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Incidence, characteristics and outcome of ICU-acquired candidemia in India

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For the SIHAM Candidemia Network.

Take home message: This multicentric study from India on ICU-acquired candidemia highlights the unique epidemiology of this country with its vast spectrum of *Candida* species and high rate of *C. tropicalis* isolation. The disease occurred comparatively early after ICU admission, even in patients with less severe physiology scores.

Electronic supplementary material
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Abstract *Purpose:* A systematic epidemiological study on intensive care unit (ICU)-acquired candidemia across India. *Method:* A prospective, nationwide, multicentric, observational study was conducted at 27 Indian ICUs. Consecutive patients who acquired candidemia after ICU admission were enrolled during April 2011 through September 2012. Clinical and laboratory variables of these patients were recorded. The present study is an analysis of data specific for adult patients. *Results:* Among 1,400 ICU-acquired candidemia cases (overall incidence of 6.51 cases/1,000 ICU admission), 65.2 % were adult. Though the study confirmed the already known risk factors for candidemia, the acquisition occurred early after admission to ICU (median 8 days; interquartile range 4–15 days), even infecting patients with lower APACHE II score at admission (median 17.0; mean ± SD 17.2 ± 5.9; interquartile range 14–20). The important finding of the study was the vast spectrum of agents (31 *Candida* species) causing candidemia and a high rate of isolation of *Candida tropicalis* (41.6 %). Azole and multidrug resistance were seen in 11.8 and 1.9 % of isolates. Public sector hospitals reported a significantly higher presence of the relatively resistant *C. auris* (8.2 vs. 3.9 %; $p = 0.008$) and *C. rugosa* (5.6 vs. 1.5 %; $p = 0.001$). The 30-day crude and attributable mortality rates of candidemia patients were 44.7 and 19.6 %, respectively. Logistic regression analysis revealed significant independent predictors of mortality including admission to public sector hospital, APACHE II score at admission, underlying renal failure, central venous catheterization and steroid therapy. *Conclusion:* The study highlighted a high burden of candidemia in Indian ICUs, early onset after ICU admission, higher risk despite less severe physiology score at admission and a vast spectrum of agents causing the disease with predominance of *C. tropicalis.*

Keywords Candidemia · Intensive care unit · *Candida tropicalis* · Risk factor · Mortality

Introduction

Candida bloodstream infection (candidemia) is a life-threatening affliction in intensive care unit (ICU) patients. Its incidence varies from 0.24 to 34.3 patients/1,000 ICU admissions [1–4]. With a high mortality rate of 35–75 % [2], early antifungal treatment is essential for survival. ICU-acquired candidemia patients characteristically have several underlying medical and surgical risk factors, and are frequently exposed to high-risk medications [5]. Furthermore many regions of the world are witnessing a surge in non-*albicans Candida* species [6, 7], which have diverse virulence and susceptibility profiles [8]. Geographic variation in causative species, ethnically diverse at-risk population and varying diagnostic and management capabilities of ICUs further add to the complexity. As there are very few multicentric studies on candidemia from Asian countries, we undertook this study to comprehensively elucidate the disease burden, epidemiology, microbial circulation, resistance pattern and management

challenges of adult ICU-acquired candidemia in India. We aim to utilize this information for better management and survival of these patients.

Methods

Study design

This was a prospective, multicentric, observational study undertaken from April 2011 to September 2012 at 27 medical and surgical ICUs across India. The Postgraduate Institute of Medical Education and Research, Chandigarh, India was the coordinating centre. Ethics approval was obtained from each institution's review board. Being an observational study, it entailed no additional risk to the patients. Prior to commencing work, the study was registered as "SIHAM (Society for Indian Human and Animal Mycologists) Candidemia Network: an observational study" (identifier NCT01281345) with ClincalTrials.gov.

Definitions

A patient older than 18 years of age was considered an adult. Candidemia was defined as the isolation of *Candida* species from blood cultures. A case was defined as ICU-acquired candidemia if it occurred more than 48 h after ICU admission or less than 48 h after discharge from ICU. Patients already diagnosed with candidemia before ICU admission or those transferred from another ICU with a positive culture for any yeast infection were excluded from the study. A patient was defined to have contracted more than one episode of *Candida* bloodstream infection if the subsequent episode occurred more than 30 days after the previous one. Date of onset of candidemia was taken as the date when the first positive blood culture was drawn from the patient. A surgery or invasive procedure undertaken within 30 days of contracting candidemia was considered a potential risk factor. Outcome was determined at the end of 30 days after onset of candidemia and cure was considered complete microbiological resolution. A death attributed to candidemia was ascertained by the treating physician independently on the basis of clinical judgement and microbiology reports.

Data collection

All consecutive patients who contracted ICU-acquired candidemia during April 2011 through September 2012 were enrolled after informed consent. A total of 398 variables were recorded for every patient in standardized proforma. These included demographic details; clinical presentations at admission; severity scores including Acute Physiology and Chronic Health Evaluation II (APACHE II) and Glasgow Coma Scale (GCS); comorbid medical conditions; surgical and invasive procedures; exposure to antibiotics, corticosteroids, anticancer chemotherapeutics, prior antifungals; secondary bacterial infections; candidemia-associated complications; antifungal treatment instituted in the ICU; treatment adverse effects; *Candida* species isolated; antifungal susceptibility and final outcome. All data from participating centres were collected and analysed at the coordinating centre.

Microbiological methods

Candida isolates were identified and tested for antifungal susceptibility at the coordinating centre. Isolates were identified by a Vitek YBC system, and ITS2 and D1/D2 region sequencing was performed when concordance was less than 98 %. Antifungal susceptibility was performed using the Clinical and Laboratory Standards Institute's (CLSI) broth microdilution M27-A3 method [9]. MIC breakpoints were interpreted from the CLSI M27-S4 supplement for yeasts [10]. Isolates with a MIC greater than 1 μg/ml for amphotericin B were considered resistant. Multidrug resistance (MDR) was defined as resistance to two or more classes of antifungals.

Statistical analysis

Descriptive analysis is presented as frequencies and confidence intervals (CI); medians and range; or means and standard deviation (SD), as appropriate. Pearson's Chi square test and Fisher's exact test were used to compare categorical variables, while the Student *t* test, ANOVA, Mann–Whitney or Kruskal–Wallis tests were employed for continuous data. A predictive model for 30-day mortality was developed using logistic regression. Its predictive power was evaluated by the Hosmer–Lemeshow goodness-of-fit test and area under the receiver operating characteristic (ROC) curve. Kaplan–Meier statistics was used for survival analysis. Two-tailed p values <0.05 were taken as significant.

Results

Demography and burden

A total of 215,112 patients were admitted to 27 ICUs from April 2011 to September 2012. Of these 1,400 patients contracted ICU-acquired candidemia, amounting to a burden of 6.51 cases/1,000 ICU admissions (95 % CI

6.18–6.86). Eleven ICUs were from north, three each from east and west, four from central and six from south India (Fig. 1). Eleven were public sector institutions, while 16 were private/corporate hospitals. The incidence varied significantly across regions ($p < 0.001$), with the highest burden from the north (8.95/1,000 ICU admissions; 95 % CI 8.29–9.66) and lowest from west (3.61/1,000 admissions; 95 % CI 2.82–4.63). Of 1,400 patients, 913 (65.2 %) were adults with a median age of 50.0 years (interquartile range 34–63; mean ± SD 49.7 ± 17.7). Further analysis pertains only to adult patients.

ICU presentation

The majority of our adult patients were non-neutropenic (98.7 %) and were admitted to medical ICUs ($n = 464$; 50.8 %). The median duration of onset of candidemia in ICU was 8.0 (interquartile range 4–15) days. Adult candidemia patients had a median APACHE II score of 17.0 (interquartile range 14–20; mean ± SD 17.2 ± 5.9) at admission. GCS was measured in 34 patients with a median score of 15.0 (interquartile range 7–15).

Circulating *Candida* species

The majority of patients experienced only a single episode ($n = 855$; 93.6 %) of candidemia, though 58 (6.4 %) suffered from more than one episode and five (0.5 %) of these were infected with two different *Candida* species during different candidemia episodes. Of the 918 *Candida* strains thus isolated, *Candida tropicalis* ($n = 382$; 41.6 %) was the most prevalent followed by *Candida albicans* ($n = 192$; 20.9 %) and *Candida parapsilosis* ($n = 100$; 10.9 %) (Electronic supplementary material Fig. 1). Eight species caused 92.8 % (852) of the infections while the remaining 7.2 % were inflicted by 22 less common species. Non-*albicans Candida* infections affected 79.1 % (726) of cases. While *C. tropicalis* was significantly higher (44.8 % vs. 37.7 %; $p = 0.035$) in private/corporate ICUs, *C. auris* (8.2 % vs. 3.9 %; $p = 0.008$) and *C. rugosa* (5.6 % vs. 1.5 %; $p = 0.001$) were significantly more common in public sector ICUs. There was no significant difference between times of onset of candidemia when all species were compared. The emerging multidrug-resistant *C. auris* was isolated from 19 of 27 ICUs and comprised 5.2 % of all *Candida*

Fig. 1 Map of India depicting the 27 intensive care units which participated in this study. The *red dot* represents the coordinating centre for this study

isolates. The species was also significantly more common in patients with central venous catheterization (6.8 % vs. 2.9 %; $p = 0.035$).

Antifungal resistance

The antifungal susceptibility profiles of the commonest species are summarised in Table 1. Overall 46.6 % of isolates were sensitive to all antifungals. Resistance to amphotericin B was noted in 19 (2.1 %), azoles 108 (11.8 %), and echinocandin 63 (6.9 %) isolates, respectively. MDR was noted in 17 (1.9 %) isolates, with three (0.3 %) pan-resistant to all antifungal classes. Common MDR isolates were *C. tropicalis* ($n = 4$; 23.5 %), *C. auris* ($n = 4$; 23.5 %) and *C. krusei* ($n = 3$; 17.6 %).

Underlying diseases and risk factors

Underlying respiratory illness was noted in 228 (25.0 %) patients. Pneumonia ($n = 75$; 32.9 %), acute respiratory distress syndrome ($n = 41$; 17.9 %) and chronic obstructive pulmonary disease (COPD) ($n = 35$; 15.4 %) were the major respiratory afflictions. Underlying renal disease was equally prevalent ($n = 209$; 22.9 %), with the majority in acute ($n = 128$; 61.2 %) or chronic ($n = 63$; 30.1 %) renal failure. Malignancy was present in 117 (12.8 %) cases, 82.9 % being solid organ malignancies and 17.1 % haematological. Nearly half of the malignancies (47.9 %) were gastrointestinal while 60.7 % were intraperitoneal. More than a third ($n = 341$; 37.3 %) of patients had undergone one or more surgical procedures in the 30 days or less prior to the onset of candidemia. Nearly half ($n = 165$; 48.4 %) of these comprised gastrointestinal, hepatobiliary and pancreatic surgeries (Electronic supplementary material Table 1). Central venous catheterization was instituted in 74.0 % of patients for a median duration of 8.0 (interquartile range 7–26) days. Parenteral nutrition was instituted in 122 (13.4 %) patients for a median of 9.0 (interquartile range 5–16) days before the onset of candidemia. Median duration of any dialysis performed prior to development of candidemia was 8.0 (interquartile range 2–15) days.

Nearly all candidemia patients were receiving antibiotics ($n = 849$; 93.0 %) with the majority on broad-spectrum agents ($n = 784$; 92.3 %) before the onset of candidemia. The median duration of any antibiotic therapy prior to development of candidemia was 16.0 (interquartile range 7–36) days and that for broad-spectrum agents was 11.0 (interquartile range 4–23) days (Electronic supplementary material Table 1). Corticosteroids were given to 164 cases (18.0 %), at a median dose of 50.0 mg per day (interquartile range 25–100) and median duration of 7.0 (interquartile range 4–12) days before the onset of candidemia.

Antifungal exposure before onset of candidemia was recorded in 143 (15.7 %) cases for a median duration of 8.0 (interquartile range 5–13) days (Electronic supplementary material Table 1). Prior antifungal exposure significantly increased the propensity for subsequent non-*albicans Candida* infection (85.5 vs. 77.9 %; $p = 0.045$) and azole-resistant *Candida* infection (7.1 vs. 3.3 %; $p = 0.045$).

Treatment

Antifungal therapy after definitive diagnosis of ICU-acquired candidemia could be instituted in 59.9 % (547) cases with a median duration of 9.0 (interquartile range 5–15) days (Electronic supplementary material Table 2). Azoles ($n = 394$; 72.0 %) were preferred, followed by echinocandins ($n = 100$; 18.3 %) and amphotericin B (including dexoycholate and lipid preparations) ($n = 79$; 14.4 %). While amphotericin B deoxycholate was used more commonly in public sector ICUs (11.5 vs. 5.3 %; $p < 0.001$), azole (47.1 vs. 37.7 %; $p = 0.006$) and echinocandin (13.4 vs. 7.4 %; $p = 0.005$) use was more common in private/corporate hospitals. Antifungal regimen was altered during the course of therapy in 81 (14.8 %) patients, regimen escalation and antifungal resistance being the major reasons. Only eight (1.5 %) patients on treatment suffered any adverse reactions (Electronic supplementary material Table 2). Central venous catheter (CVC) was removed from 32.1 % (217/676) catheterized patients, with the majority (54.4 %) withdrawn within 48 h of diagnosis. Kaplan–Meier analysis revealed that CVC removal significantly increased 30-day survival (mean ± standard error 19.0 ± 0.9 vs. 15.9 ± 0.6 days; $p = 0.002$). Regression models of the effect of the antifungal therapy and CVC removal on the outcome after adjusting for the comorbidities (APACHE II) showed significant survival ($p = 0.016$) only when treated with antifungal agents with simultaneous removal of the catheter within 48 h (Table 2). Survival was poor in patients treated at public sector hospitals with respiratory and renal disease, invasive ventilation, CVC, dialysis, corticosteroid and polymyxin therapy (Fig. 2).

Outcome and mortality predictors

Candidemia microbiologically resolved in 251 (27.5 %) cases. The 30-day crude mortality was 44.7 % (408/913) and 30-day attributable mortality was 19.6 % (179/913) (Electronic supplementary material Table 1). Univariate analysis between survivors and non-survivors revealed 31 key factors associated with 30-day crude mortality (Electronic supplementary material Table 3). Logistic regression was used to construct a predictive model for 30-day crude mortality ($R^2 = 0.399$, $p < 0.001$,

Table 1 Antifungal susceptibility profile of highest burden *Candida* species circulating among adult candidemia intensive care patients from India, based on the CLSI M27-S4 (2012) guidelines

Antifungal	AFST	All species ($n = 918$)	*C. tropicalis* ($n = 382$)	*C. albicans* ($n = 192$)	*C. parapsilosis* ($n = 100$)	*C. auris* ($n = 52$)	*C. glabrata* ($n = 65$)	*C. rugosa* ($n = 29$)	*C. krusei* ($n = 16$)	*C. guilliermondii* ($n = 16$)
Amphotericin B	MIC_{50} (μg/ml)	–	0.50	0.25	0.50	1.00	0.25	0.25	0.50	0.25
	MIC_{90} (μg/ml)	–	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00
	Resistant (%)	2.1 %	4 (1.0)	1 (0.5)	2 (2.0)	7 (13.5)	2 (3.1)	1 (3.4)	0 (0.0)	0 (0.0)
	MIC percentile (25–75)		0.25–1	0.12–1	0.25–1	0.25–1	0.12–0.5	0.12–0.5	0.25–0.7	0.22–1
Fluconazole	MIC_{50} (μg/ml)	–	0.50	0.50	1.00	8.00	0.50	0.50	6.00	0.50
	MIC_{90} (μg/ml)	–	2.00	2.00	4.00	64.00	2.00	8.00	8.00	4.00
	Resistant (%)	6.2 %	10 (2.6)	10 (5.2)	4 (4.0)	16 (30.8)	1 (1.5)	0 (0.0)	16 (100.0)	0 (0.0)
	SDD (%)	11.0 %	9 (2.4)	8 (4.2)	9 (9.0)	7 (13.5)	64 (98.5)	1 (3.4)	0 (0.0)	0 (0.0)
	MIC percentile (25–75)		0.25–1	0.12–1	0.25–1	1–64	0.25–1	0.5–2	3.25–8	0.5–1
Itraconazole	MIC_{50} (μg/ml)	–	0.06	0.06	0.06	0.03	0.03	0.03	0.12	0.12
	MIC_{90} (μg/ml)	–	0.12	0.25	0.12	0.50	0.12	0.12	0.50	1.00
	Resistant (%)	1.2 %	1 (0.3)	1 (0.5)	1 (1.0)	2 (3.8)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)
	SDD (%)	9.3 %	27 (7.1)	22 (11.5)	2 (2.0)	11 (21.2)	4 (6.2)	2 (6.9)	4 (25.0)	4 (25.0)
	MIC percentile (25–75)		0.03–0.12	0.03–0.12	0.03–0.06	0.03–0.18	0.03–0.06	0.03–0.06	0.05–0.25	0.03–0.25
Posaconazole	MIC_{50} (μg/ml)	–	0.03	0.03	0.03	0.06	0.03	0.03	0.12	0.06
	MIC_{90} (μg/ml)	–	0.25	0.25	0.12	0.50	0.12	0.25	0.50	0.25
	MIC percentile (25–75)		0.03–0.12	0.03–0.06	0.03–0.06	0.03–0.18	0.03–0.06	0.03–0.12	0.03–0.12	0.03–0.15
Voriconazole	MIC_{50} (μg/ml)	–	0.12	0.06	0.06	0.50	0.06	0.06	0.25	0.06
	MIC_{90} (μg/ml)	–	0.50	0.50	0.25	1.00	0.50	1.00	0.50	1.00
	Resistant (%)	5.6 %	31 (8.1)	15 (7.8)	3 (3.0)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	SDD (%)	22.9 %	128 (33.5)	58 (30.2)	18 (18.0)	1 (1.9)	1 (1.5)	2 (6.9)	0 (0.0)	0 (0.0)
	MIC percentile (25–75)		0.06–0.25	0.03–0.25	0.03–0.12	0.12–1	0.03–0.12	0.03–0.25	0.12–0.25	0.03–0.07
Anidulafungin	MIC_{50} (μg/ml)	–	0.03	0.03	0.25	0.12	0.03	0.12	0.06	0.12
	MIC_{90} (μg/ml)	–	0.25	0.25	1.00	1.00	0.25	2.00	0.50	2.00
	Resistant (%)	1.7 %	8 (2.1)	2 (1.0)	0 (0.0)	0 (0.0)	4 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Intermediate (%)	1.6 %	8 (2.1)	3 (1.6)	0 (0.0)	–	3 (4.6)	–	1 (6.3)	0 (0.0)
	MIC percentile (25–75)		0.03–0.06	0.03	0.06–1	0.06–0.04	0.03	0.03–0.5	0.03–0.09	0.03–0.62
Caspofungin	MIC_{50} (μg/ml)	–	0.25	0.25	0.50	0.50	0.25	0.50	0.50	0.50
	MIC_{90} (μg/ml)	–	0.50	0.50	1.00	2.00	0.50	2.00	1.00	1.00
	Resistant (%)	5.6 %	16 (4.2)	7 (3.6)	0 (0.0)	4 (7.7)	15 (23.1)	2 (6.9)	3 (18.8)	0 (0.0)
	Intermediate (%)	10.1 %	50 (13.1)	19 (9.9)	0 (0.0)	–	19 (29.2)	–	5 (31.3)	0 (0.0)
	MIC percentile (25–75)		0.12–0.25	0.12–0.25	0.25–0.5	0.25–1	0.12–0.25	0.5–1	0.25–0.5	0.25–0.62
Micafungin	MIC_{50} (μg/ml)	–	0.03	0.03	0.25	0.12	0.03	0.06	0.05	0.12
	MIC_{90} (μg/ml)	–	0.12	0.25	1.00	1.00	0.12	2.00	0.50	1.00
	Resistant (%)	1.7 %	5 (1.3)	2 (1.0)	0 (0.0)	0 (0.0)	4 (6.2)	1 (3.4)	0 (0.0)	0 (0.0)
	Intermediate (%)	2.2 %	11 (2.9)	4 (2.1)	1 (1.0)	–	3 (4.6)	–	1 (6.3)	0 (0.0)
	MIC percentile (25–75)		0.03	0.03	0.06–0.5	0.03–0.25	0.03	0.03–0.5	0.03–0.12	0.3

AFST antifungal susceptibility testing, *MIC* minimum inhibitory concentration, *SDD* susceptible dose dependent

Table 2 Logistic regression model depicting the effect of antifungal therapy and catheter removal (within 48 h of diagnosis) on the outcome of the candidemia patients

Treatment modalities	OR	*P*	95 % CI	
			Lower	Upper
No antifungal + no catheter removal	1.000	–	–	–
No antifungal + catheter removal	1.006	0.996	0.125	8.064
Antifungal + no catheter removal	0.655	0.171	0.358	1.200
Antifungal + catheter removal	0.389	0.016	0.180	0.839
APACHE II at admission	1.117	<0.001	1.058	1.180

OR odds ratio, *CI* confidence intervals, *APACHE II* Acute Physiology and Chronic Health Evaluation II

predictive accuracy = 69.5 %, area under ROC curve = 0.75). The most significant independent predictors of 30-day crude mortality include admission to a public sector hospital, APACHE II score at admission, underlying renal failure, central venous catheterization and steroid therapy (Table 3).

Discussion

This is the first and largest multicentre observational study of ICU-acquired candidemia from India. We found an overall incidence of 6.51 cases per 1,000 ICU admissions, though the incidence varied significantly across the country. The variation may be due to difference in patient groups and management protocol of respective ICUs. In addition, significant variation in the rate of candidemia between private/corporate and public sector hospitals was noted. A large number of patients attend public sector hospital (in the coordinating centre 10,000 new patients attend outpatient departments every working day) as the hospital charges are subsidized, which may lead to compromise in the standard of the health care and higher rate of candidemia. In comparison to the nationwide survey reports from other countries, the incidence in the present study approaches the higher end of values from Australia, France, Germany and the EPIC II study (0.24–6.9/1,000 ICU admission) [1, 11–13], yet is much lower than reported in Spain and Argentina (34.3/1,000 ICU admission) [2].

Our adult candidemia patients were considerably younger (mean 49.7 years) than in other countries (mean 59.0–66.2 years) [2, 14]. Notably our patients contracted ICU-acquired candidemia significantly earlier (8 days) than in other series (11–15 days) ($p = 0.03$) [1, 15]; however, Playford et al. from Australia and Leroy et al. from France have also reported similar early onset of infection [11, 16]. Our patients had lower mean APACHE II scores (17.2) than studies from Spain (20.1), Argentina (20.1) and the USA (18.6) [2, 17]. The reasons for such younger and comparatively less serious patients acquiring candidemia may be due to prior exposures to broad-spectrum antibiotics and steroids in large numbers of our patients and compromised health care.

Our study revealed high prevalence of *C. tropicalis* (41.6 %) while *C. albicans* and *C. parapsilosis* affected only 20.9 and 10.9 % of cases, respectively. This is in contrast to the developed world, where *C. tropicalis* is uniformly less common (5.6–12.0 %) [11, 17–20], and *C. albicans* (45.0–74.0 %) and *C. glabrata* (16.7–22.6 %) are more prevalent [1, 15–17, 20]. We encountered *C. glabrata* candidemia in only 7.1 % of patients. The rise in *C. glabrata* in the Western world can be linked to increased use of azole prophylaxis [1, 11, 15, 21]. Though our patients had a significantly higher propensity of developing candidemia due to non-*albicans Candida* species after azole exposure, such a link is not possible in our patients with *C. tropicalis* candidemia. Prior antifungal exposure ($p = 0.09$), prior azole therapy ($p = 0.24$) or prior fluconazole therapy ($p = 0.26$) was not significantly high in *C. tropicalis* candidemia. Moreover, the majority of our *C. tropicalis* isolates were sensitive to amphotericin B ($n = 378$, 99.0 %), azoles ($n = 344$, 90.1 %), fluconazole ($n = 372$, 97.4 %) and echinocandins ($n = 360$, 94.2 %), thereby indicating interplay of other undetermined factors for their high prevalence. In the present study, we did not attempt to find the possible reasons for the high prevalence of *C. tropicalis* candidemia as it was purely an observational study. A study form Paris and surrounding areas noted pre-exposure to the fluconazole as an independent risk factor for acquiring *C. tropicalis* candidemia [22], whereas the present study did not find this to be an independent risk factor for *C. tropicalis* candidemia. A detailed case–control and environmental study is essential to clarify the reason for the high prevalence of *C. tropicalis* candidemia in India. In an earlier study at the coordinating centre, 82 % of health care providers were found to carry yeast on their hands and 80 % were *C. tropicalis* [23]. Therefore, horizontal transmission and compromise of infection control systems are distinct possibilities for the high rate of *C. tropicalis* candidemia in India. The high rate of *C. tropicalis* candidemia was observed in other Asian countries as well [24]. But no study has evaluated the exact reasons for the high rate of *C. tropicalis* candidemia and hand carriage in these countries. We noted a low prevalence of *C. glabrata* despite prior exposure to antifungal agents in 15.7 % of patients. The higher rate of non-*albicans Candida* infections in patients exposed to prior antifungals was influenced by significantly the higher prevalence of *C. auris* (32.7 vs. 14.8 %, $p = 0.002$) and *C. krusei* (37.5 vs. 15.4 %, $p = 0.029$). In another study Fournier et al. reported a significantly higher proportion of *C. parapsilosis* due to prior exposure to caspofungin [25]. In contrast, Blot et al. reported no change in *Candida* species

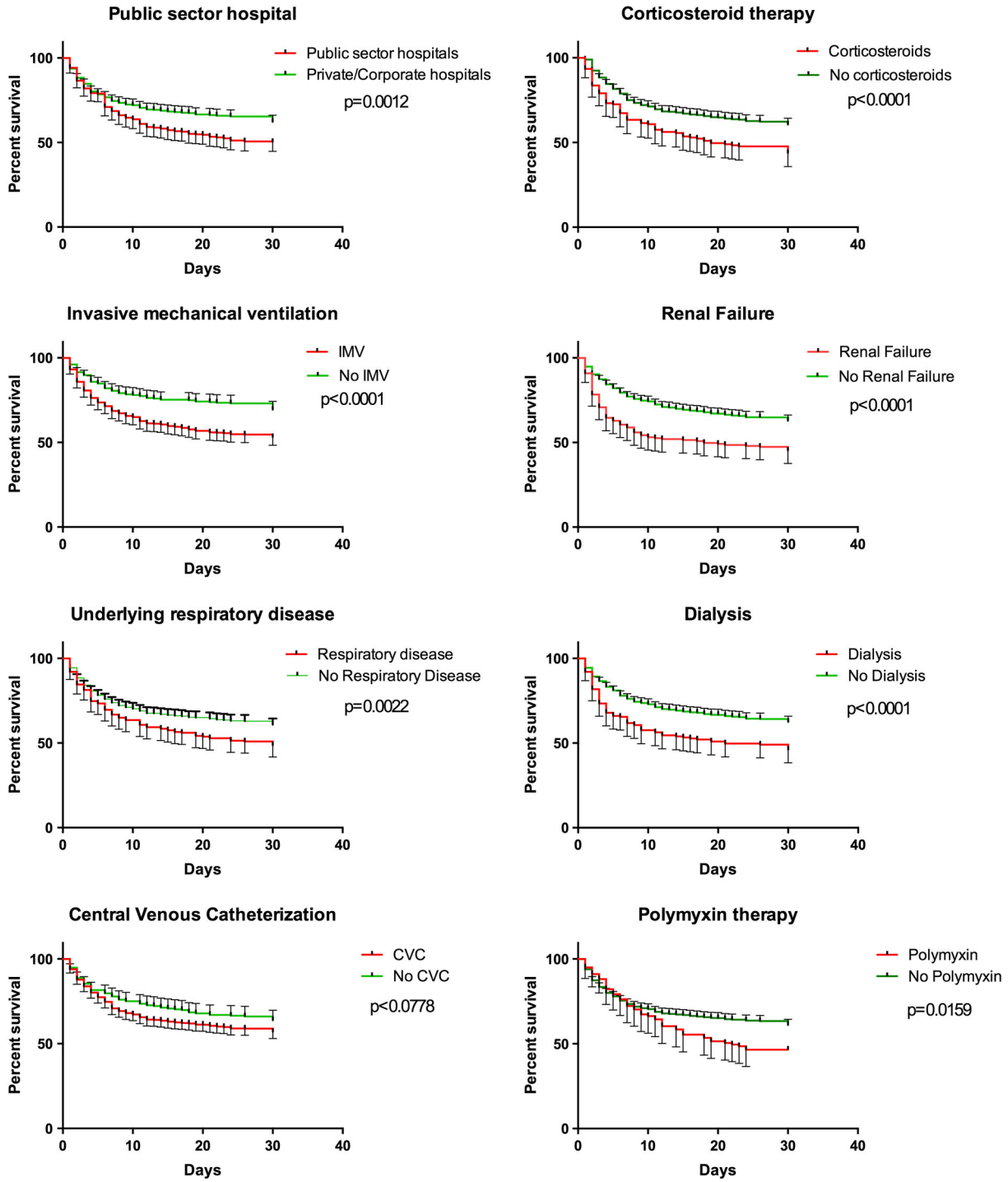

Fig. 2 Kaplan–Meier survival curves (with confidence intervals) according to risk factors for mortality. Comparison of the survival curve was performed by Log-rank (Mantel–Cox) test

distribution despite long-term exposure to fluconazole [26]. Therefore, more studies are required to understand the interplay of the factors responsible for any shift in *Candida* species distribution. In our study, *C. tropicalis* candidemia was more common in private/corporate sector ICUs, while *C. auris* and *C. rugosa* were more prevalent in public sector ones. The emergence of MDR *C. auris* in India is a matter of concern, as this fungus was isolated

Table 3 Logistic regression predictive model summarizing the risk factors for 30-day mortality in adult candidemia intensive care patients

Predictor	OR	*P*	95 % CI	
			Lower	Upper
Public sector hospital	2.062	0.006	1.235	3.446
APACHE II at admission	1.114	<0.001	1.061	1.169
Renal failure	2.237	0.016	1.161	4.312
Central venous catheterization	2.343	0.003	1.330	4.129
Steroid therapy	5.425	<0.001	2.627	11.201
Antifungals treatment for candidemia[a]	0.494	0.007	0.295	0.827

OR odds ratio, *CI* confidence intervals, *APACHE II* Acute Physiology and Chronic Health Evaluation II

[a] Therapy instituted after definitive microbiological diagnosis of candidemia in the ICU

from 19 of 27 ICUs and comprised 5.2 % of all *Candida* isolates in the present study.

Overall, 46.6 % of our isolates were susceptible to all antifungals. Species-specific resistance rates against fluconazole were 2.6 % in *C. tropicalis*, 5.2 % in *C. albicans*, 4.0 % in *C. parapsilosis* and 1.5 % in *C. glabrata*. Corresponding figures from across the globe include *C. tropicalis* (4.5–14.3 %), *C. albicans* (1.4–4.4 %), *C. parapsilosis* (2.7–10.5 %) and *C. glabrata* (5.9–93.8 %) [11, 14, 16, 20]. Likewise, resistance to voriconazole (1.2–5.9 %), itraconazole (4.7 %) and echinocandins (0.3–2.2 %) from international studies are different from our isolates [14, 20]. Low resistance of our *C. glabrata* isolates emphasizes the need to compare our isolates with MDR isolates from other centres, as cryptic species are already known under *C. glabrata* [27]. In contrast to *C. glabrata*, we observed more MDR *C. tropicalis*, *C. auris* and *C. krusei*.

Co-morbidities of our patients are similar to a certain extent to earlier reports. Like in our study, underlying respiratory, renal and gastrointestinal illnesses were significant in other studies as well. But they have also reported sizable proportions of diabetes (10.7–28.0 %), cardiovascular (15.8–48.3 %) and neurological (13.2 %) illnesses in their patients, which were much less common in our cohort, 0.1 %, 15.1 % and 19.5 %, respectively [2, 11–16, 19]. Underlying malignancy was present in 12.8 % of our patients, compared to 24.6–36.1 % in other studies [13, 14]. HIV/AIDS (0.4 %) and neutropenia (1.3 %) were rare, unlike in other series, 4.0–6.0 % and 6.6–19.7 %, respectively [15–17, 19]. A third of our patients (37.3 %) had undergone recent surgery as compared to 44.7–66.1 % seen in other series [2, 11]. Among types of surgery, abdominal surgery is considered a leading risk factor for candidemia [28]. Half of our surgeries (18.1 % of total) also were gastrointestinal, similar to other series (17.0–31.6 %) [2, 12, 28]. Central venous catheterization (74.0 %), invasive mechanical ventilation (52.9 %), urinary catheterization (75.9 %), haemodialysis (17.3 %) and total parenteral nutrition (13.4 %) prior to onset of candidemia were also encountered at lower proportions in our cohort as compared to other series (88.5–100 % [2, 13], 72.1–97.4 % [2, 13], 86.7–97.4 % [2, 16], 17.5–32.5 % [11, 15] and 43.7–71.1 % [2, 11]).

Antifungal therapy after microbiological diagnosis of ICU-acquired candidemia could be evaluated in only 59.9 % of cases because of delayed diagnosis and early death of our patients unlike other studies (74.5–94.1 %) [4, 16–18]. In certain situations the patient left for another hospital or could not afford the therapy. The delay in diagnosis at a few centres was due to use of conventional biphasic media for *Candida* isolation instead of commercial systems. Removal of CVCs and start of targeted antifungal therapy within 48 h of onset of candidemia improved 30-day survival in our patients ($p = 0.016$) like other reports [2, 16, 29, 30], yet the catheter was removed only in one-third of our patients. The reason is difficult to explain. We did not interfere with the existing protocol of any ICU and some critical care specialists believe those studies where a lack of benefit of CVC removal was demonstrated [4, 30].

Our 30-day crude mortality (44.7 %) is similar to the EPIC II international series (42.6 %) [13]. Mortality rates vary across the globe (35–75 %) [2]. Candidemia-attributable mortality also varies widely (5.0–49.0 %) between centres [2, 14, 18, 31] possibly because of lack of standardized criteria. Lower attributable mortality (10.9–21.7 %) has been reported in some studies [3, 20, 32], as compared to the present one (19.6 %).

Comparison of independent mortality predictors modelled in our and other series highlight common and divergent patterns, though the large number (398) of variables studied might act as a limitation of the study by increasing the likelihood of false positive results. However, we have factored in the higher alpha error expected out of multiple testing owing to the large number of variables tested. A stringent Bonferroni's test was used to filter out only those significant variables which stood the test. APACHE II scores in our study proved useful for developing a robust predictive model as has been previously described [30]. Other severity scores like SAPS II and SOFA, central venous catheterization, corticosteroid therapy, total parenteral nutrition, antibiotic use, sepsis/shock and antifungal treatment are common predictors [15–18, 33]. In contrast, admission to a public sector ICU and renal failure appear additional significant predictors for our patients. Similarly, increasing age, underlying diabetes, immunosuppression, neutropenia, *C. glabrata* and *C. parapsilosis* infection, mechanical ventilation, haemodialysis, gastrointestinal surgery and underlying malignancy were unique to other countries, but did not stand out in our study [4, 15–18, 33].

Conclusions

This is the largest prospective multicentre study of ICU-acquired candidemia from India. The overall incidence of ICU-acquired candidemia is high and marked by an early onset infection after ICU admission. Our patients are comparatively young and have lower APACHE II scores at admission. *C. tropicalis* is the leading pathogen in our patients, though its predominance is not explained by higher exposure to prior azoles or antifungals. Emergence of MDR *C. auris* in the majority of ICUs is a matter of concern. Our 30-day mortality prediction model can help triage and manage high-risk candidemia patients better.

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