases with two or more positive blood cultures of different pathogens), they were independently judged by two infectious disease specialists (YT and HI), who were blinded from the information on food consumption and shaking chills to avoid incorporation bias.[14] Those specialists made

their judgement based on other clinical information including the clinical course and the type of bacteria. Conflicts between two specialists were resolved by discussion between them.

Statistical analyses

Sample size estimation

Based on the study by Komatsu et al.,[9] we assumed a sensitivity of food consumption and the algorithm as 94%. To estimate the assumed sensitivity with 3% absolute precision and a 95% confidence level, a sample size of at least 241 patients with bacteraemia was required.

Missing data

In our dataset, there were some missing values (ranging from 0.0 to 11.5%). To avoid biased results by excluding patients with missing values, we imputed them using chained equations with all available information including the outcome under the assumption of missing at random.[15 16] Ten imputed datasets were separately analyzed and the results were pooled using Rubin's rules.[17]

Agreement in the judgement of bacteraemia

The agreement in the judgement of the presence of bacteraemia between the two infectious disease specialists was assessed using Cohen's kappa coefficient (κ).[18]

Diagnostic performance of food consumption and the algorithm

Between those with and without bacteraemia, food consumption and the proportion of patients with shaking chills were compared using the Mann-Whitney-Wilcoxon test and the chi-square test, respectively. The diagnostic performance of food consumption was evaluated in terms of sensitivity (Sn), specificity (Sp), positive and negative predictive values (PPV and NPV, respectively), positive and negative likelihood ratio (LR+ and LR-, respectively), and diagnostic odds ratio (DOR). DOR was calculated by dividing LR+ by LR-. Higher DOR indicates better performance of discrimination, while a DOR of 1 indicates that the information does not contribute to the diagnosis at all.[19] These indexes were assessed using

various cut-off points. In addition, we used the area under the curve (AUC) to evaluate discriminative performance. AUC ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination).[20] The diagnostic performance of shaking chills was also evaluated.

Next, we applied Komatsu et al.'s algorithm to our patients. The prevalence of bacteraemia in each of the four groups was calculated. Also, the diagnostic performance of the algorithm was calculated in a conservative scenario in which all patients in group 2 and group 3 were categorized as the high-risk group (i.e., blood cultures should be performed).

Subgroup analysis

Because self-reported food consumption could be unreliable, especially in elderly patients, we performed a subgroup analysis based on age with the cut-offs of 65, 75, and 85 years old. In this subgroup analysis, the diagnostic performance of food consumption was evaluated with the cut-off of 80%.

Value of adding food consumption to previously reported predictors

We also evaluated if the information about food consumption had any additional diagnostic value to previously reported predictors for the diagnosis of bacteraemia. Based on a systematic review of existing prediction models for bacteraemia,[21] we selected the following predictors: age, performance status, living in a nursing home, indwelling vascular catheter, shaking chills, suspicion of infective endocarditis, consciousness disturbance, systolic blood pressure, pulse rate, respiratory rate, body temperature, serum creatinine and C-reactive protein. For performance status, a simplified scale with four levels was used.[22] First, we fitted a logistic regression model including those predictors and the presence/absence of bacteraemia as the outcome (base model). Next, we added food consumption to the base model (extended model). The functional form of all continuous variables was evaluated using restricted cubic splines with three knots, and incorporated as such when a non-linearity association was significant.[23] The added value of food consumption for the diagnosis of bacteraemia was quantified as the difference in model performance between the base model

and the extended model. The model performance was evaluated in terms of likelihood ratio test, discrimination (c-index), and calibration (calibration plots).

All values above were reported as point estimates with 95% confidence intervals (CI). The Wilson Score method was used to estimate 95% CI for Sn, Sp, PPV, and NPV.[24] P values less than 0.05 were considered statistically significant. We used R statistical software (version 3.6.0; R foundation for Statistical Computing, www.R-project.org) for all analyses.

Patient and public involvement

No patients were involved in the development of the research question, the outcome measures, or in the design and implementation of the study.

Results

Patient characteristics

Among the 2226 eligible patients, 12 patients under tube-feeding, 205 patients with the use of glucocorticoid or immunosuppressants were excluded. A total of 2009 patients were analyzed. Patient characteristics are shown in Table 1. Median age was 81.0 years (interquartile range [IQR] 69.0 – 88.0). Bacteraemia was diagnosed in 326 patients (16.2%). *Escherichia coli* was the most frequent pathogen (n = 157, 48.2%). Among patients with bacteraemia, common clinical diagnoses were urinary tract infection (n = 153 [46.9%]), hepatobiliary tract infection (n = 24 [7.4%]), and skin and soft tissue infection (n = 18 [5.5%]). On the other hand, among those without bacteraemia, respiratory infection (n = 514 [30.5%]), urinary tract infection (n = 204 [12.1%]), and viral infection (n = 82 [4.9%]) were common diagnoses. The assessment of food consumption was completed in 96.7% of the patients. Food consumption was not significantly different between patients with and without bacteraemia (30.0% [IQR 10.0 – 60.0] vs. 40.0% [IQR 10.0 – 70.0]; p = 0.194). The proportion of patients with shaking chills was significantly higher in those with bacteraemia than in those without (22.7% vs. 5.2%; p < 0.001).

Agreement in the judgement of bacteraemia

The agreement in the judgement between the two specialists was κ of 0.83 (substantial agreement).[18]

Diagnostic performance of food consumption and shaking chills

In Table 2, the diagnostic performance of food consumption and shaking chills are summarized. With the cut-off of 80%, the diagnostic performance of food consumption was Sn of 84.4% (95% CI 80.1 – 88.0), NPV of 86.8% (95% CI 83.1 – 89.8), and DOR of 1.3 (95% CI 1.0 – 1.9). With the cut-off between 60% and 90%, the diagnostic performance of food consumption did not change dramatically with Sn around 80%, NPV less than 90%, and DOR around 1.3. The AUC of food consumption was 0.53 (95% CI 0.50 – 0.56). Shaking chills showed Sp of 94.7 (95% CI 93.6 – 95.7), PPV of 45.4 (95% CI 37.9 – 53.1), and DOR of 5.3 (95% CI 3.7 – 7.4).

Diagnostic performance of the algorithm

In Figure 1, the prevalence of bacteraemia in each group categorized based on the algorithm is shown. Among 352 patients categorized as low risk of bacteraemia (with normal food consumption without shaking chills), 36 (10.2%) patients were diagnosed with bacteraemia. The prevalence of bacteraemia was 10.2% (95% CI 7.5 – 13.9) in group 1, 46.9% (95% CI 30.9 – 63.6) in group 2, 14.5% (95% CI 12.8 – 16.4) in group 3, and 44.6% (95% CI 36.3 – 53.2) in group 4. In a conservative scenario assuming that all patients in group 2 and 3 underwent blood cultures, the diagnostic performance of the algorithm was Sn of 89.0% (95% CI 85.1 – 91.9), Sp of 18.8% (95% CI 17.0 – 20.7), PPV of 17.5% (95% CI 15.7 – 19.4), NPV of 89.8% (95% CI 86.2 – 92.5), LR+ of 1.1 (95% CI 1.1 – 1.1), LR- of 0.6 (95% CI 0.6 – 0.6), and DOR of 1.9 (1.7 – 2.0).

Subgroup analysis

The results of the subgroup analysis based on age are summarized in Table 3. The diagnostic performance was not different among the subgroups with Sn around 80% and NPV around 86%.

Added value of food consumption

The base model and the extended model are shown in online supplemental Table 1. The model fit did not improve by adding food consumption (p = 0.095). The c-index of the base model and the extended model was 0.761 (95% CI 0.732 – 0.790) and 0.762 (95% CI 0.734 – 0.791), respectively (p = 0.546). The calibration plots of the base model and the extended model are shown in Figure 2. The base model already shows good calibration and adding food consumption resulted in minimal improvement.

Discussion

Diagnostic performance of self-reported food consumption for bacteraemia was poor in patients admitted to hospital with suspected infection, with Sn of 84.4% (95% CI 80.1 – 88.0), NPV of 86.8% (95% CI 83.1 – 89.8), and DOR of 1.3 (95% CI 1.0 – 1.9) at the previously reported cut-off point of 80%. This poor performance of food consumption was consistent with various cut-off points between 60% and 90%. The performance of the algorithm using food consumption and shaking chills was also poor, missing 36 patients (10.2% [95% CI 7.5 – 13.9]) with bacteraemia among 352 patients categorized in the low risk of bacteraemia group. Furthermore, the information about food consumption did not show added diagnostic value to previously reported predictors.

Comparison with previous findings

In the study by Komatsu et al., the performance of food consumption was reported as Sn of 93.7%, Sp of 34.6%, LR+ of 1.43, LR- of 0.18, and DOR of 7.9,[9] which was much better than our findings. Also, only 2.4% of patients were diagnosed with bacteraemia in the low-risk group categorized by the algorithm using food consumption and shaking chills.[9]

There were several possible explanations for these dissociated findings. First, food consumption was rated by nursing staff in the study by Komatsu et al., while it was self-reported in this study. Compared to the food consumption rated by nursing staff who received instruction on how to evaluate food consumption, self-reporting by patients themselves or their caregivers could be much less reliable. We hypothesized that self-reported food consumption was imprecise because there might be many patients with memory disturbance in this super-aged population (median age 81.0 [IQR 69.0 – 88.0]). Thus, we conducted a subgroup analysis comparing the performance of self-reported food consumption between younger and older patients. However, performance did not differ among age groups, which implies that the poor diagnostic performance of self-reported food consumption was not due to the high proportion of older patients in the present study. Also, food consumption in the study by Komatsu et al. was based on the meal just before the blood cultures were taken, while it was based on 24-hour food intake before presentation in proportion to the usual intake in this study. The food consumption of the last meal latest before presentation may reflect patients' status better than that of meals during the 24 hours before presentation. Second, the study population was different between the two studies. We included patients who were admitted for work-up/management of suspected infection (i.e., community-acquired infection), while Komatsu et al. included hospitalized patients (i.e., infection could have been acquired either in the community or in the hospital). While the prevalence of bacteraemia was similar in the two studies (16.2% in this study and 13.6% in Komatsu et al.), patients with bacteraemia in the study by Komatsu et al. could be more severe than our patients as the former included severe hospital-acquired conditions like catheter-related blood stream infection. A larger difference in severity between patients with and without bacteraemia might lead to better discriminative performance of food consumption. However, vital sign parameters in patients with bacteraemia (e.g., body temperature, heart rate, systolic blood pressure, and respiratory rate) showed almost similar values in both studies, implying this hypothesis for the difference between the findings of the two studies is not very convincing.

Furthermore, our findings were not in line with our previous study which suggested the usefulness of self-rated food consumption (using the same definition as the present study) for the diagnosis of community-acquired pneumonia in older patients who presented with upper respiratory symptoms.[11] In this previous study, food consumption with the cut-off of 50% showed Sn of 66.7%, Sp of 79.3%, LR+ of 3.2, LR- of 0.4, and DOR of 7.7 for the diagnosis of community-acquired pneumonia.[11] The previous study aimed to differentiate pneumonia from other viral infection (i.e., upper respiratory infection), while we aimed to differentiate bacteraemia from other bacterial infection in the present study. Thus, the severity between the two conditions was less prominent in the present study than in the previous one, which might have led to the poorer performance of food consumption.

Clinical implications

Our findings suggest that self-reported food consumption is not useful for the diagnosis of bacteraemia in patients admitted for work-up of suspected infection. In a questionnaire survey, Lautenbach et al. asked physicians about the acceptability of the performance of a clinical prediction rule for the diagnosis of bacteraemia.[25] They revealed that physicians required a very high Sn of 95% and infectious disease specialists required an even higher Sn of 98% for the clinical implementation of a prediction rule for the diagnosis of bacteraemia. This high expectation hampered the use of existing prediction rules for the diagnosis of bacteraemia. Considering the diagnostic performance of Sn of less than 90% when applied to patients admitted with suspected infection, food consumption alone and its algorithm in combination with shaking chills seemed unacceptable in clinical practice, at least with the current definition of self-reported food consumption. The performance of the algorithm in the original paper by Komatsu et al. (Sn of 94.1%) also did not satisfy this expected high Sn. Physicians may use the prediction model developed by Shapiro et al.[7] The model consists of three major criteria (suspected endocarditis, body temperature > 39.4°C and indwelling vascular catheter) and nine minor criteria (body temperature between 38.3 – 39.3°C, age > 65 years, chills, vomiting, systolic blood pressure < 90mmHg, white blood cell count > 18,000/ μL, bands > 5%, platelets < 150,000/ μL and creatinine > 2.0mg/dL).[7] Either one major

criterion or two or more minor criteria are deemed an indication for blood culture. Although the model is less simple than the algorithm using only the two items of food consumption and shaking chills, it has been well validated in emergency and in-hospital settings with Sn of around 95%.[26 27]

Strength and limitations

To the best of our knowledge, this is the first study to evaluate the external validity of the diagnostic performance of food consumption for bacteraemia. Some limitations should be noted. First, our cohort included many elderly patients (median age 81.0 years). Thus, the external validity of our findings, particularly in young patients, should be further evaluated. Second, we included those who underwent at least two sets of blood culture. This criterion has been frequently used as a surrogate indicator of suspected infection in previous studies reporting prediction rules/algorithms for the diagnosis of bacteraemia.[6 7 9] Whether to order blood culture was based on physicians' judgement, therefore, it could be subjective. To improve the reproducibility of our findings, more objective criteria (e.g., based on patient's signs and symptoms) would be more appropriate. However, it is unethical and unfeasible to obtain blood cultures in patients who do not have clinical indication. Third, we performed the subgroup analysis based on age to investigate the effect of memory disturbance on the performance of food consumption. However, this should be assessed by subgroup analysis based on the presence/absence of memory disturbance and whether the judgement was rated by patients themselves or their caregivers. Unfortunately, since we did not collect these variables, we could not conduct such subgroup analyses. In addition, it should be noted that the sample size calculation of this study was performed for the main analyses. Therefore, the number of patients in each subgroup was not large enough to precisely estimate the diagnostic performance of food consumption.

Conclusions

Contrary to previous findings, our results did not show the usefulness of food consumption and the algorithm using food consumption and shaking chills for the diagnosis of bacteraemia in patients admitted to hospital with suspected infection.

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The authors report no conflict of interest.

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Not required.

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The ethics committee of Shirakawa Kosei General Hospital (HAKURIN 17-003) and Iizuka Hospital (R-17135) granted ethical approval.

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Data are available upon reasonable request to the corresponding author.

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Tables

Table 1. Patient characteristics

	Missing proportion	All patients N = 2009	Patients without bacteraemia N = 1683	Patients with bacteraemia N = 326	P value*
Age, years, median (IQR)	0.0	81.0 (69.0, 88.0)	81.0 (68.0, 88.0)	82.0 (70.0, 88.0)	0.132
Male sex, n (%)	0.0	1007 (50.1)	866(51.5)	141(43.3)	0.008
Performance status	0.0				0.933
Bedridden		265 (13.2)	224 (13.3)	41 (12.6)	
Need attendance for most daily activities		347 (17.3)	287 (17.1)	60 (18.4)	
Limited activity		577 (28.7)	485 (28.8)	92 (28.2)	
Full activity		820 (40.8)	687 (40.8)	133 (40.8)	
Living in nursing home, n (%)	0.0	668 (33.3)	555 (33.0)	113 (34.7)	0.598
Indwelling vascular catheter, n (%)	0.0	19 (0.9)	11 (0.7)	8 (2.5)	0.006
Diabetes mellitus, n (%)	0.0	439 (21.9)	346 (20.6)	93 (28.5)	0.002
Food consumption, proportion, median (IQR)	3.3	30.0 (10.0, 70.0)	40.0 (10.0, 70.0)	30.0 (10.0, 60.0)	0.078
Shaking chills, n(%)	2.0	162 (8.1)	88 (5.2)	74 (22.7)	< 0.001
Suspicion of infective endocarditis, n (%)	0.4	43 (2.1)	24 (1.4)	19 (5.9)	< 0.001
Consciousness disturbance, n (%)	0.1	717 (35.7)	588 (34.9)	129 (39.6)	0.122
Systolic blood pressure, mmHg, median (IQR)	0.9	126.0 (107.0, 147.0)	127.0 (108.0, 147.0)	122.0 (102.0, 143.0)	0.007
Diastolic blood pressure, mmHg, median (IQR)	1.6	72.0 (62.0, 85.0)	73.0 (62.0, 86.0)	69.0 (58.0, 81.0)	< 0.001
Pulse rate, /min, median (IQR)	0.3	93.0 (80.0, 108.0)	92.0 (80.0, 107.0)	97.5 (83.0, 110.0)	< 0.001

Respiratory rate, /min, median (IQR)	11.5	20.0 (18.0, 24.0)	20.0 (18.0, 24.0)	22.0 (18.0, 25.0)	0.157
Body temperature, °C, median (IQR)	0.6	37.4 (36.7, 38.3)	37.3 (36.6, 38.1)	38.0 (37.2, 39.1)	< 0.001
White blood cell, /μl, median (IQR)	0.0	10000.0 (7000.0, 13960)	9800.0 (6940.0, 13600.0)	10885.0 (760.0, 15487.5)	0.008
Creatinine, mg/dL, median (IQR)	0.0	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)	0.9 (0.7, 1.5)	< 0.001
C-reactive protein, mg/dL, median (IQR)	0.0	6.8 (1.8, 13.6)	6.4 (1.7, 13.2)	8.8 (3.1, 15.9)	< 0.001
Death, n (%)	0.0	153 (7.6)	120 (7.1)	33 (10.1)	0.080

IQR = interquartile range.

*P value for comparison between patients with and without bacteraemia.

Table 2. Diagnostic performance of food consumption and shaking chills

	Sn	Sp	PPV	NPV	LR+	LR-	DOR
Food consumption with cut-off of 60%	77.6 (72.7-81.8)	29.0 (26.9-31.2)	17.5 (15.6-19.5)	87.0 (83.9-89.5)	1.1 (1.0-1.2)	0.8 (0.6-1.0)	1.4 (1.1-1.9)
Food consumption with cut-off of 70%	79.4 (74.7-83.5)	24.5 (22.5-26.6)	16.9 (15.1-18.9)	86.0 (82.6-88.8)	1.1 (1.0-1.1)	0.8 (0.7-1.1)	1.3 (0.9-1.7)
Food consumption with cut-off of 80%	84.4 (80.1-88.0)	19.8 (18.0-21.8)	16.9 (15.2-18.9)	86.8 (83.1-89.8)	1.1 (1.0-1.1)	0.8 (0.6-1.0)	1.3 (1.0-1.9)
Food consumption with cut-off of 90%	86.0 (81.8-89.3)	17.8 (16.1-19.7)	16.9 (15.1-18.7)	86.8 (82.8-90.0)	1.1 (1.0-1.1)	0.8 (0.6-1.1)	1.3 (1.0-1.9)
Shaking chills	22.5 (18.3-27.4)	94.7 (93.6-95.7)	45.4 (37.9-53.1)	86.3 (84.7-87.8)	4.3 (3.2-5.7)	0.8 (0.8-0.9)	5.3 (3.7-7.4)

Values in parentheses are 95% confidence intervals.

Sn = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, DOR = diagnostic odds ratio

Table 3. Diagnostic performance of food consumption in subgroups based on age

	Sn	Sp	PPV	NPV	LR+	LR-	DOR
Age <65 years n = 371	80.9 (62.3-95.9)	20.2 (11.7-29.4)	16.1 (10.7-22.3)	86.3 (75.1-93.5)	1.0 (0.8-1.4)	0.8 (0.3-2.4)	1.2 (0.3-4.5)
Age 65-75 years n = 334	80.0 (60.7-95.4)	20.6 (12.0-30.0)	15.9 (10.3-22.5)	86.7 (75.3-93.6)	1.0 (0.8-1.3)	0.8 (0.3-2.6)	1.2 (0.3-4.9)
Age 75-85 years n = 523	81.1 (64.7-94.9)	20.5 (13.0-28.5)	16.1 (11.3-21.6)	86.8 (77.8-93.0)	1.0 (0.8-1.3)	0.8 (0.3-2.4)	1.3 (0.4-4.8)
Age ≥85 years n = 781	82.8 (71.0-92.8)	19.9 (13.4-26.7)	16.6 (12.6-20.9)	86.6 (79.5-91.7)	1.0 (0.9-1.2)	0.8 (0.4-1.6)	1.3 (0.6-2.9)

Values in parentheses are 95% confidence intervals.

Sn = sensitivity, Sp = specificity, PPV = positive predictive value, NPV = negative predictive value, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, DOR = diagnostic odds ratio

Figure legends

Figure 1. Categorization of patients based on the algorithm using food consumption and shaking chills

Among 352 patients categorized as low risk of bacteraemia (with normal food consumption without shaking chills), 36 (10.2%) patients were diagnosed with bacteraemia.

Figure 2. Calibration plots of the base model and the extended model

The base model (left) already shows good agreement, with the calibration curve close to the dashed diagonal line (the line of perfect calibration). Improvement in the extended model (right) is minimal.

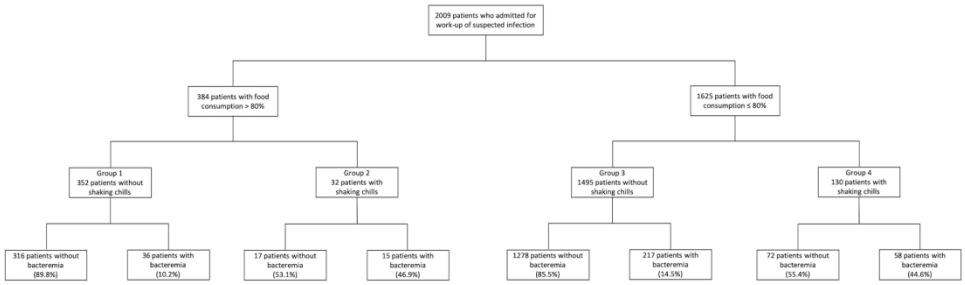

Figure 1

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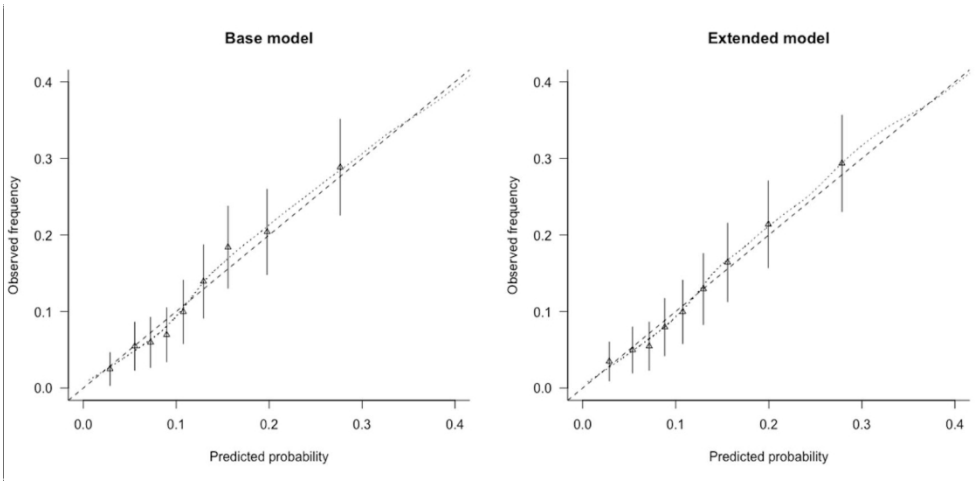

Figure 2

Supplementary material

Diagnostic performance of food consumption for bacteraemia in patients admitted with suspected infection: a prospective cohort study

Supplementary Table 1. The base model and the extended model

Supplementary Table 1. The base model and the extended model

	Base model			Extended model		
	Coefficient	Standard error	P value	Coefficient	Standard error	P value
(Intercept)	-9.17	3.80	0.016	-9.29	3.81	0.015
Age 1	0.04	0.01	< 0.001	0.04	0.01	< 0.001
Age 2	-0.03	0.01		-0.03	0.01	
Performance status (reference: bedridden)						
Need attendance for most daily activities	0.03	0.24	0.907	0.04	0.24	0.868
Limited activity	0.00	0.24	0.997	0.04	0.24	0.864
Full activity	0.05	0.26	0.848	0.09	0.26	0.732
Living in nursing home	0.30	0.17	0.079	0.30	0.17	0.078
Indwelling vascular catheter	1.40	0.54	0.009	1.34	0.54	0.013
Shaking chills	1.48	0.20	< 0.001	1.49	0.20	< 0.001
Suspicion of infective endocarditis	1.54	0.35	< 0.001	1.57	0.35	< 0.001
Consciousness disturbance	0.23	0.14	0.110	0.20	0.14	0.167
Systolic blood pressure 1	-0.02	0.01	0.005	-0.02	0.01	0.006
Systolic blood pressure 2	0.01	0.01		0.01	0.01	
Pulse rate 1	0.01	0.01	0.233	0.01	0.01	0.251
Pulse rate 2	-0.01	0.01		-0.01	0.01	
Respiratory rate	-0.01	0.01	0.341	-0.01	0.01	0.354
Body temperature 1	0.10	0.10	< 0.001	0.11	0.10	< 0.001
Body temperature 2	0.48	0.14		0.48	0.14	
Creatinine 1	0.91	0.33	0.007	0.90	0.33	0.009
Creatinine 2	-1.36	0.55		-1.36	0.55	
C-reactive protein	0.03	0.01	< 0.001	0.02	0.01	0.001
Food consumption				-0.03	0.02	0.098

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1, 3, 4
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3, 4
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	6
	4	Study objectives and hypotheses	6
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	6
Participants	**6**	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
Test methods	**10a**	Index test, in sufficient detail to allow replication	7, 8
	10b	Reference standard, in sufficient detail to allow replication	8, 9
	11	Rationale for choosing the reference standard (if alternatives exist)	8
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	7, 8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	NA
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7, 8
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9-11
	15	How indeterminate index test or reference standard results were handled	7-9
	16	How missing data on the index test and reference standard were handled	9
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	10
	18	Intended sample size and how it was determined	9
RESULTS			
Participants	**19**	Flow of participants, using a diagram	NA
	20	Baseline demographic and clinical characteristics of participants	11
	21a	Distribution of severity of disease in those with the target condition	Table 1
	21b	Distribution of alternative diagnoses in those without the target condition	Table 1
	22	Time interval and any clinical interventions between index test and reference standard	NA
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	NA
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	16
	27	Implications for practice, including the intended use and clinical role of the index test	15, 16
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	18

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.