JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlaf078

JAC-Antimicrobial Resistance

Pitt candidaemia score as an assessment tool for mortality in patients with candidaemia caused by *Candida tropicalis* and other *Candida* species: a multicentre study conducted in Japan

Takashi Ueda [1]*, Hiroshi Kakeya[2], Koichiro Yoshida[3], Akihiro Hisato[3], Akira Ukimura[4,5], Taku Ogawa[6], Kazuhiko Nakajima[1], Kosuke Iijima[7], Miki Nagao[8], Yasuhiro Tsuchido[8], Hideki Kawamura[9], Akari Shigemi[10], Muneki Hotomi[11], Masamitsu Kono[11], Kei Kasahara[12], Natsuko Imakita[12], Yukihiro Kaneko[13], Makoto Niki[14], Koichi Yamada[2], Shigeki Kakuno[2], Taiga Miyazaki[15], Makoto Sumiyoshi[15], Yasushi Murakami[16], Miki Doi[17], Mutsunobu Yoshioka[18], Yoshitsugu Miyazaki[19] and Yoshio Takesue[1,20]

[1]Department of Infection Prevention and Control, Hyogo Medical University Hospital, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan; [2]Department of Infection Control Science, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan; [3]Division of Infection Control and Prevention, Department of Medical Safety Management, Kindai University Hospital, Osaka, Japan; [4]Division of Infection Control and Prevention, Medical Safety Management Office, Hirakata City Hospital, Osaka, Japan; [5]Department of General Medicine, Osaka Medical and Pharmaceutical University Hospital, Osaka, Japan; [6]Infection Control Center, Osaka Medical and Pharmaceutical University Hospital, Osaka, Japan; [7]Department of Clinical Technology, Hyogo Medical University Hospital, Nishinomiya, Japan; [8]Department of Clinical Laboratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [9]Department of Infection Control and Prevention, Kagoshima University Hospital, Kagoshima, Japan; [10]Department of Pharmacy, Kagoshima University Hospital, Kagoshima, Japan; [11]Department of Otorhinolaryngology-Head and Neck Surgery, Wakayama Medical University, Wakayama, Japan; [12]Department of Infectious Diseases, Nara Medical University, Nara, Japan; [13]Department of Bacteriology, Osaka Metropolitan University, Graduate School of Medicine, Osaka, Japan; [14]Department of Infection Control and Prevention, Osaka Metropolitan University Hospital, Osaka, Japan; [15]Division of Respirology, Rheumatology, Infectious Diseases, and Neurology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan; [16]Department of Respiratory Medicine, Tokoname City Hospital, Tokoname, Japan; [17]Department of Clinical Technology, Tokoname City Hospital, Tokoname, Japan; [18]Department of Pharmacy, Takarazuka City Hospital, Takarazuka, Japan; [19]Department of Chemotherapy and Mycoses, National Institute of Infectious Diseases, Tokyo, Japan; [20]Department of Clinical Infectious Diseases, Tokoname City Hospital, Tokoname, Japan

*Corresponding author. E-mail: taka76@hyo-med.ac.jp

Received 3 January 2025; accepted 18 April 2025

Background: A bedside scoring system to assess the severity of disease is lacking for candidaemia. The Pitt candidaemia score (PCS) was evaluated for its association with mortality.

Methods: The PCS consists of five components, namely dialysis, hypotension, mechanical ventilation, cardiac arrest and mental status. Patients were classified into four categories according to their PCS. The correlation between PCS category at blood culture collection and 30 day mortality was studied individually for five *Candida* species.

Results: Leading rates of mortality were observed in *Candida tropicalis* and *Candida krusei*. The interval from inoculation to positive culture was 19.4 ± 9.7 h for *C. tropicalis* and 21.3 ± 5.6 h for *C. krusei*; these intervals were significantly shorter than those for other *Candida* species. In a Kaplan–Meier survival curve, a significant risk stratification by PCS category was demonstrated in all *Candida* species. A high PCS was an independent risk factor for mortality, and source control decreased the risk for *C. tropicalis* and *Candida glabrata* infections. Regarding antifungal therapy, the median PCS was 8 for liposomal amphotericin B, 2 for echinocandins and 0 for azoles, and this trend was consistent among four *Candida* species.

Conclusions: The mortality rate was well stratified by the PCS, and the PCS affected the selection of antifungals. A future prospective study is required for the PCS in guiding therapy for candidaemia.

Introduction

Candidaemia is variously reported as the fourth to seventh most common nosocomial bloodstream infection (BSI).[1–3] Despite the development of several antifungals, mortality still remains at 40%.[4,5] Invasive candidiasis caused by *Candida tropicalis* is associated with the poorest clinical outcomes.[6] The highest attributable mortality was observed for *C. tropicalis*, at 63.6%.[5] Nakada-Motokawa *et al.*[7] reported that the OR for 30 day mortality was 2.39 for candidaemia caused by *C. tropicalis*, compared with 0.59 for *Candida parapsilosis* candidaemia.

High mortality rate was also demonstrated in BSI with *Candida krusei*, a potentially MDR pathogen that inhabits normal microflora.[8–10] In a systematic review, candidaemia with *C. krusei* was associated with high mortality rates ranging from 44% to 67%.[11] Compared with patients with *Candida albicans*, patients with *C. krusei* more often had leukaemia, whereas catheter-related BSI was less common.[10] Nguyen *et al.*[11] demonstrated that the high mortality rate for *C. krusei* likely reflects patient confounders rather than the virulence of the pathogen itself.

In critically ill patients, early identification of risk factors for a poor prognosis is essential for timely intervention and optimal resource allocation. To identify patients at risk of mortality, several scoring systems have been proposed. The SOFA and the APACHE II scoring systems have been used in ICUs to assess the severity of illness.[12,13] However, these scoring systems might be too complicated for use on general wards. APACHE II was calculated by summing the points (ranging from 0 to 4) of the acute physiology score, which consists of 12 components, age points and chronic health points.

Alternatively, several early warning systems have been developed for initial bedside assessment of the severity of illness. In a systematic review, a Modified Early Warning Score of ≥5 and a National Early Warning Score of ≥7 had ORs of 3.0 and 4.7, respectively, to predict mortality in patients with sepsis.[14] The Pitt bacteraemia score (PBS) has been used to predict mortality in patients with BSIs and outperformed APACHE II in patients with sepsis in ICUs.[15] To date, only a few reports have been published regarding a risk scoring system specific for candidaemia.[7,16] In the evaluation of the PBS in patients with candidaemia, the combined use of another scoring system was required for predicting mortality.[16] A modified version of the PBS was proposed for candidaemia wherein fever was replaced with dialysis.[7] The 30 day mortality rates were 13.8%, 36.8% and 69.4% for patients with modified PBS of 0–3, 4–7 and ≥8 points, respectively.[7]

Aggressive management of candidaemia, which includes liposomal amphotericin B (L-AMB) and invasive drainage or debridement, is required for critically ill patients as early as possible. Here, a retrospective multicentre study was conducted to verify the efficacy of the modified version of the PBS, hereafter called the Pitt candidaemia score (PCS). The purpose of this study was to investigate a tool to assess empirical management on the basis of the PCS for patients with candidaemia. The stratification accuracy of the PCS was evaluated in five main *Candida* species, to confirm whether the PCS can be applied irrespective of *Candida* species.

Patients and methods

Study design

We evaluated the all-cause 30 day mortality and early (Days 0–14) mortality in patients with candidaemia in cases where *Candida* species were solely isolated from blood culture. After excluding patients without antifungal therapy, the PCS was calculated in patients with *C. tropicalis*, *C. krusei* and *C. glabrata* infections and the association between the PCS and 30 day mortality was investigated in a multicentre study. The association was also evaluated for *C. albicans* and *C. parapsilosis* in a single-centre study.

Researchers in each institution retrospectively reviewed the medical records of patients diagnosed with culture-proven candidaemia, assigned the PCS and assessed 30 day mortality between January 2016 and December 2021 at 11 hospitals in Japan (Table S1, available as Supplementary data at *JAC-AMR* Online). The study was approved by the Institutional Review Board of Hyogo Medical University, as a batch review (no. 4192) and as a single-centre study (no. 4902). The board waived the requirement for informed consent from patients included in this study and an opt-out approach was used.

Calculation of the PCS

The PCS consists of five components: dialysis, hypotension, mechanical ventilation, cardiac arrest and mental status (Table 1). Hypotension was defined as an acute drop in systolic blood pressure of >30 mm Hg and diastolic pressure of >20 mmHg, or the requirement for a vasopressor to sustain systolic blood pressure at ≥90 mmHg. The PCS was the total number of points, based on the highest point for each component recorded within 24 h before or after collection of the first positive blood culture sample.[7]

In the evaluation of initial antifungal use according to the PCS, patients with combination antifungal therapy, except for flucytosine, were excluded. Because diagnosis of ocular candidiasis at the time of antifungal initiation or prior antifungal use within 1 month could affect the selection of antifungals, these patients were also excluded.

Identification of Candia spp. and an antifungal susceptibility test

Candida species were identified using MALDI-TOF MS. The MALDI Biotyper (Bruker Daltonics K.K.) was used in six hospitals and the VITEK MS PRIME (bioMérieux S.A.) was used in five hospitals. Antifungal susceptibility testing for fluconazole, voriconazole and micafungin was performed in accordance with the CLSI M60, 2017 criteria,[17] along with antifungal testing for L-AMB by the EUCAST guidelines (Table S2).[18] Because of significant inter-laboratory variation in MIC ranges for caspofungin, especially against *C. glabrata*, breakpoints have not yet been established by EUCAST.[19] Hence, susceptibility test results for micafungin were used in substitution for the susceptibility to caspofungin for the evaluation of inappropriate therapy.

Definitions

Initial antifungal therapy was defined as the first antifungal used once yeast was identified in blood culture. Antifungal therapy was considered inappropriate if the recommended dose was not used or isolated *Candida* species were not susceptible to the initial antifungals based on antimicrobial susceptibility testing (Table S2). Immunosuppression was defined as

Table 1. Criteria for the calculation of the PCS

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

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

steroid or immunosuppressant use, anticancer therapy or neutropenia (<500 cells/μL).

Statistical methods

Continuous variables are presented as the mean ± SD if the data followed a symmetric distribution. The median (IQR) was used if the data were skewed. Parametric variables were analysed using Student's *t*-test, whereas non-parametric variables were analysed using the Mann–Whitney *U*-test.

The 30 day mortality rates stratified according to four categories in the PCS (risk 1: 0–1 point; risk 2: 2–3 points; risk 3: 4–7 points; and risk 4: ≥8 points) were compared using the Cochran–Armitage trend test. The Kaplan–Meier survival curves in each PCS category were compared using the log-rank trend test. Receiver operating characteristic (ROC) curves were used to identify PCS cut-off values for the association of 30 day mortality, and the AUC with a 95% CI by 2000 stratified bootstrap replicates (R v. 4.4.3; https://cran.rstudio.com/bin/windows/base/) was demonstrated. Multivariate analyses were performed to determine the adjusted OR for factors associated with 30 day mortality. Univariate analysis was performed to estimate each variable using the chi-squared test, and potential confounders were examined via cross-tabulation. Variables selected in the univariate analysis ($P < 0.1$) were subsequently entered into a stepwise logistic regression model to estimate the magnitude of association (adjusted OR and 95% CI). The PCSs according to the initial antifungals were compared by the Kruskal–Wallis test. The level of significance was set at $P < 0.05$. JMP Pro 17 (SAS Institute Inc.) was used for survival curve analysis and SPSS Statistics v. 30 (SPSS Inc., NY, USA) was used for other analyses.

Results

In total, 1017 patients were enrolled in the multicentre study. Mortality associated with each *Candida* species was evaluated in 975 patients after excluding 42 patients for whom more than one *Candida* species was isolated. After the exclusion of patients who had not received antifungal therapy, 54 patients with *C. tropicalis*, 165 patients with *C. glabrata*, 14 patients with *C. krusei*, 52 patients with *C. albicans* and 25 patients with *C. parapsilosis* infections were eligible for PCS evaluation (Figure 1).

Overall early and 30 day mortality rates were 24.4% and 34.1%, respectively. The highest 30 day mortality rates were observed for *C. krusei* (46.7%) and *C. tropicalis* (43.3%), followed by *C. albicans* (39.6%), *C. glabrata* (28.6%) and *C. parapsilosis* (25.5%) (Figure 2). Compared with the 30 day mortality rate for *C. tropicalis*, significantly lower rates were demonstrated for *C. glabrata* and *C. parapsilosis* ($P = 0.034$ and $P = 0.008$, respectively). Compared with the early mortality rate for *C. krusei*, significantly lower rates were demonstrated for *C. glabrata*, *C. parapsilosis* and *C. guilliermondii* ($P = 0.023$, $P = 0.012$ and $P = 0.016$, respectively).

The characteristics of patients included in the PCS evaluation for each *Candida* species are presented in Table 2. The 30 day mortality rate was 37.0% for *C. tropicalis*, 25.5% for *C. glabrata*, 42.9% for *C. krusei*, 26.9% for *C. albicans* and 16.0% for *C. parapsilosis* infections in this patient group. Candidaemia developed during the ICU stay in approximately one-third of patients for all *Candida* species. The rate of haematological malignancy ranged from 7.7% to 24.0%. Intravascular catheter-related BSI accounted for less than half of patients with *C. glabrata* ($P = 0.001$) and *C. krusei* ($P = 0.012$), compared with 84.0% of patients with *C. parapsilosis*. In candidaemia with *C. krusei*, neutropenia was associated with 35.7% of patients and source control was achieved in only half of patients.

The rate of occurrence of a time lag shorter than 24 h from blood culture collection to initiation of antifungals was lowest for *C. glabrata* (37.0%), which was a significantly lower percentage than all other *Candida* species. The rate of occurrence of a time lag longer than 72 h was higher for *C. glabrata* than for *C. tropicalis* ($P = 0.019$) or *C. albicans* ($P = 0.074$) (Figure 1). The time interval from inoculation to positive culture was evaluated in 237 patients (no data were available for 65 patients and assessment was not possible because of co-isolation with bacteria in 8 patients) (Figure 2) and was significantly longer for *C. glabrata* (61.71 ± 28.82 h) than for the other four *Candida* species ($P < 0.001$ for each). The time interval was significantly shorter for *C. tropicalis* (19.43 ± 9.65 h) and *C. krusei* (21.33 ± 5.57 h) than for *C. albicans* (41.61 ± 25.34 h) ($P < 0.001$ and $P = 0.009$, respectively) and *C. parapsilosis* (36.84 ± 11.72 h) ($P < 0.001$ for each).

In vitro susceptibility to antifungals was demonstrated for *Candida* species isolated from blood culture, as shown in Table S3. There were substantial differences in the geometric mean MIC between fluconazole and voriconazole for *C. glabrata* (10.77 versus 0.36 mg/L) and *C. krusei* (47.95 versus 0.57 mg/L), respectively. The resistance rate against micafungin remained at 5.1% for *C. glabrata*. Although the geometric mean MIC of micafungin (0.51 mg/L) for *C. parapsilosis* was higher than for the other *Candida* species (ranging from 0.02 to 0.10 mg/L), none of the strains exhibited resistance against micafungin.

The PCS for *C. krusei* (4.21 ± 3.33) was significantly higher than that for *C. glabrata* (2.75 ± 3.25, $P = 0.040$) and *C. parapsilosis* (2.68 ± 3.91, $P = 0.039$) and tended to be higher than that in *C. albicans* (2.75 ± 3.18, $P = 0.083$). However, the PCS for *C. tropicalis* (3.24 ± 3.65) showed no significant difference compared with the PCSs for these three *Candida* species (Figure 4). Although the mortality rate was 16.0% in *C. parapsilosis* infection compared with 26.9% in *C. albicans* infection, the PCSs were similar for these *Candida* species.

The 30 day mortality rate increased incrementally with higher PCS categories for each *Candida* species (Figure 3). The overall 30 day mortality rate was 7.9% for category 1, 24.4% for category 2, 41.2% for category 3 and 78.4% for category 4. Even within the same PCS category, the mortality rate differed

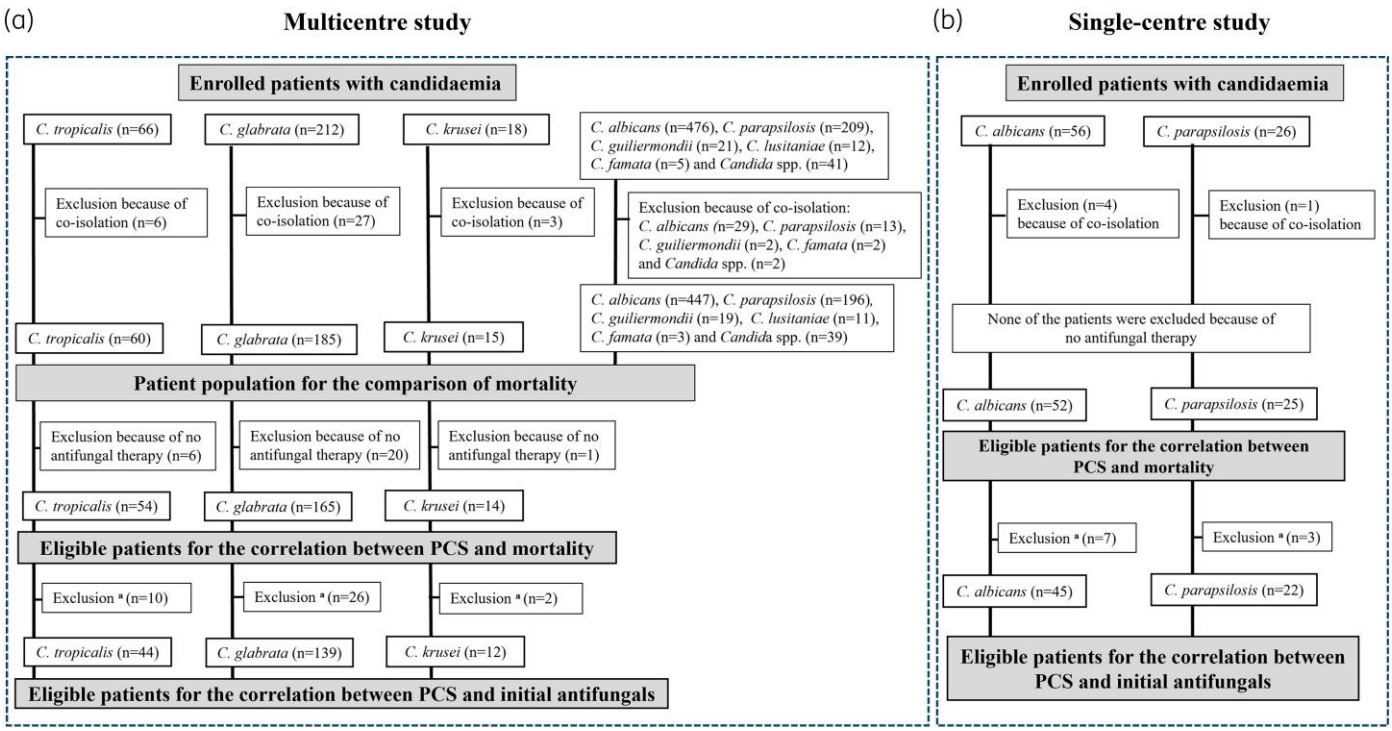


Figure 1. Flow chart for patient selection. (a) Multicentre study, (b) single-centre study. [a]Because of combination therapy, diagnosis of ocular disease at the time of antifungal initiation or preceding antifungal therapy within 1 month.

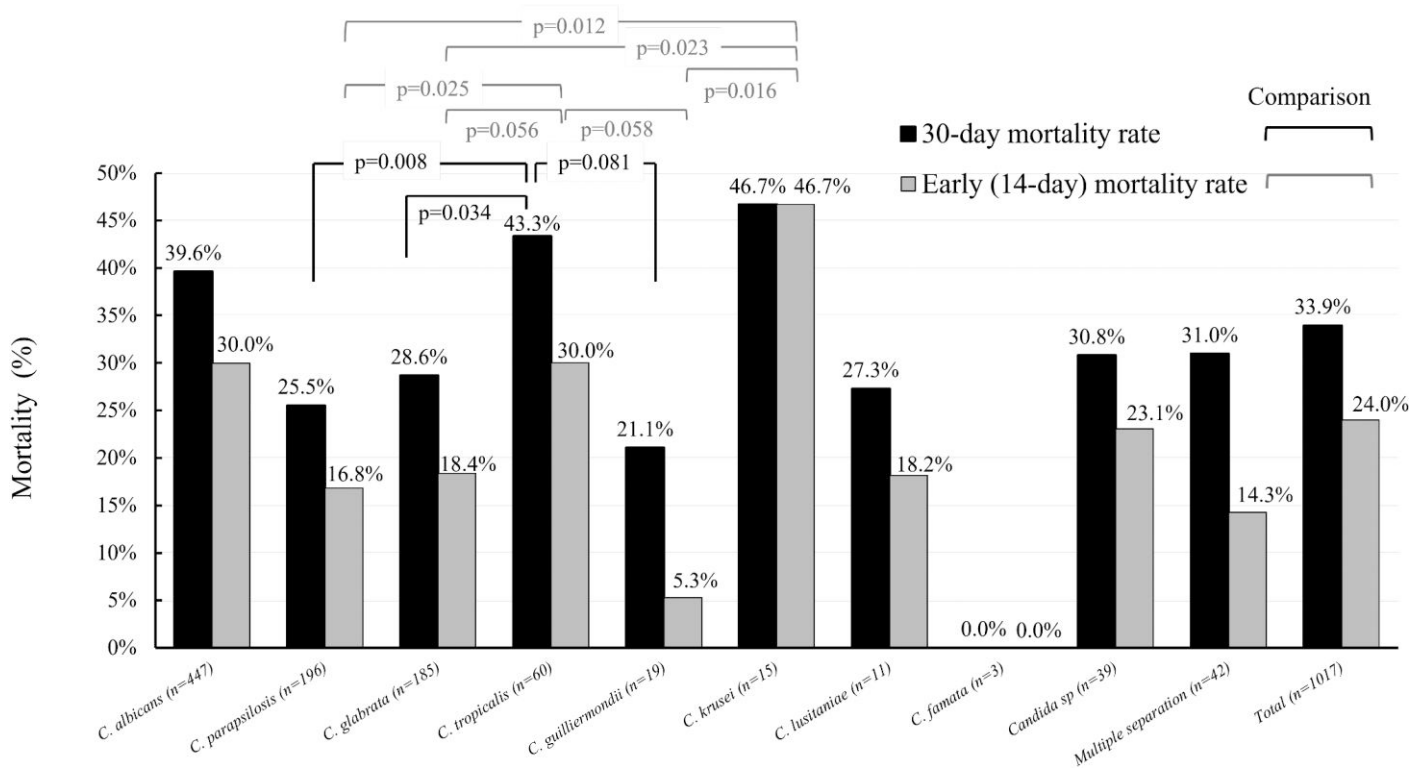


Figure 2. The 30 day and early (within 14 days) mortality rates in patients with candidaemia, as determined in a multicentre study.

Table 2. Characteristics of patients with candidaemia by each *Candida* species

	Multicentre study					Single-centre study	
Variables	*C. tropicalis* (*n* = 54)	*C. glabrata* (*n* = 165)	*P* value[a]	*C. krusei* (*n* = 14)	*P* value[a]	*C. albicans* (*n* = 52)	*C. parapsilosis* (*n* = 25)
Male, *n* (%)	41 (75.9)	94 (57.0)	0.013	9 (64.3)	0.379	36 (69.2)	14 (56.0)
Average age (years), mean ± SD	65.0 ± 17.0	68.1 ± 15.6	0.208	75.4 ± 11.1	0.032	65.5 ± 19.6	53.8 ± 14.1
Age ≥ 65 years, *n* (%)	31 (57.4)	113 (68.5)	0.136	11 (78.6)	0.219	35 (67.3)	6 (24.0)
Average BMI, mean ± SD	20.3 ± 4.3	21.4 ± 4.6	0.109	21.1 ± 4.8	0.554	20.2 ± 4.7	20.1 ± 5.2
BMI < 18.5, *n* (%)	16 (29.6)	48 (29.1)	0.940	3 (21.4)	0.219	23 (44.2)	10 (40.0)
BMI ≥ 25, *n* (%)	8 (14.)	35 (21.2)	0.304	2 (14.3)	1.000	8 (15.4)	2 (8.0)
ICU admission, *n* (%)	21 (38.9)	54 (32.7)	0.408	5 (35.7)	0.828	19 (36.5)	6 (24.0)
Comorbidities, *n* (%)							
Heart disease	12 (22.2)	42 (25.5)	0.632	5 (35.7)	0.299	19 (36.5)	2 (8.0)
Chronic hepatic dysfunction	14 (25.9)	33 (20.0)	0.357	2 (14.3)	0.492	7 (13.5)	2 (8.0)
Chronic kidney disease	21 (38.9)	59 (35.8)	0.678	6 (42.9)	0.787	13 (25.0)	4 (16.0)
Dialysis	12 (22.2)	31 (18.8)	0.581	2 (14.3)	0.717	13 (25.0)	3 (12.0)
Diabetes mellitus	18 (33.3)	57 (34.5)	0.871	4 (28.6)	1.000	13 (25.0)	2 (8.0)
Solid cancer	22 (40.7)	65 (39.4)	0.861	3 (21.4)	0.226	16 (30.8)	5 (20.0)
Haematological malignancy	11 (20.4)	18 (10.9)	0.075	3 (21.4)	1.000	4 (7.7)	6 (24.0)
Organ transplant	1 (1.9)	5 (3.0)	1.000	0 (0.0)	1.000	1 (1.9)	0 (0.0)
Immunosuppression, *n* (%)	18 (33.3)	58 (35.2)	0.808	7 (50.0)	0.249	19 (36.5)	10 (40.0)
Steroids	12 (22.2)	42 (25.5)	0.632	6 (42.9)	0.119	18 (34.6)	9 (36.0)
Immunosuppressant	4 (7.4)	21 (12.7)	0.336	3 (21.4)	0.147	6 (11.5)	5 (20.0)
Anti-cancer chemotherapy	5 (9.3)	15 (9.1)	1.000	4 (28.6)	0.050	4 (7.7)	4 (16.0)
Neutropenia (<500 cells/μL)	5 (9.3)	14 (8.5)	0.788	5 (35.7)	0.014	2 (3.8)	3 (12.0)
Risk factors, *n* (%)							
Acute kidney injury	18 (33.3)	55 (33.3)	1.000	7 (50.0)	0.249	12 (23.1)	5 (20.0)
Abdominal surgery within 30 days	10 (18.5)	36 (21.8)	0.605	1 (7.1)	0.437	14 (26.9)	1 (4.0)
Invasive mechanical ventilation	13 (24.1)	45 (27.3)	0.644	5 (35.7)	0.379	15 (28.8)	5 (20.0)
Albumin < 3.0 mg/dL	44 (81.5)	138 (83.6)	0.714	13 (92.9)	0.437	46 (88.5)	19 (76.0)
Total parenteral nutrition	25 (46.3)	80 (48.5)	0.780	4 (28.6)	0.364	34 (65.4)	24 (96.0)
Presence of central venous catheter, *n* (%)	40 (74.1)	105 (63.6)	0.159	7 (50.0)	0.082	38 (73.1)	23 (92.0)
Source of candidaemia, *n* (%)							
Intravascular catheter	36 (66.7)	74 (44.8)	0.005	6 (42.9)	0.102	29 (55.8)	21 (84.0)
Cardiac implantable electronic device	1 (1.9)	2 (1.2)	0.574	0 (0.0)	1.000	0 (0.0)	0 (0.0)
Artificial graft	0 (0.0)	0 (0.0)	—	0 (0.0)	—	1 (1.9)	0 (0.0)
Infectious endocarditis	0 (0.0)	3 (1.8)	1.000	0 (0.0)	—	0 (0.0)	0 (0.0)
Intra-abdominal infection	7 (13.0)	40 (24.2)	0.080	1 (7.1)	1.000	8 (15.4)	1 (4.0)
Osteomyelitis	1 (1.9)	1 (0.6)	0.433	0 (0.0)	1.000	1 (1.9)	1 (4.0)
Renal abscess	1 (1.9)	2 (1.2)	0.574	0 (0.0)	1.000	0 (0.0)	0 (0.0)
Urinary tract infection	2 (3.7)	13 (7.9)	0.369	1 (7.1)	0.505	4 (7.7)	0 (0.0)
Other	1 (1.9)	1 (0.6)	0.574	0 (0.0)	1.000	1 (1.9)	0 (0.0)
Unknown	5 (9.3)	29 (17.6)	0.143	6 (42.9)	0.002	8 (15.4)	2 (8.0)
Achievement of source control, *n* (%)	36 (66.7)	111 (67.3)	0.934	7 (50.0)	0.249	39 (75.0)	20 (80.0)
Removal of intravascular catheter or cardiac implantable electronic device	31/37 (83.8)	63/76 (82.9)	0.906	5/6 (83.3)	1.000	29/29 (100.0)	19/21 (90.5)
Drainage/debridement/surgery in patients	5/17 (29.4)	48/89 (53.9)	0.064	2/8 (25.0)	1.000	10/23 (43.5)	1/4 (25.0)
Ocular candidiasis, *n* (%)	8/43 (18.6)	8/135 (5.9)	0.027	0/9 (0.0)	0.323	10/52 (19.2)	1/24 (4.2)
Persistent candidaemia, *n* (%)	9 (16.7)	28 (17.0)	0.959	5 (35.7)	0.116	12 (23.1)	10 (40.0)
Bacterial coinfection, *n* (%)	4 (7.4)	31 (18.8)	0.048	2 (14.3)	0.595	6 (11.5)	1 (4.0)
Mean PCS, mean ± SD	3.24 ± 3.65	2.75 ± 3.25	0.531	4.21 ± 3.33	0.181	2.75 ± 3.18	2.68 ± 3.91
Prior antifungal exposure within 1 month, *n* (%)	10 (18.5)	27 (16.4)	0.484	2 (14.3)	1.000	4 (7.7)	3 (12.0)
Initiation of antifungals within 24 h after collection of blood culture, *n* (%)	44 (81.5)	61 (37.0)	<0.001	9 (64.3)	0.275	28 (53.8)	15 (60.0)

Continued

Table 2. *Continued*

Variables	Multicentre study					Single-centre study	
	C. tropicalis (*n* = 54)	*C. glabrata* (*n* = 165)	*P* value[a]	*C. krusei* (*n* = 14)	*P* value[a]	*C. albicans* (*n* = 52)	*C. parapsilosis* (*n* = 25)
Initially selected antifungals, *n* (%)							
Azoles	4 (7.4)	17 (10.3)	0.790	2 (14.3)	0.595	7 (13.5)	6 (24.0)
Echinocandins	43 (79.6)	136 (82.4)	0.645	6 (42.9)	0.006	40 (76.9)	15 (60.0)
L-AMB	8 (14.8)	14 (8.5)	0.179	6 (42.9)	0.021	6 (11.5)	4 (16.0)
30 Day mortality rate, *n* (%)	20 (37.0)	42 (25.)	0.101	6 (42.9)	0.690	14 (26.9)	4 (16.0)

[a]Versus *C. tropicalis*.

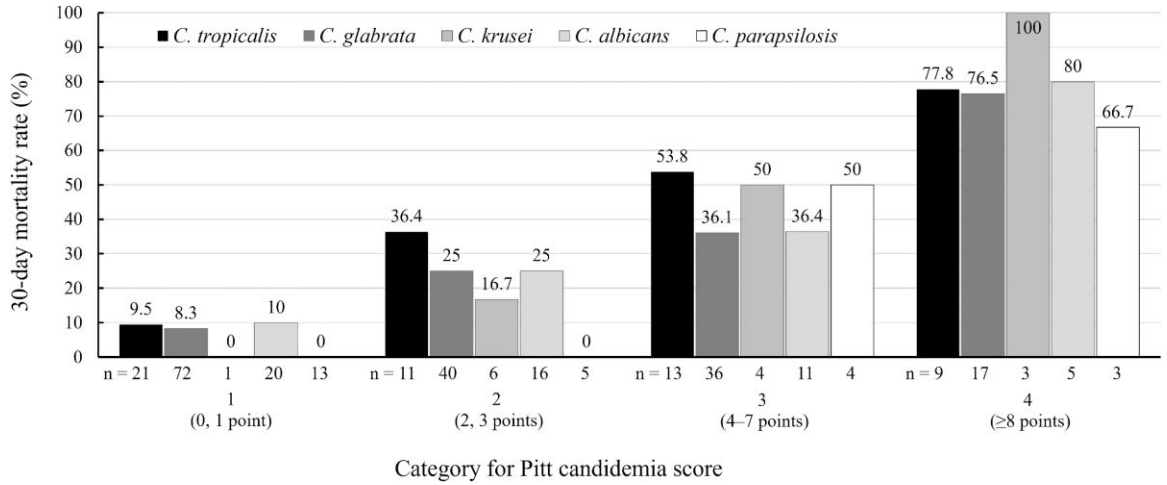


Figure 3. The 30 day mortality rate stratified by the four categories of PCS in patients with candidaemia caused by each *Candida* species. The 30 day mortality rate increased incrementally with higher PCS risk categories for *C. tropicalis* ($P < 0.001$), *C. glabrata* ($P < 0.001$), *C. krusei* ($P < 0.013$), *C. albicans* ($P = 0.004$) and *C. parapsilosis* ($P = 0.002$).

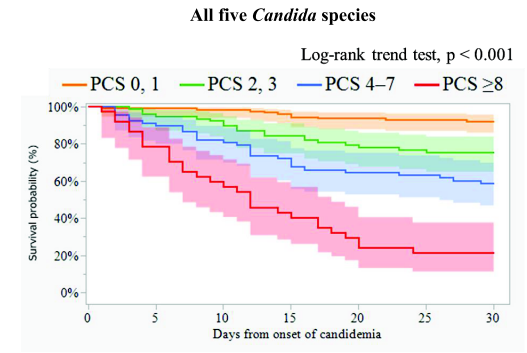
according to *Candida* species in categories 2 and 3 (Figure 3). When these two categories were combined, the mortality rate for *C. tropicalis* was 45.8% and that of the remaining four *Candida* species was 29.5%, although there was no significant difference ($P = 0.118$). Although all patients with a PCS of category 2 survived for 30 days with *C. parapsilosis* infection, the 30 day mortality rate in this category ranged from 16.7% to 36.4% for the other *Candida* species.

In Kaplan–Meier survival curves (Figure 4, Figure 3), the significant incremental predictive value of the PCS category for mortality was demonstrated for all patients with candidaemia (log-rank trend test: $P < 0.001$) and for patients with candidaemia caused by each *Candida* species. Sustained survival in PCS category 1 and an early steep decrease in survival in PCS category 4 were demonstrated for all *Candida* species, whereas the pattern of the survival curve was different among *Candida* species in PCS categories 2 and 3.

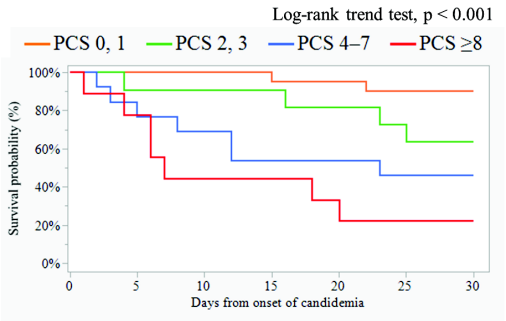
The performance characteristics of the PCS for the association of 30 day mortality showed significant discrimination ability for all *Candida* species (Table S4). The cut-off value was 6 for *C. parapsilosis*, compared with 3 to 4 for the other *Candida* species. The AUC ranged from 0.748 to 0.964 and the lower limit value of the bootstrap 95% CI was >0.5 for all *Candida* species, which demonstrates a high to moderate degree of accuracy.

The variables associated with 30 day mortality in patients with candidaemia with *C. tropicalis* are presented in Table 3. The PCS (adjusted OR 1.60, 95% CI 1.19–2.15, 1-point increments) and chronic hepatic dysfunction were independent risk factors for 30 day mortality; by contrast, source control was a factor that decreased the risk. The PCS (adjusted OR 1.64, 95% CI 1.33–2.01, 1-point increments) and source control were also independent factors for 30 day mortality in patients with candidaemia by *C. glabrata* (Table S5), while the PCS tended to be associated with mortality in *C. krusei* (crude OR 2.49, 95% CI 0.92–6.71). (Table S6)

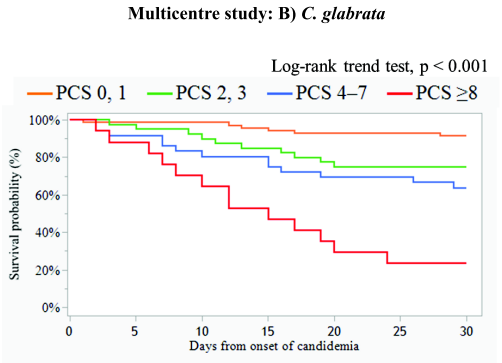
Echinocandins were used in 79.4% of patients with candidaemia. Although there was no trend of echinocandin use according to PCS category, the rate of use significantly increased incrementally with higher PCS category for L-AMB. By contrast, the rate of use significantly decreased incrementally with higher PCS category for azoles (Table 4). The median PCS was 8 for L-AMB (IQR 4–10), 2 for echinocandins (IQR 0–4) and 0 for azoles (IQR 0–2). A similar antifungal selection pattern was demonstrated for each *Candida* species, except for *C. glabrata* (Table S7).



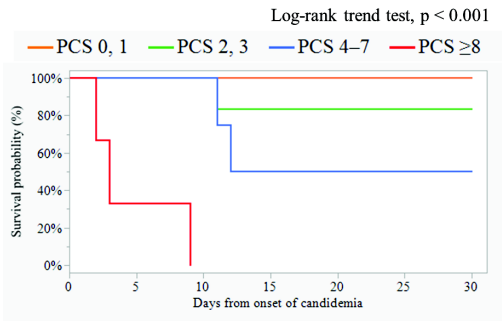
PCS	No. of surviving patients						
0, 1	0	5	10	15	20	25	30
2, 3	127	126	125	120	119	118	117
4–7	78	74	70	66	61	59	59
≥8	68	61	55	46	44	43	40



PCS	No. of surviving patients						
0, 1	21	21	21	20	20	19	19
2, 3	11	10	10	10	9	7	7
4–7	13	10	9	7	7	6	6
≥8	9	7	4	4	2	2	2



PCS	No. of surviving patients						
0, 1	72	71	71	68	67	67	66
2, 3	40	38	36	34	30	30	30
4–7	36	33	29	27	25	25	23
≥8	17	15	11	8	5	4	4



PCS	No. of surviving patients						
0, 1	1	1	1	1	1	1	1
2, 3	6	6	6	5	5	5	5
4–7	4	4	4	2	2	2	2
≥8	3	1	0	0	0	0	0

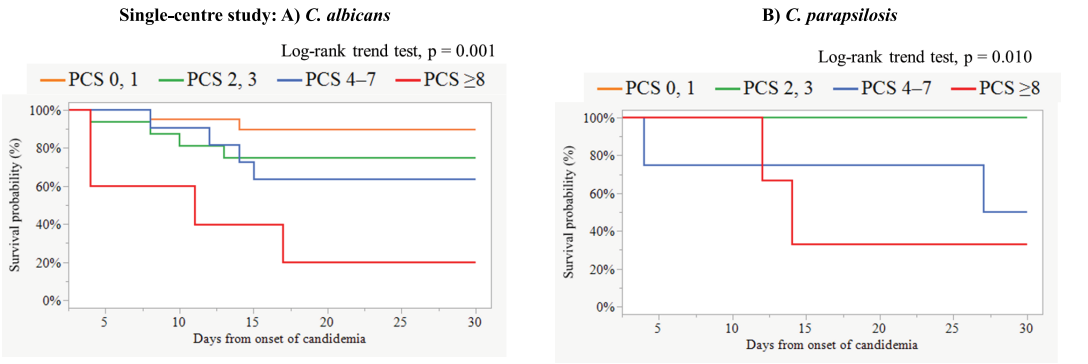
Figure 4. Kaplan–Meier survival curve for patients with candidaemia caused by all *Candida* species and each *Candida* species individually, stratified by the PCS. PCS 0, 1 = category 1; PCS 2, 3 = category 2; PCS 4–7 = category 3; PCS ≥8 = category 4. Multicentre study: (a) *C. tropicalis*, (b) *C. glabrata*, (c) *C. krusei*. Single-centre study: (a) *C. albicans*, (b) *C. parapsilosis*.

Discussion

Higher PCS was an independent risk factor for mortality in candidaemia patients with *C. tropicalis* and *C. glabrata*, and there was a trend toward increased mortality with 1-point increments for the PCS in patients with *C. krusei* infection. In addition, a significant risk stratification by the PCS category was demonstrated with the Kaplan–Meier survival curve in all five *Candida* species. Thus, usefulness of the PCS for the association of mortality was confirmed among patients with candidaemia in each *Candida* species.

The highest 30 day mortality rates were observed for *C. tropicalis* and *C. krusei*; however, the reasons for these high mortality rates were different between these two *Candida* species. The highest PCS would cause poor prognosis for *C. krusei* infection. Unexpectedly, however, the PCS for *C. tropicalis* showed no significant difference compared with those for *C. albicans*, *C. glabrata* and *C. parapsilosis* despite considerable differences in mortality rates. Although the lowest 30 day mortality rate was observed for *C. parapsilosis*, the PCS for *C. parapsilosis* was similar to those for *C. albicans* and *C. glabrata*. Inter-species assessment for mortality by the PCS was less effective than the stratification of risk for mortality by the PCS in each *Candida* species.

Even within the same PCS category, the mortality rate differed according to *Candida* species in categories 2 and 3, with a mortality rate of 45.8% for patients infected with *C. tropicalis* and 29.5% for the other four *Candida* species. Although all patients with a PCS of category 2 survived for 30 days with *C. parapsilosis*



PCS	No. of surviving patients						
0, 1	20	20	19	18	18	18	18
2, 3	16	15	13	12	12	12	12
4–7	11	11	10	7	7	7	7
≥8	5	3	3	2	1	1	1

PCS	No. of surviving patients						
0, 1	13	13	13	13	13	13	13
2, 3	5	5	5	5	5	5	5
4–7	4	3	3	3	3	3	2
≥8	3	3	3	1	1	1	1

Figure 4. Continued

infection, 30 day mortality rate was ranging from 16.7% to 36.4% for the other *Candida* species. The cut-off value for increased risk of 30 day mortality was 6 for *C. parapsilosis*, compared with 3 to 4 for other *Candida* species, which suggested that patients with *C. parapsilosis*, even with higher PCSs, may show better survival rates than those infected with other *Candida* species.

Pathogenicity in each *Candida* species had different impacts on the clinical course after PCS evaluation. The time interval from blood culture inoculation to a positive blood culture result was approximately 20 h for *C. tropicalis* and *C. krusei*, which was significantly shorter than for other *Candida* species. Zhang *et al.*[20] reported that the mean time to positivity was 22.2 h for *C. tropicalis*, compared with 38.4 h for all other *Candida* species. Horvath *et al.*[21] also reported that the time to positivity was 20.1 h for *C. tropicalis*. In addition to biofilm production,[22] the larger number of cells in the blood with a faster growth rate might increase the risk of mortality in patients infected with *C. tropicalis*.

Kronen *et al.*[23] suspected that not virulence of *C. krusei* itself but the life-threatening underlying comorbidities would cause the high mortality rate in this organism. Either a fast growth rate during the culture or a high bacterial load in the blood at the time of blood culture collection would cause the shorter interval from the inoculation to a positive blood culture. Because of the higher PCS measured at the time of blood culture collection, the latter might be the reason for the shorter time for positive culture in patients infected with *C. krusei*. In addition to high PCS, the combined effect of the underlying comorbidities (neutropenia 35.7% and immunosuppression 50%), low rate of source control (50.0%) could cause the high mortality rate for *C. krusei* in this study.

Nakada-Motokawa *et al.*[7] reported that patients with more severe illness were treated with L-AMB, and those with less severe illness were treated with azoles. Similarly, the median PCS was 8 with L-AMB, 2 with echinocandins and 0 with azoles for the initial treatment of candidaemia in our study. A similar correlation between the selection of antifungals and the PCS was demonstrated for all *Candida* species, except for *C. glabrata*. A possible reason for this exception may be the delay in isolation of *C. glabrata* after blood culture collection, with septic shock potentially being alleviated by the removal of intravascular catheters and cardiovascular management prior to the initiation of antifungals, and echinocandins or azoles maybe being used instead of L-AMB in such patients, even with a high PCS.

The clinical practice guidelines for the management of invasive candidiasis by the Japanese Society for Medical Mycology suggest the initial selection of antifungals according to disease severity, as follows: fluconazole for patients with an APACHE II score of <10 (estimated mortality rate 5%), echinocandins for patients with an APACHE II score of ≥10, and L-AMB for patients with an APACHE II score of ≥25 (estimated mortality rate of ≥35%).[24] Considering our finding that overall 30 day mortality was 7.9% for PCS category 1, 24.4% for category 2 and 41.2% for category 3, the Japanese guidelines might be replaced with the following empirical antifungal selection policy: azoles for patients with a PCS of category 1, and echinocandins for patients with PCSs of categories higher than 1. The use of L-AMB could be considered for patients with PCSs of categories higher than 2. Modification of the protocol is required with the consideration of other factors including incomplete source control, as mentioned in Table S8.

This study had several limitations. First, a comparison between the PCS and APACHE II or other early warning systems was not performed. However, a higher discrimination accuracy, as assessed by the AUC, was obtained for the PCS than for previously reported risk scoring systems.[7,25,26] Second, a greater sample size is required for *C. krusei* to evaluate independent risk factors for mortality. PCS should be adjusted by other possible covariates such as haematological malignancy. Third, the potential beneficial effect of L-AMB therapy in patients with a high PCS category was not demonstrated in this study. In systematic review, there was no significant difference in clinical efficacy for invasive candidiasis[27] or febrile neutropenia[28] between echinocandins and

Table 3. Variables associated with 30 day mortality in patients with candidaemia caused by *C. tropicalis* in univariate and multivariate analyses

	No of patients with 30 day mortality		Univariate analysis		Multivariate analysis	
Factors	Patients with factor	Patients without factor	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Male, *n* (%)	18/41 (43.9)	2/13 (15.4)	4.30 (0.85–21.93)	0.100		
Age ≥ 65 years, *n* (%)	15/31 (48.4)	5/23 (21.7)	3.38 (1.00–11.38)	0.045	2.75 (0.43–17.61)	0.285
BMI < 18.5, *n* (%)	7/16 (43.8)	13/38 (34.2)	1.50 (0.45–4.93)	0.507		
BMI ≥ 25, *n* (%)	3/8 (37.5)	17/46 (37.0)	1.02 (0.22–4.83)	1.000		
ICU admission, *n* (%)	12/21 (57.1)	8/33 (24.2)	4.17 (1.29–13.49)	0.015	2.29 (0.23–12.52)	0.264
Comorbidities, *n* (%)						
Heart disease	6/12 (50.0)	14/42 (33.3)	2.00 (0.54–7.34)	0.326		
Chronic hepatic dysfunction	9/14 (64.3)	11/40 (27.5)	4.75 (1.30–17.32)	0.014	12.65 (1.57–101.82)	0.017
Diabetes mellitus	8/18 (44.4)	12/36 (33.3)	1.60 (0.50–5.10)	0.425		
Chronic kidney disease	11/21 (52.4)	9/33 (27.3)	2.93 (0.93–9.26)	0.063	4.62 (0.08–14.59)	0.717
Dialysis	8/12 (66.7)	12/42 (28.6)	5.00 (1.27–19.76)	0.039	Excluded because of confounding with PCS	
Solid cancer	8/22 (36.4)	12/32 (37.5)	0.95 (0.31–2.94)	0.932		
Haematological malignancy	5/11 (45.5)	15/43 (34.9)	1.56 (0.41–5.95)	0.728		
Organ transplant	1/1 (100.0)	19/53 (35.8)	—	0.370		
Immunosuppression, *n* (%)	7/11 (38.9)	13/36 (36.1)	1.13 (0.35–3.61)	0.842		
Steroids	5/12 (41.7)	15/42 (35.7)	1.29 (0.35–4.76)	0.744		
Immunosuppressant	2/4 (50.0)	18/50 (36.0)	1.78 (0.23–13.72)	0.622		
Anti-cancer chemotherapy	1/5 (20.0)	19/49 (38.8)	0.39 (0.04–3.80)	0.640		
Neutropenia (<500 cells/μL)	1/5 (20.0)	19/49 (38.8)	0.39 (0.04–3.80)	0.640		
Risk factors, *n* (%)						
Acute kidney injury	8/18 (44.4)	12/36 (33.3)	1.60 (0.50–5.10)	0.425		
Abdominal surgery within 30 days	2/10 (20.0)	18/44 (40.9)	0.36 (0.07–1.90)	0.291		
Invasive mechanical ventilation	8/13 (61.5)	12/41 (29.3)	3.87 (1.05–14.25)	0.050	Excluded because of confounding with PCS	
Albumin < 3.0 mg/dL	17/44 (38.6)	3/10 (30.0)	1.47 (0.33–6.47)	0.728		
Total parenteral nutrition	12/25 (48.0)	8/29 (27.6)	2.42 (0.78–7.51)	0.121		
Presence of central venous catheter, *n* (%)	17/40 (42.5)	3/14 (21.4)	2.71 (0.65–11.24)	0.208		
Source control, *n* (%)[a]	9/36 (25.0)	11/18 (61.1)	0.21 (0.06–0.71)	0.010	0.06 (0.01–0.43)	0.005
Prior antifungal exposure within 1 month, *n* (%)	3/10 (30.0)	17/44 (38.6)	0.68 (0.15–3.00)	0.610		
PCS, *n* (%)						
0	2/21 (9.5)		1.47 (1.18–1.82)	0.001	1.60 (1.19–2.15)	0.002
1	0/0		1-point increments		1-point increments	
2	4/10 (40.0)					
3	0/1 (0.0)					
4	3/7 (42.9)					
5	1/1 (100.0)					
6	2/4 (50.0)					
7	1/1 (100.0)					
≥8	7/9 (77.8)					
Type of candidaemia, *n* (%)						
Ocular candidiasis	1/8 (12.5)	9/35 (25.7)	0.41 (0.04–3.83)	0.656		
Complicated candidaemia	8/18 (44.4)	12/36 (33.3)	1.60 (0.50–5.10)	0.425		
Bacterial coinfection, *n* (%)	2/4 (50.0)	18/50 (36.0)	1.78 (0.23–13.72)	0.622		
Within 24 h from blood culture collection to starting antifungals, *n* (%)	18/44 (40.9)	2/10 (20.0)	2.77 (0.53–14.59)	0.291		
Initially selected antifungals, *n* (%)						
Azoles	1/4 (25.0)	19/50 (38.0)	0.54 (0.05–5.61)	1.000		
Echinocandins	14/43 (32.6)	6/11 (54.5)	0.40 (0.10–1.55)	0.294		
Liposomal amphotericin B	6/8 (75.0)	14/46 (30.4)	6.86 (1.23–38.26)	0.041	2.02 (0.14–28.88)	0.604

Continued

Table 3. *Continued*

	No of patients with 30 day mortality		Univariate analysis		Multivariate analysis	
Factors	Patients with factor	Patients without factor	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Inappropriate initial antifungal therapy, *n* (%)[b]	0/0	20/54 (37.0)	—	—		

[a]If infectious focus was not determined, patients were classified for those without source control.
[b]Because inappropriate therapy was confirmed in none of the patients, statistical analysis could not be performed.

Table 4. Antifungal use according to PCS category

Antifungal	No. of patients in each category of PCS, *n* (%)				*P* value
Patients eligible for evaluation of the correlation between the PCS and antifungal treatment	1 (*N*=101)	2 (*N*=68)	3 (*N*=60)	4 (*N*=33)	
L-AMB (*N*=19)	1 (1.0)	3 (4.4)	4 (6.7)	11 (33.3)	<0.001
Echinocandins (*N*=208)	79 (78.2)	56 (82.3)	51 (85.0)	22 (66.7)	0.753
Azoles (*N*=35)	21 (20.8)	9 (13.2)	5 (8.3)	0 (0)	0.001
Patients with prior antifungal use (within 1 month)[a]	1 (*N*=22[b])	2 (*N*=9[b])	3 (*N*=8)	4 (*N*=4[b])	
L-AMB (*N*=15)	7 (31.8)	4 (44.4)	3 (37.5)	1 (25.0)	0.856
Echinocandins (*N*=31)	16 (72.7)	6 (66.7)	5 (62.5)	4 (100.0)	0.824
Azoles (*N*=0)	0	0	0	0	—
Patients in whom ocular candidiasis had been diagnosed at the time of antifungal initiation[a]	1 (*N*=5)	2 (*N*=0)	3 (*N*=0)	4 (*N*=0)	
L-AMB (*N*=5)	5 (100)	0	0	0	—
Echinocandins (*N*=0)	0	0	0	0	—
Azoles (*N*=0)	0	0	0	0	—
Patients with combination therapy except for flucytosine[a]	1 (*N*=1)	2 (*N*=2)	3 (*N*=0)	4 (*N*=1)	
L-AMB (*N*=3)	1 (100)	1 (50.0)	0	1 (100)	—
Echinocandins (*N*=4)	1 (100)	2 (100)	0	1 (100)	—
Azoles (*N*=1)	0 (0.0)	1 (50.0)	0	0 (0.0)	—

[a]Patients excluded from evaluation of the correlation between the PCS and antifungal treatment.
[b]One patient treated with combination therapy.

L-AMB. Hence, the role of echinocandins versus L-AMB in this patient group should be clarified in future research. Fourth, the limited entry of echinocandins into the urinary tract may have been another factor in the preferential use of azoles or L-AMB in cases of urinary tract candidiasis. Fifth, inter-species differences in PCSs were shown only for *C. krusei* despite variable mortality rates among *Candida* species, and even within the same PCS category (for categories 2 and 3) mortality rates differed according to *Candida* species. Hence, some modification of the use of the PCS would be required in the selection of antifungals to take into consideration the risk of adverse effects, especially regarding the use of L-AMB, and the risk for mortality in identified *Candida* species with rapid diagnostic testing. Finally, this was a retrospective study; thus, the findings may not be generalizable because of a lack of sufficient evidence.

In conclusion, risk stratification for mortality using the PCS was demonstrated in patients with candidaemia caused by all frequently isolated *Candida* species. An aggressive approach to source control and the initial empirical antifungal therapy involving L-AMB would be required for patients with a high PCS category. Because of the associative nature of these findings, however, prospective validation to clarify how the PCS could be integrated into real-world antifungal decision-making is required.

Acknowledgements

We thank Kate Fox, DPhil, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Funding

This work was supported in part by the Research Program on Emerging and Re-emerging Infectious Diseases of the Japan Agency for Medical Research and Development under grants 24fk0108679h0302, JP23fk0108679, JP22fk0108135 and JP21fk0108135. The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Transparency declarations

H. Kakeya has received payment for lectures from MSD Japan, Pfizer Japan Inc., Sumitomo Dainippon Pharma Co. and Asahi Kasei Pharma Corporation. A. Ukimura has received payment for lectures from Shionogi & Co., Ltd. T. Ogawa has received collaborative research funding from FUJIFILM Wako Pure Chemical Corporation. Y. Kaneko has received independent medical education grant support from Pfizer Japan Inc. T. Miyazaki has received payment for lectures from MSD Japan, Pfizer

Japan Inc., Asahi Kasei Pharma Corporation, AstraZeneca K.K., KYORIN Pharmaceutical Co., Ltd and GlaxoSmithKline K.K. outside of this work. The other authors have no conflicts of interest to declare. All authors meet the ICMJE authorship criteria.

Supplementary data

Figures S1 to S4 and Tables S1 to S8 are available as Supplementary data at *JAC-AMR* Online.

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