ORIGINAL ARTICLE

mycoses
Diagnosis,Therapy and Prophylaxis of Fungal Diseases

WILEY

Modified Pitt bacteremia score for predicting mortality in patients with candidaemia: A multicentre seven-year retrospective study conducted in Japan

Nana Nakada-Motokawa[1] | Taiga Miyazaki[1,2] | Takashi Ueda[3] | Yuka Yamagishi[4] | Koichi Yamada[5] | Hideki Kawamura[6] | Hiroshi Kakeya[5] | Hiroshi Mukae[1] | Hiroshige Mikamo[4] | Yoshio Takesue[3] | Shigeru Kohno[1]

[1]Department of Respiratory Medicine, Nagasaki University, Nagasaki, Japan

[2]Division of Respirology, Rheumatology, Infectious Diseases, and Neurology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

[3]Department of Infection Control and Prevention, Hyogo College of Medicine, Nishinomiya, Japan

[4]Department of Clinical Infectious Diseases, Aichi Medical University, Nagakute, Japan

[5]Department of Infection Control Science, Graduate School of Medicine, Osaka City University, Osaka, Japan

[6]Division of Medical and Environmental Safety, Department of Infection Control and Prevention, Kagoshima University Hospital, Kagoshima, Japan

Correspondence
Taiga Miyazaki, Division of Respirology, Rheumatology, Infectious Diseases, and Neurology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan.
Email: taiga_miyazaki@med.miyazaki-u.ac.jp

Funding information
Japan Agency for Medical Research and Development, Grant/Award Number: JP21fk0108094

Abstract

Background: Several severity indexes have been reported for critically ill patients. The Pitt bacteremia score (PBS) is commonly used to predict the risk of mortality in patients with bacteraemia.

Objectives: To develop a scoring system for predicting mortality in candidaemia patients.

Methods: Medical records at five Japanese tertiary hospitals were reviewed. Factors associated with mortality were analysed using logistic regression modelling. The discriminatory power of scoring models was evaluated by assessing the area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results: In total, 422 candidaemia patients were included. Higher PBS, dialysis and retainment of central venous catheter were independent risk factors for all-cause 30-day mortality. However, among the five PBS components, fever was not associated with mortality; therefore, we developed a modified version of the PBS (mPBS) by replacing fever with dialysis. AUC for PBS and mPBS were 0.74 (95% confidence interval [CI]: 0.68–0.80) and 0.76 (95% CI: 0.71–0.82), respectively. The increase in predictive ability of mPBS for 30-day mortality was statistically significant as assessed by NRI (0.24, 95% CI: 0.01–0.46, $p = .04$) and IRI (0.04, 95% CI: 0.02–0.06, $p = .0008$). When patients were stratified by mPBS into low (scores 0–3), moderate (4–7) and high risk (≥8), there were significant differences among the survival curves ($p < .0001$, log-rank test), and 30-day mortality rates were 13.8% (40/290), 36.8% (28/76) and 69.4% (34/49), respectively.

Conclusions: mPBS can be a useful tool for predicting mortality in candidaemia patients.

KEYWORDS
bloodstream infection, *Candida*, candidaemia, candidiasis, mortality, Pitt bacteremia score, prognosis, risk factors

1 | INTRODUCTION

Candidaemia is one of the most common fungal infections among hospitalised patients, and the mortality rate for candidaemia is high at 30%–40%, even after the administration of antifungal therapy.[1,2] Appropriate and timely antifungal therapy and source control are essential to improve the prognosis of patients with candidaemia.[3–7] Appropriate antifungal agents should be selected for candidaemia patients based on multiple factors, including the severity of the disease and causative organisms. Many studies have elucidated the risk factors for predicting the likelihood of developing candidaemia,[8,9] along with the variables associated with mortality due to candidaemia.[10–12] A patient-level quantitative review of seven randomised trials for the treatment of invasive candidiasis identified old age, higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score, immunosuppressive therapy and infection with *Candida tropicalis* as predictors of mortality.[1] Conversely, removal of a central venous catheter (CVC) and treatment with an echinocandin antifungal agent were associated with reduced mortality. However, simplified and validated criteria to determine the severity of the disease and predict the prognosis of patients with candidaemia are scarce.

The Sequential Organ Failure Assessment (SOFA) and the APACHE II scoring systems have been used mainly in intensive care units (ICUs); however, they are cumbersome and complicated.[13–15] The Pitt bacteremia score (PBS) is widely used to predict mortality in patients with bacteraemia; moreover, it uses a simple scoring method and is applicable even in the general wards.[16–19] A recent study has demonstrated its usefulness as a prognostic score for patients with candidaemia[20]; however, to date, the contribution of each component in the PBS has not been assessed.

In the present study, we collected the clinical and microbiological information for patients with culture-proven candidaemia who were administered antifungal therapy. The primary aim of our study was to identify the potential variables associated with all-cause 30-day mortality. Secondary objectives included the determination of variables associated with early (days 1–14) and late (days 15–30) mortality. We developed a scoring system to estimate the risk of mortality in patients with candidaemia, solely based on patient-specific variables available at the time of initial physical examination at the bedside on the day blood samples were collected for culture.

2 | PATIENTS AND METHODS

2.1 | Study design and data collection

We retrospectively reviewed the medical records of patients aged ≥18 years diagnosed with culture-proven candidaemia between January 2009 and December 2015 at five university hospitals in Japan. The hospitals participating in this study were Nagasaki University Hospital, Hyogo Medical University Hospital, Aichi Medical University Hospital, Osaka City University Hospital and Kagoshima University Hospital (712–980 beds per hospital).

The medical records of all enrolled patients were reviewed, and the data for the following variables were collected: age, sex, body mass index, intensive care unit (ICU) admission, underlying conditions/treatment potentially related to candidaemia risk factors (diabetes mellitus, solid cancer, blood cancer, organ transplant, use of immunosuppressants, neutropenia at onset, recently administered chemotherapy, acute kidney injury [AKI], chronic kidney disease [CKD], undergone dialysis, prior abdominal surgery within 30 days, required mechanical ventilation, presence of a CVC, total parenteral nutrition, serum albumin level <3.0 mg/dl and presence of inflammatory bowel disease), severity of illness determined by PBS (Supplementary Table S1), microbiological findings including *Candida* isolates and bacterial co-infections, antifungal therapy and clinical outcome. *Candida* spp. was identified according to standard microbiological methods without using rapid diagnostic tests such as T2Candida. Vital signs and laboratory data within 24 h before or on the day of collection of the first sample for positive blood culture were recorded. PBS was calculated using the highest point scores recorded during that time.

We excluded patients who did not receive any antifungal therapy and/or those whose doctors did not follow their outcome for 30 days after the onset of candidaemia. The onset of candidaemia was set at day 0, which was the date of collection of the sample for the first positive blood culture. The endpoints were all-cause 14-day mortality, all-cause 30-day mortality and survival period within 30 days from the onset of candidaemia.

2.2 | Ethics statement

This study was approved by the research ethics committees of all five participating hospitals. The institutional review boards waived the requirement of informed consent from the patients included in this study because of the retrospective design. The summary and information of this study had been disclosed following the regulations of each participating hospital.

2.3 | Definitions

All definitions used in the study were established before data analyses. An episode of candidaemia was defined as the isolation of any pathogenic species of *Candida* from at least one blood culture specimen from a patient with signs and symptoms of infection. A second episode of candidaemia occurring in the same patient within 4 weeks of the first episode was counted as the same episode. Persistent candidaemia was defined as persistently positive blood cultures for the same *Candida* species for ≥3 days after the initiation of antifungal treatment.[21] Bacterial co-infection was defined based on one or more positive blood cultures for bacteria within 48 h before or after the first episode of candidaemia.[22] *Candida* endophthalmitis was diagnosed based on the evaluation by an ophthalmologist. *Candida*

endocarditis was diagnosed by transthoracic or transoesophageal echocardiography according to the modified Duke criteria.[23]

Immunosuppressants included corticosteroids and other immunosuppressive agents, such as calcineurin inhibitors. Neutropenia was defined as an absolute neutrophil count of <500 cells/µl. AKI was diagnosed based on the Kidney Disease: Improving Global Outcomes definition as described previously.[24] CKD was defined as a reduced glomerular filtration rate (<60 ml/min/1.73 m^2) for more than 3 months.[25] Dialysis included haemodialysis, haemodialysis filtration, peritoneal dialysis and continuous renal replacement therapy. Severity was assessed at the time of the first positive blood culture collection using PBS (Supplementary Table S1).[16]

2.4 | Statistical analysis

To evaluate the factors associated with mortality, univariable analyses were performed using the chi-square test or Fisher's exact test for categorical variables and logistic regression analysis for continuous variables. Values with normal distribution are expressed as means and standard deviations (SDs). Non-normally distributed values are expressed as medians and interquartile ranges (IQRs). Statistical comparison of mortality and patients' characteristics stratified by antifungal regimens was performed using the Kruskal-Wallis test. Variables with clinical relevance and those found to be significant in the univariable analyses were included in a multivariable logistic regression model mainly based on the previous evidence, clinical significance, correlation between potential predictors and the availability of data.

The discriminatory power of a derivative scoring model was evaluated by assessing the area under the receiver operating characteristic curve (AUC). Calibration was assessed using Nagelkerke's R^2.[26] The most appropriated cut-off value for dichotomisation of severity scores was determined based on the AUC and Youden index.[27] Risk stratification models were also compared using net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as described previously.[28] Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. The differences with p value <.05 were considered statistically significant. All analyses were performed using JMP Pro 15 (SAS Institute Inc).

3 | RESULTS

3.1 | Patients' characteristics

In total, 454 patients with candidaemia were identified, of whom 32 were excluded (31 because they received no antifungal therapy and one because of missing prognostic data). Among 422 patients included in the final analysis, the mean age was 65.0 ± 15.8 years, and the proportion of men was 64.0% (Table 1). All-cause 14-day and 30-day mortality rates were 15.6% (66/422) and 24.6% (104/422), respectively. The median time from the first positive blood culture sample collection to death was 11 days (interquartile range, 5–18 days). The exact source of infection was unclear, but 76.3% (322/422) of patients had CVC when the sample for the index blood culture (first blood culture that tested positive for *Candida* spp.) was collected.

The characteristics of patients with candidaemia and univariable analysis for all-cause 30-day mortality are shown in Table 1. The risk factors significantly associated with mortality were ICU admission, AKI, dialysis, mechanical ventilation, total parenteral nutrition, higher PBS, infection with *C tropicalis*, treatment with polyene and indwelling CVC retained for more than 24 h after collection of the index blood culture. Among 322 patients who had a CVC, removal of the CVC within 24 h following the collection of the sample for index blood culture, was significantly associated with lower 30-day mortality. It was 19.1% (35/183) for those with CVC removal within 24 h and 36.0% (50/139) for those with CVC retention or CVC removal after 24 h (odds ratio [OR]: 0.42, 95% confidence interval [CI]: 0.25–0.70, p = .0007). The presence of *Candida* endophthalmitis or *Candida* endocarditis was not associated with mortality. No patient in our study had both *Candida* endophthalmitis and *Candida* endocarditis.

3.2 | *Candida* isolates

Candida albicans (43.4%) was the most prevalent species, followed by *C parapsilosis* (21.6%), *C glabrata* (16.6%), *C tropicalis* (9.7%), *C krusei* (2.0%) and other *Candida* spp., including *C guilliermondii* (Table 1). Infection with two *Candida* species occurred in 1.7% of the patients. In the univariable analysis, infection with *C tropicalis* was significantly associated with 30-day mortality. Neither bacterial co-infection nor persistent candidaemia was significantly associated with 30-day mortality.

3.3 | Antifungal treatment

Among 422 patients with candidaemia, 290 (68.7%) were treated with echinocandins (214 with micafungin and 76 with caspofungin), 77 (18.3%) with azoles (74 with fluconazole, 2 with itraconazole and 1 with voriconazole) and 51 (12.1%) with polyene (liposomal amphotericin B) (Table 1). The remaining four patients (0.9%) received combination therapy with two antifungal drugs.

The highest 14-day and 30-day mortality rates were observed in the liposomal amphotericin B-treated group, followed by the echinocandins-treated and azoles-treated groups (Supplementary Table S2). The higher rates of ICU admission, renal dysfunction, mechanical ventilation, persistent candidaemia and indwelling CVC over 24 h, along with higher PBS were observed in the liposomal amphotericin B group followed by the echinocandins-treated and azoles-treated groups, suggesting that the patients with more severe disease were treated with liposomal amphotericin B, and those with less severe disease were treated with azoles. We could not identify the exact number of patients who developed breakthrough candidaemia and who received empiric antifungal therapy prior to culture positivity in this retrospective study.

TABLE 1 Characteristics of patients with candidaemia, and univariable analysis for all-cause 30-day mortality

Variable	Total (n = 422)	No. of patients who Survived (n = 318)	Died (n = 104)	OR (95% CI)	p value
Age (years), mean ± SD	65.0 ± 15.8	64.2 ± 16.4	67. 2 ± 14.0	1.01 (0.99–1.03)	.093
Men	270 (64.0)	198 (62.3)	72 (69.2)	1.36 (0.85–2.19)	.199
BMI (kg/m²), mean ± SD	20.7 ± 4.7 (n = 410)	20.5 ± 4.6 (n = 311)	21.5 ± 4.7 (n = 99)	1.04 (0.99–1.09)	.071
ICU admission	120 (28.4)	69 (21.7)	51 (49.0)	3.47 (2.17–5.54)	<.0001
Comorbidities and risk factors					
Diabetes mellitus	93 (22.0)	67 (21.1)	26 (25.0)	1.25 (0.74–2.10)	.401
Solid cancer	141 (33.4)	102 (32.1)	39 (37.5)	1.27 (0.80–2.02)	.309
Blood cancer	26 (6.2)	18 (5.7)	8 (7.7)	1.39 (0.59–3.30)	.482
Organ transplant	15 (3.5)	10 (3.0)	5 (4.8)	1.56 (0.52–4.66)	.541
Immunosuppressant	129 (30.1)	92 (28.9)	37 (35.6)	1.36 (0.85–2.17)	.221
Anti-cancer chemotherapy	38 (9.0)	24 (7.6)	14 (13.5)	1.91 (0.95–3.84)	.077
Neutropenia (<500 cells/μl)	12/421 (2.9)	8/318 (2.5)	4/103 (3.9)	1.57 (0.46–5.31)	.498
Acute kidney injury	82 (19.4)	54 (17.0)	28 (26.9)	1.80 (1.07–3.04)	.026
Chronic kidney disease	107 (25.4)	77 (24.2)	30 (28.9)	1.27 (0.77–2.08)	.346
Dialysis[a]	77 (18.3)	36 (11.3)	41 (39.4)	5.10 (3.02–8.61)	<.0001
Prior abdominal surgery within 30 days	83 (19.7)	64 (20.1)	19 (18.3)	0.89 (0.50–1.57)	.679
Mechanical ventilation	126 (29.9)	69 (21.7)	57 (54.8)	4.38 (2.74–7.00)	<.0001
Albumin <3.0 mg/dl	323/417 (77.5)	236/314 (75.2)	87/103 (84.5)	1.80 (0.99–3.25)	.057
Inflammatory bowel disease	54 (12.8)	50 (15.7)	4 (3.8)	0.21 (0.08–0.61)	.001
Total parenteral nutrition	254 (60.2)	181 (56.9)	73 (70.2)	1.78 (1.11–2.87)	.016
Presence of CVC[b]	322 (76.3)	237 (74.5)	85 (81.7)	1.53 (0.88–2.67)	.147
Indwelling CVC over 24 h[c]	139 (32.9)	89 (28.0)	50 (48.1)	2.38 (1.51–3.76)	.0002
Severity					
Pitt bacteraemia score, median (IQR)	2 (0–4) (n = 405)	1 (0–3) (n = 307)	4.5 (2–7) (n = 98)	1.42 (1.29–1.56)	<.0001
Candida isolates and complications					
C albicans	183 (43.4)	138 (43.4)	45 (43.3)	0.99 (0.64–1.56)	.982
C parapsilosis	91 (21.6)	75 (23.6)	16 (15.4)	0.59 (0.33–1.07)	.099
C glabrata	70 (16.6)	52 (16.4)	18 (17.3)	1.07 (0.59–1.93)	.880
C tropicalis	41 (9.7)	24 (7.6)	17 (16.4)	2.39 (1.23–4.66)	.013
C krusei	9 (2.1)	6 (1.9)	3 (2.9)	1.54 (0.38–6.23)	.695
Other Candida spp.	21 (5.0)	18 (5.7)	3 (2.9)	0.50 (0.14–1.72)	.311
Bacterial co-infection	57 (13.5)	39 (12.3)	18 (17.3)	1.50 (0.81–2.75)	.190
Persistent candidaemia	79/386 (20.5)	59/316 (18.7)	20/70 (28.6)	1.74 (0.97–3.15)	.072
Candida endophthalmitis[d]	62/347 (17.9)	50/283 (17.7)	12/64 (18.8)	1.08 (0.54–2.16)	.857
Candida endocarditis[d]	11/360 (3.1)	9/283 (3.2)	2/77 (2.6)	0.81 (0.17–3.84)	1.000
Treatment					
Azoles	77 (18.3)	64 (20.1)	13 (12.5)	0.57 (0.30–1.08)	.107
Echinocandins	290 (68.7)	223 (70.1)	67 (64.4)	0.77 (0.48–1.23)	.276
Polyene	51 (12.1)	28 (8.8)	23 (22.1)	2.94 (1.61–5.38)	.0003
Combination therapy	4 (0.9)	3 (0.9)	1 (1.0)	1.02 (0.10–9.91)	1.000

Note: Data are presented as number of patients (%), mean ± SD or median (IQR).

Abbreviations: BMI, body mass index; CI, confidence interval; CVC, central venous catheter; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; SD, standard deviation.

[a]Among 77 patients undergoing dialysis, 19 were diagnosed with AKI.

[b]Presence of CVC when sample for index blood culture was collected.

[c]Presence of CVC for more than 24 h after collection of the sample for index blood culture.

[d]No patient had both endophthalmitis and endocarditis.

3.4 | Multivariable analysis for the predictors of 30-day mortality

Multivariable logistic regression analysis identified dialysis (OR: 2.58, 95% CI: 1.34–4.98, $p = .005$), higher PBS (OR: 1.40, 95% CI: 1.24–1.58, $p < .0001$), and presence of CVC for more than 24 h after collection of the sample for index blood culture (OR: 2.23, 95% CI: 1.29–3.86, $p = .004$), as risk factors associated with higher 30-day mortality (Table 2). Conversely, treatment with echinocandins was associated with lower 30-day mortality (OR: 0.54, 95% CI: 0.30–0.98, $p = .041$).

3.5 | Pitt bacteraemia score and modified Pitt bacteraemia score

In this study, we also evaluated the contributions of individual components of the PBS in predicting 30-day mortality in patients with candidaemia. Among the five parameters in the PBS, hypotension, mechanical ventilation, cardiac arrest and mental status were significantly associated with mortality, but fever was not (Table 3). Dialysis was independently associated with an increased risk of 30-day mortality in the multivariable analysis as described above (Table 2), and it can be easily assessed at the time of collection of the sample for blood culture. Therefore, we derived a modified version of the PBS (mPBS) by replacing fever with dialysis (Table 4). The score point of dialysis was set as 2 based on the highest Nagelkerke's R^2 value among the score points 1–5.

The performance characteristics of the PBS and mPBS for predicting 30-day mortality at selected cut-off values are summarised in Supplementary Table S3. The Youden index (sensitivity + specificity − 1) was at a maximum when dichotomised at <4 versus ≥4 for both PBS and mPBS. Using a score ≥4 to identify patients at high risk of 30-day mortality, the AUC for the PBS and mPBS were 0.74 (95% CI: 0.68–0.80) and 0.76 (95% CI: 0.71–0.82), respectively (Figure 1).

The increase in predictive ability of mPBS for 30-day mortality was high as assessed by NRI (0.24, standard error: 0.11, 95% CI: 0.01–0.46, $p = .04$) and IRI (0.04, standard error: 0.01, 95% CI: 0.02–0.06, $p = .0008$).

3.6 | Risk factors for early (days 1–14) and late (days 15–30) mortality in patients with candidaemia

Among 104 patients who died within 30 days after the onset of candidaemia, 66 (63.5%) died within the first 14 days and 38 (36.5%) died during days 15–30. Therefore, the rates of early (days 1–14) and late (days 15–30) mortality were 15.6% (66/422) and 10.7% (38/356), respectively. In the univariable analysis, ICU admission, dialysis, mechanical ventilation, indwelling CVC over 24 h, higher PBS and higher mPBS were significantly associated with both early and late mortality (Supplementary Table S4). These results were consistent with those obtained by the Cox regression analysis of potential risk factors associated with 30-day mortality in patients with candidaemia (Supplementary Table S5). The following multivariable logistic regression analysis identified only mPBS as an independent predictor of both early and late mortality (Table 5).

A 1–2-day delay in the initiation of empiric antifungal therapy approximately doubled hospital mortality in the literature[3,6]; however, this was not apparent in our study. The group of patients who received antifungal therapy on day 0 had higher mortality and higher mPBS than those observed in other groups (Supplementary Table S6). It was likely that patients with more severe disease (higher mPBS) received early empiric therapy and that disease severity rather than time to initiation of antifungal therapy was associated with mortality in this study.

The Kaplan-Meier curve showed that the patients with a lower mPBS had a significantly higher likelihood of survival among the three groups stratified by mPBS (Figure 2A). The 30-day mortality rates were 13.8% (40/290), 36.8% (28/76) and 69.4% (34/49) in

Variable	OR (95% CI)	*p* value
Age	1.02 (1.00–1.03)	.089
Male sex	1.45 (0.82–2.56)	.205
ICU admission	0.78 (0.39–1.54)	.467
Acute kidney injury	0.78 (0.39–1.54)	.475
Dialysis	2.58 (1.34–4.98)	.005
Total parenteral nutrition	1.16 (0.66–2.05)	.608
Pitt bacteraemia score (1-point increments)	1.40 (1.24–1.58)	<.0001
Infection with *Candida tropicalis*	1.87 (0.83–4.20)	.129
Treatment with echinocandins	0.54 (0.30–0.98)	.041
Indwelling CVC over 24 h[a]	2.23 (1.29–3.86)	.004

TABLE 2 Multivariable logistic regression analysis for factors potentially associated with 30-day mortality in patients with candidaemia ($n = 405$; 307 survived, 98 died)

Abbreviations: CI, confidence interval; CVC, central venous catheter; ICU, intensive care unit; OR, odds ratio.

[a]Presence of CVC for more than 24 h after collection of the sample for index blood culture.

TABLE 3 Evaluation of the association of each item in the Pitt bacteraemia score (PBS) with 30-day mortality using univariable analysis

Variable in PBS	Total	Survived	Died	p value
Fever	(n = 411)	(n = 311)	(n = 100)	
0	237 (57.7)	175 (56.3)	62 (62.0)	.600
1	131 (31.9)	103 (33.1)	28 (28.0)	
2	43 (10.5)	33 (10.6)	10 (10.0)	
Hypotension	(n = 422)	(n = 318)	(n = 104)	
0	321 (76.1)	267 (84.0)	54 (51.9)	<.0001
2	101 (23.9)	51 (16.0)	50 (48.1)	
Mechanical ventilation	(n = 422)	(n = 318)	(n = 104)	
0	296 (70.1)	249 (78.3)	47 (45.2)	<.0001
2	126 (29.9)	69 (21.7)	57 (54.8)	
Cardiac arrest	(n = 422)	(n = 318)	(n = 104)	
0	408 (96.7)	313 (98.4)	95 (91.4)	.0016
4	14 (3.3)	5 (1.6)	9 (8.7)	
Mental status	(n = 415)	(n = 313)	(n = 102)	
0	235 (56.6)	210 (67.1)	25 (24.5)	<.0001
1	43 (10.4)	33 (10.5)	10 (9.8)	
2	114 (27.5)	63 (20.1)	51 (50.0)	
4	23 (5.5)	7 (2.2)	16 (15.7)	

Note: Data are presented as number of patients (%).

TABLE 4 Modified Pitt bacteraemia score

Criterion	Points
Dialysis	2
Hypotension[a]	2
Mechanical ventilation	2
Cardiac arrest	4
Mental status	
Alert	0
Disoriented	1
Stuporous	2
Comatose	4

Note: All criteria were graded using the highest point scores recorded within 24 h before or on the day of collection of the first positive blood culture.

[a]Acute hypotensive event with drop in systolic blood pressure >30 mm Hg and diastolic blood pressure >20 mm Hg, or requirement of intravenous vasopressor, or systolic blood pressure <90 mm Hg.
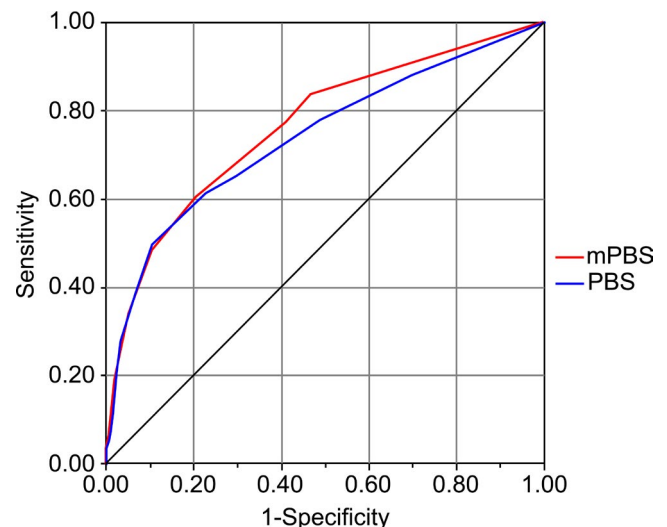

FIGURE 1 Receiver operating characteristic curve analysis for the discriminatory power of the modified Pitt bacteraemia score (mPBS) for predicting 30-day mortality of patients with candidaemia. The area under the curve was 0.76 (95% confidence interval: 0.71–0.82) for mPBS and 0.74 (95% confidence interval 0.68–0.80) for PBS [Colour figure can be viewed at wileyonlinelibrary.com]

patients with mPBS 0–3, 4–7 and ≥8, respectively (p < .001 for each comparison by log-rank Bonferroni multiple test).

These results suggest the incremental predictive value of mPBS compared with the original PBS for both early and late mortality in patients with candidaemia.

3.7 | Application of mPBS to patients without cancer and organ transplant

Some variables in patients with cancer or organ transplant may substantially affect the prognosis of candidaemia.[29–32] Therefore, we excluded all patients with solid cancer, blood cancer or organ transplant from the analysis set and conducted a subgroup analysis for non-cancer, non-organ transplant patients (n = 246). The Kaplan-Meier curves of the three groups stratified by mPBS as described above are shown in Figure 2B. The 30-day mortality rates were 10.3% (16/156), 30.2% (16/53) and 60.6% (20/33) in patients with mPBS 0–3, 4–7 and ≥8, respectively (p < .001 for mPBS 0–3 vs.

TABLE 5 Multivariable logistic regression analysis of risk factors for early and late mortality in patients with candidaemia

Variables	Early (days 1–14) mortality		Late (days 15–30) mortality		30-day mortality	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.02 (1.00–1.04)	.040			1.01 (0.99–1.03)	.170
ICU admission	0.54 (0.25–1.19)	.128	1.20 (0.49–2.90)	.690	0.66 (0.33–1.32)	.240
Albumin <3.0 mg/dl	2.45 (1.02–5.92)	.046			1.80 (0.89–3.64)	.103
Infection with *Candida tropicalis*	2.46 (1.05–5.77)	.038			2.12 (0.96–4.68)	.063
Indwelling CVC over 24 h[a]	2.09 (1.15–3.79)	.016	1.43 (0.67–3.05)	.360	2.01 (1.19–3.41)	.009
mPBS (1-point increments)	1.39 (1.24–1.55)	<.0001	1.34 (1.17–1.54)	<.0001	1.43 (1.29–1.59)	<.0001

Abbreviations: CI, confidence interval; CVC, central venous catheter; ICU, intensive care unit; mPBS, modified Pitt bacteraemia score; OR, odds ratio.
[a]Presence of CVC for more than 24 h after collection of the sample for index blood culture.
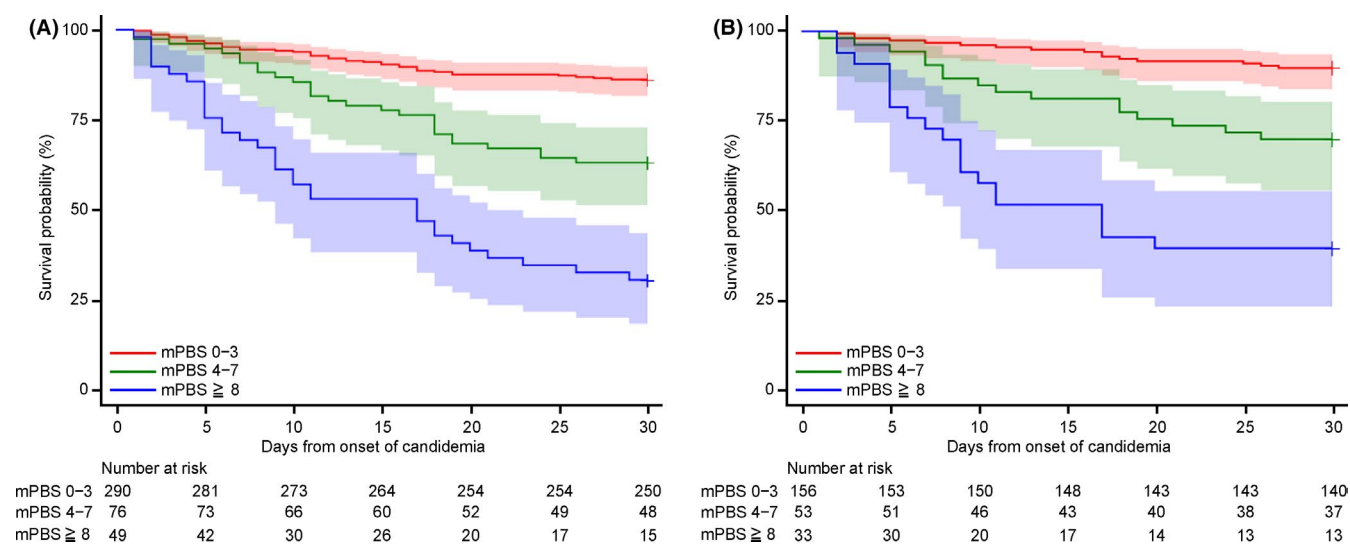

FIGURE 2 Kaplan-Meier survival curve of patients with candidaemia stratified by the modified Pitt bacteraemia score (mPBS). (A) All patients with candidaemia. Log-rank Bonferroni multiple test: mPBS 0–3 versus mPBS 4–7, mPBS 4–7 versus mPBS ≥8, mPBS 0–3 versus mPBS ≥8, *p* < .0001 each. (B) Non-cancer, non-transplanted patients with candidaemia. Log-rank Bonferroni multiple test: *p* < .001 for mPBS 0–3 versus mPBS 4–7, *p* < .001 for mPBS 0–3 versus mPBS ≥8, *p* < .035 for mPBS 4–7 versus mPBS ≥8 [Colour figure can be viewed at wileyonlinelibrary.com]

mPBS 4–7, *p* < .001 for mPBS 0–3 vs. mPBS ≥8, *p* < .035 for mPBS 4–7 vs. mPBS ≥8, by log-rank Bonferroni multiple test). The results suggest that the risk stratification strategy using mPBS was applicable even for non-cancer, non-transplant patients.

4 | DISCUSSION

This study identified the key risk factors associated with early and late all-cause mortality in patients with candidaemia who received antifungal treatment. To the best of our knowledge, our present study and the one by Vaquero-Herrero et al[20] are the first two to report the predictive ability of PBS in patients with candidaemia. Moreover, we developed mPBS, which is a simple scoring system that has better discriminatory capability than the original PBS for predicting mortality. All information for score calculation is readily available at the bedside when candidaemia is suspected.

The rates of 14-day mortality (15.6%) and 30-day mortality (24.6%) observed in this cohort of 422 patients with candidaemia were similar to those reported in previous studies conducted in Japan.[33,34] If patients who died before receiving antifungal therapy were included, the 30-day mortality rate would probably be around 30%, which is consistent with that reported in other literature.[1,2] In our study, 71.6% of the cohort was comprised of non-ICU patients and the severity of disease in patients was reflected widely from low to high PBS scores, suggesting that the scoring model could be generalised to critical and non-critical care settings. Among *Candida* isolates, *C albicans* was the most frequent species (43%), but non-*albicans Candida* species predominated, which is consistent with trends observed globally.[35–39] Infection with *C tropicalis* and *C parapsilosis* was associated with higher and lower 14-day mortality, respectively; however, the causative *Candida* species did not influence mortality in the later period.

Treatment strategies also have a significant impact on the prognosis of patients with candidaemia. For example, Andes et al,[1] using

data from seven randomised clinical trials, identified the removal of CVCs and use of echinocandins as treatment-related factors associated with improved 30-day survival. In our study, the antifungal regimen was not a main factor influencing mortality; however, we could not draw any conclusions regarding the efficacy of antifungal drugs because the design of this study was not appropriate for this comparison. Puig-Asensio et al[15] reported that prompt therapeutic interventions, including antifungal treatment and CVC removal, are important for reducing early mortality, while host factors and disease severity are the main variables influencing late mortality. Consistent with the findings of Puig-Asensio et al,[15] multivariable analysis in our study also showed a significant association between CVC retention and an increased risk of early mortality, supporting current clinical guidelines that recommend prompt removal of CVCs, when feasible, in patients with candidaemia.[40-43] Of note, in our multivariable analysis, only mPBS was an independent predictor of both early and late mortality.

PBS is widely used as a predictor of mortality in patients with bloodstream infections caused by bacteria.[16-19] Our study is one of the two studies that reported the predictive ability of PBS in patients with candidaemia, and ours is the first study conducted in Japan. A previous study by Vaquero-Herrero et al demonstrated that the original PBS is useful for the prediction of 30-day mortality in patients with candidaemia,[20] but the contributions of each component had not been assessed. An association between fever and increased mortality has not been demonstrated in patients with sepsis, a bloodstream infection with gram-negative bacteria or candidaemia.[6,44-46] Consistent with the aforementioned observations, fever was not associated with mortality in our study; therefore, the parameter of temperature was replaced with dialysis, which was significantly associated with 30-day mortality in our multivariable analysis, leading to the development of mPBS. For the evaluation of predictive ability, the AUC, also known as c-statistic, is a popular measure of discrimination, but it has limited sensitivity.[47] Therefore, it is recommended to calculate continuous NRI and IDI for the evaluation of improvement in discrimination of derivative models.[48-50] Although mPBS only demonstrated a minor increase in AUC, the results of NRI and IDI suggested that mPBS had better discrimination in predicting mortality than the original PBS in patients with candidaemia.

Risk stratification using mPBS 0–3 (low risk), 4–7 (moderate risk) and ≥8 (high risk) had increased predictive capacity compared with the PBS. It is noteworthy that all variables included in the mPBS are available at the time of collection of samples for blood culture at the bedside. The simplicity of mPBS has a major advantage over other scoring systems, such as the APACHE II and SOFA scores, which require laboratory results. Epidemiology and clinical outcomes of candidaemia in patients with cancer or organ transplant are different when compared with those in other ICU patients.[29-32] The 30-day mortality rates of a subset of non-cancer, non-transplanted patients were lower than those of the full analysis set; however, risk stratification by mPBS was also successful for such a subset.

Recently, Keighley et al[51] analysed 133 patients with candidaemia and reported a risk predictive score stratifying patients into <20% and ≥20% risk of all-cause 30-day mortality. The score was based on age >65 years, ICU admission, chronic organ dysfunction, preceding surgery within 30 days, haematological malignancy, source of candidaemia and antibiotic therapy for ≥10 days. This scoring system appears to be useful because information for all items in the scoring system is available at the time of candidaemia diagnosis. However, several factors in this scoring system, such as preceding surgery within 30 days and haematological malignancy, were not significantly associated with mortality in our cohort; in addition, the source of candidaemia and duration of preceding antibiotic therapy were not assessed in the present study. Therefore, we did not evaluate the usefulness of the scoring system proposed by Keighley et al in this study.

The present study has several limitations. First, the data were obtained retrospectively; therefore, we could not evaluate the severity of illness using other scoring systems such as the APACHE II score, because it is not routinely calculated for non-ICU patients. Additionally, although the presence or absence of metastatic infection was relatively well examined (e.g., 82.2% for ophthalmological examination and 85.3% for echocardiography), we could not determine the precise number of patients with metastatic candidiasis because diagnostic procedures were performed at the physicians' discretion. In addition, incidence rates of chorioretinitis and vitritis were unclear, because these cases were diagnosed as endophthalmitis in this study. Second, it was difficult to evaluate the appropriateness of treatment regimens because antifungal susceptibility results of the isolates were not collected. Although some isolates such as C glabrata and C krusei are resistant to azoles, echinocandin- or amphotericin B-resistant Candida isolates are extremely rare in Japan.[39,52] The majority (>80%) of patients in this study were treated with an echinocandin or liposomal amphotericin B. In general, an empiric therapy was initiated with an echinocandin, otherwise, an appropriate drug was selected based on the Candida species and/or antifungal susceptibility of the isolates for targeted therapy according to the Japanese guidelines for the management of invasive candidiasis.[43] Third, the epidemiology described may have been influenced by local medical practices and may not have been similar across all sites, thereby limiting the ability to generalise the results to other geographical areas. Fourth, residual confounding is possible. External validation needs to be performed using an independent historical dataset or by conducting a prospective study.

In conclusion, this study developed a simplified risk stratification model to predict early and late mortality in patients with candidaemia. The mPBS is based solely on patient-specific variables available at the time of initial physical examination. Stratification of the risk of mortality may be helpful in guiding therapeutic strategies (e.g., an aggressive approach to source control and initiation of empiric antifungal therapy in high-risk patients and an earlier transition to oral step-down therapy in low-risk patients) in daily clinical practice and may also be useful for the general classification of patients in clinical trials.

AUTHOR CONTRIBUTION

Nana Nakada-Motokawa: Formal analysis (equal); Investigation (lead); Methodology (equal); Resources (equal); Writing-original draft (equal); Writing-review & editing (equal). **Taiga Miyazaki:** Conceptualization (lead); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (lead); Resources (equal); Supervision (equal); Writing-original draft (equal); Writing-review & editing (lead). **Takashi Ueda:** Investigation (equal); Writing-review & editing (equal). **Yuka Yamagishi:** Investigation (equal); Writing-review & editing (equal). **Koichi Yamada:** Investigation (equal); Writing-review & editing (equal). **Hideki Kawamura:** Investigation (equal); Writing-review & editing (equal). **Hiroshi Kakeya:** Funding acquisition (equal); Investigation (supporting); Supervision (equal); Writing-review & editing (equal). **Hiroshi Mukae:** Investigation (supporting); Supervision (equal); Writing-review & editing (equal). **Hiroshige Mikamo:** Funding acquisition (equal); Investigation (supporting); Supervision (equal); Writing-review & editing (equal). **Yoshio Takesue:** Conceptualization (supporting); Investigation (supporting); Supervision (equal); Writing-original draft (supporting); Writing-review & editing (equal). **Shigeru Kohno:** Funding acquisition (lead); Project administration (lead); Resources (lead); Supervision (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Taiga Miyazaki https://orcid.org/0000-0002-0962-5758
Takashi Ueda https://orcid.org/0000-0002-5176-9050

REFERENCES

1. Andes DR, Safdar N, Baddley JW, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis*. 2012;54:1110-1122.
2. Kullberg BJ, Arendrup MC. Invasive candidiasis. *N Engl J Med*. 2015;373:1445-1456.
3. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis*. 2006;43:25-31.
4. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to *Candida* infection: importance of empiric therapy and source control. *Clin Infect Dis*. 2012;54:1739-1746.
5. Labelle AJ, Micek ST, Roubinian N, Kollef MH. Treatment-related risk factors for hospital mortality in *Candida* bloodstream infections. *Crit Care Med*. 2008;36:2967-2972.
6. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother*. 2005;49:3640-3645.
7. Ostrosky-Zeichner L, Kullberg BJ, Bow EJ, et al. Early treatment of candidemia in adults: a review. *Med Mycol*. 2011;49:113-120.
8. Ostrosky-Zeichner L, Pappas PG, Shoham S, et al. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. *Mycoses*. 2011;54:46-51.
9. Playford EG, Lipman J, Jones M, et al. Problematic dichotomization of risk for intensive care unit (ICU)-acquired invasive candidiasis: results using a risk-predictive model to categorize 3 levels of risk from a multicenter prospective cohort of Australian ICU patients. *Clin Infect Dis*. 2016;63:1463-1469.
10. Barchiesi F, Orsetti E, Mazzanti S, et al. Candidemia in the elderly: what does it change? *PLoS One*. 2017;12:e0176576.
11. Marriott DJ, Playford EG, Chen S, et al. Determinants of mortality in non-neutropenic ICU patients with candidaemia. *Crit Care*. 2009;13:R115.
12. Puig-Asensio M, Fernandez-Ruiz M, Aguado JM, et al. Propensity score analysis of the role of initial antifungal therapy in the outcome of *Candida glabrata* bloodstream infections. *Antimicrob Agents Chemother*. 2016;60:3291-3300.
13. Bassetti M, Righi E, Ansaldi F, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. *Intensive Care Med*. 2014;40:839-845.
14. Hu B, Du Z, Kang Y, et al. Catheter-related *Candida* bloodstream infection in intensive care unit patients: a subgroup analysis of the China-SCAN study. *BMC Infect Dis*. 2014;14:594.
15. Puig-Asensio M, Peman J, Zaragoza R, et al. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. *Crit Care Med*. 2014;42:1423-1432.
16. Paterson DL, Ko W-C, Von Gottberg A, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. *Ann Intern Med*. 2004;140:26-32.
17. Chow JW, Fine MJ, Shlaes DM, et al. *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med*. 1991;115:585-590.
18. Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents*. 1999;11:7-12.
19. Yu VL, Chiou CCC, Feldman C, et al. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. *Clin Infect Dis*. 2003;37:230-237.
20. Vaquero-Herrero MP, Ragozzino S, Castano-Romero F, et al. The Pitt bacteremia score, Charlson comorbidity index and chronic disease score are useful tools for the prediction of mortality in patients with *Candida* bloodstream infection. *Mycoses*. 2017;60:676-685.
21. Li WS, Chen YC, Kuo SF, Chen FJ, Lee CH. The impact of biofilm formation on the persistence of candidemia. *Front Microbiol*. 2018;9:1196.
22. Jia X, Li C, Cao J, Wu X, Zhang L. Clinical characteristics and predictors of mortality in patients with candidemia: a six-year retrospective study. *Eur J Clin Microbiol Infect Dis*. 2018;37:1717-1724.
23. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633-638.
24. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013;17:204.

25. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*. 2014;63:713-735.

26. Nagelkerke NJD. A note on a general definition of the coefficient of determination. *Biometrika*. 1991;78:691-692.

27. Fluss R, Faraggi D, Reiser B. Estimation of the Youden index and its associated cutoff point. *Biom J*. 2005;47:458-472.

28. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157-172; discussion 207-212.

29. Bergamasco MD, Garnica M, Colombo AL, Nucci M. Epidemiology of candidemia in patients with hematologic malignancies and solid tumours in Brazil. *Mycoses*. 2013;56:256-263.

30. Tang H-J, Liu W-L, Lin H-L, Lai C-C. Epidemiology and prognostic factors of candidemia in cancer patients. *PLoS One*. 2014;9:e99103.

31. Puig-Asensio M, Ruiz-Camps I, Fernández-Ruiz M, et al. Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain. *Clin Microbiol Infect*. 2015;21:491.e1-491.e10.

32. Andes DR, Safdar N, Baddley JW, et al. The epidemiology and outcomes of invasive *Candida* infections among organ transplant recipients in the United States: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Transpl Infect Dis*. 2016;18:921-931.

33. Kato H, Yoshimura Y, Suido Y, et al. Mortality and risk factor analysis for *Candida* blood stream infection: A multicenter study. *J Infect Chemother*. 2019;25:341-345.

34. Takesue Y, Ueda T, Mikamo H, et al. Management bundles for candidaemia: the impact of compliance on clinical outcomes. *J Antimicrob Chemother*. 2015;70:587-593.

35. Guinea J. Global trends in the distribution of *Candida* species causing candidemia. *Clin Microbiol Infect*. 2014;20(suppl 6):5-10.

36. Guinea J, Zaragoza O, Escribano P, et al. Molecular identification and antifungal susceptibility of yeast isolates causing fungemia collected in a population-based study in Spain in 2010 and 2011. *Antimicrob Agents Chemother*. 2014;58:1529-1537.

37. Mohr A, Simon M, Joha T, Hanses F, Salzberger B, Hitzenbichler F. Epidemiology of candidemia and impact of infectious disease consultation on survival and care. *Infection*. 2020;48:275-284.

38. Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance®) registry, 2004–2008. *Diagn Microbiol Infect Dis*. 2012;74:323-331.

39. Kakeya H, Yamada K, Kaneko Y, et al. National trends in the distribution of *Candida* species causing candidemia in Japan from 2003 to 2014: a report by the epidemiological investigation committee for human mycoses in Japan. *Med Mycol J*. 2018;59:E19-E22.

40. Cornely OA, Bassetti M, Calandra T, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18(suppl 7):19-37.

41. Martin-Loeches I, Antonelli M, Cuenca-Estrella M, et al. ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. *Intensive Care Med*. 2019;45:789-805.

42. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;62:e1-e50.

43. Miyazaki T, Kohno S. Current recommendations and importance of antifungal stewardship for the management of invasive candidiasis. *Expert Rev Anti Infect Ther*. 2015;13:1171-1183.

44. Battle SE, Augustine MR, Watson CM, et al. Derivation of a quick Pitt bacteremia score to predict mortality in patients with gram-negative bloodstream infection. *Infection*. 2019;47:571-578.

45. Sunden-Cullberg J, Rylance R, Svefors J, Norrby-Teglund A, Bjork J, Inghammar M. Fever in the emergency department predicts survival of patients with severe sepsis and septic shock admitted to the ICU. *Crit Care Med*. 2017;45:591-599.

46. Tascini C, Falcone M, Bassetti M, et al. Candidemia in patients with body temperature below 37°C and admitted to internal medicine wards: Assessment of risk factors. *Am J Med*. 2016;129:1330.e1-1330.e6.

47. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007;115:928-935.

48. Leening MJG, Vedder MM, Witteman JCM, Pencina MJ, Steyerberg EW. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. *Ann Intern Med*. 2014;160:122-131.

49. Pencina MJ, D'Agostino RB Sr, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. *Stat Med*. 2012;31:101-113.

50. Pencina MJ, D'Agostino RB, Pencina KM, Janssens ACJW, Greenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol*. 2012;176:473-481.

51. Keighley C, Chen SC-A, Marriott D, et al. Candidaemia and a risk predictive model for overall mortality: a prospective multicentre study. *BMC Infect Dis*. 2019;19:445.

52. Sakagami T, Kawano T, Yamashita K, et al. Antifungal susceptibility trend and analysis of resistance mechanism for *Candida* species isolated from bloodstream at a Japanese university hospital. *J Infect Chemother*. 2019;25:34-40.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.