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Invasive Candidiasis in Critically Ill Patients: A Prospective Cohort Study in Two Tertiary Care Centers

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Abstract

Background: Invasive candidiasis is not uncommon in critically ill patients but has variable epidemiology and outcomes between intensive care units (ICUs). This study evaluated the epidemiology, characteristics, management, and outcomes of patients with invasive candidiasis at 6 ICUs of 2 tertiary care centers. **Methods:** This was a prospective observational study of all adults admitted to 6 ICUs in 2 different hospitals between August 2012 and May 2016 and diagnosed to have invasive candidiasis by 2 intensivists according to predefined criteria. The epidemiology of isolated *Candida* and the characteristics, management, and outcomes of affected patients were studied. Multivariable logistic regression analyses were performed to identify the predictors of *non-albicans* versus *albicans* infection and hospital mortality. **Results:** Invasive candidiasis was diagnosed in 162 (age 58.4 $\pm$ 18.9 years, 52.2% males, 82.1% medical admissions, and admission Acute Physiology and Chronic Health Evaluation II score 24.1 $\pm$ 8.4) patients at a rate of 2.6 cases per 100 ICU admissions. On the diagnosis day, the Candida score was 2.4 $\pm$ 0.9 in invasive candidiasis compared with 1.6 $\pm$ 0.9 in *Candida* colonization ($P < .01$). The most frequent species were *albicans* (38.3%), *tropicalis* (16.7%), *glabrata* (16%), and *parapsilosis* (13.6%). In patients with candidemia, antifungal therapy was started on average 1 hour before knowing the culture result (59.6% of therapy initiated after). Resistance to fluconazole, caspofungin, and amphotericin B occurred in 27.9%, 2.9%, and 3.1%, respectively. The hospital mortality was 58.6% with no difference between *albicans* and *non-albicans* infections (61.3% and 54.9%, respectively; $P = .44$). The independent predictors of mortality were renal replacement therapy after invasive candidiasis diagnosis (odds ratio: 5.42; 95% confidence interval: 2.16-13.56) and invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness (odds ratio: 2.87; 95% confidence interval: 1.22-6.74). **Conclusions:** In critically ill patients with invasive candidiasis, *non-albicans* was responsible for most cases, and mortality was high (58.6%). Antifungal therapy was initiated after culture results in 60% suggesting low preclinical suspicion. Study registration: NCT01490684; registered in ClinicalTrials.gov on February 11, 2012.

Keywords
intensive care, candidiasis, critical care outcomes, antifungal agents, sepsis

Background

Candida species colonizes up to 50% of critically ill patients.[1] Translocation across the gastrointestinal mucosa and spread from invasive catheters into the bloodstream are the most common mechanisms that result in invasive candidiasis,[2] which occurs in up to 9% of intensive care unit (ICU) patients.[3] *Candida albicans* accounts for the majority of *Candida* infections but an increasing number of infections due to non-*albicans* species has been reported.[2,4-6] This may be due to increased use of antifungal agents for prophylaxis[6,7] and empirical therapy.[8] However, there is significant variation in the epidemiology of *Candida* species between countries and individual ICUs.[9]

Candida infection in critically ill patients is associated with increased morbidity and mortality.[3,10] One study found that

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candidemia had a major impact on hospital length of stay with an average increase of >34 days and an estimated care cost of US$34 123 per affected Medicare patient.[11] Another study showed that candidemia in adult hospitalized patients was associated with 14.5% increase in mortality, 10.1-day increase in length of stay, and US$39 331 increase in hospital cost.[12] The mortality associated with invasive candidiasis is high and may be >70%.[13]

Most studies that evaluated *Candida* colonization and infection in the ICU come from Western countries.[1,14-16] In Saudi Arabia, multiple studies evaluated *Candida* infections but most were retrospective, focused on their epidemiology rather than management and clinical significance, and were conducted in single centers at a hospital-wide level rather than in the ICU.[17-21] Hence, the main objectives of this study were to evaluate invasive candidiasis epidemiology and susceptibility patterns in multiple ICUs, determine the risk factors for *albicans* versus non-*albicans* infections, study the practice of empirical antifungal therapy, and determine the outcomes and predictors of hospital mortality.

Methods

Patients and Setting

This was a prospective observational study conducted between August 2012 and May 2016 at the ICUs of 2 tertiary care centers in Riyadh, Saudi Arabia: King Abdulaziz Medical City (KAMC) and King Fahad Medical City (KFMC). Both centers had >1000 beds and were accredited by Joint Commission International. In KAMC, 5 adult noncardiac ICUs participated in the study (21-bed general ICU, 8-bed trauma ICU, 9-bed surgical ICU, 8-bed neuro ICU, and 14-bed step-down unit). These ICUs were closed units covered by onsite intensivists and registrars 24 hours per day, 7 days per week.[22] In KFMC, one 35-bed closed medical-surgical ICU participated in the study. The institutional review boards of the 2 centers approved the study. Informed consents were obtained from the patients or surrogate decision makers.

All adult patients (>18 years) admitted to the ICUs of these centers for >48 hours were followed to discharge or death in ICU for occurrence of a specimen culture positive for *Candida*. We excluded patients with invasive candidiasis diagnosed $\geq$72 hours before ICU admission. For ICU readmissions with recurrent invasive candidiasis during the same hospitalization, only the first admission was counted. All decisions regarding patient management including the need to obtain cultures when sepsis was clinically suspected were left to the discretion of the treating ICU team. There was no routine surveillance for fungal colonization or infection. During the study period, β-D glucan test was not available at the 2 centers.

Classification of Candida Infection and Antifungal Therapy

Two intensivists evaluated all *Candida*-positive cultures and classified them as definite/proven, probable, or possible invasive candidiasis or *Candida* colonization.[23] If they disagreed, a third intensivist resolved the disagreement. Briefly, definite invasive candidiasis included cases of isolated candidemia or positive specimen from a sterile site related to a specific focus on infection. Probable cases required the presence of a predisposing host factor, a clinical criterion of disseminated candidiasis, and a mycological criterion.[23] Cases that met the criteria for a host factor and a clinical criterion but for which mycological criteria were absent were considered possible invasive candidiasis.[23] Since multifocal *Candida* colonization (*Candida* growth in various noncontiguous foci within 5 days) is associated with relatively high invasive candidiasis incidence,[24] it was considered as possible invasive candidiasis in the presence of severe sepsis or septic shock that could not be explained by another etiology.[25]

Empirical antifungal therapy was defined as the initiation or modification of an existing antifungal regimen when patients were suspected to have invasive fungal infection.[23] It was considered appropriate if the cultured *Candida* displayed in vitro susceptibility to the antifungal therapy instituted within 24 hours of the index culture collection time.[23] Treatment of established invasive fungal infection corresponded to the initiation of antifungal therapy after the diagnosis of proven or probable invasive candidiasis.[23]

Antifungal Susceptibility Method

Antifungal susceptibility testing was performed using microbroth dilution method, YeastOne (Part #YO-9, Treck Diagnostic Systems, Thermo Scientific, Basingstoke, UK). It had the following antifungal agents: amphotericin B, 5-flucytosine, anidulafungin, caspofungin, micafungin, fluconazole, itraconazole, posaconazole, and voriconazole. Susceptibility testing was performed as per manufacturer's instructions. Quality control tests were conducted on a regular basis in accordance with approved standard laboratory procedures.

Data Collection

The following data were recorded prospectively for all patients: details of *Candida* (such as source, species, and susceptibility to antifungal agents), demographic characteristics, location of the patient prior to ICU admission, admission category (medical, surgical, and trauma), admission diagnosis by system involvement, severity of illness on ICU admission assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II,[26] and Sequential Organ Failure Assessment (SOFA) scores. In addition, SOFA score was calculated on day 1 (the day of diagnosing invasive candidiasis), 3, 5, 14, and 21 days of ICU stay if applicable, Candida score[27] on the diagnosis day, *Candida* infection risk factors (such as diabetes mellitus, chronic renal failure, surgery within the past 3 months, antimicrobial therapy for >5 days within the past month, immunosuppression, use of total parenteral nutrition, and previous *Candida* colonization); use of invasive procedures; treatment of organ failures (inotropic support, hemodialysis, and

Table 1. Characteristics of Patients With Invasive Candidiasis at the ICUs of 2 Tertiary care Centers.

	All Patients, N = 162	*Albicans*,[a] n = 62	Non-*albicans*,[a] n = 91	*P* Value
Age (years), mean (SD)	58.4 (18.9)	56.4 (19.7)	60.2 (17.8)	.22
Male gender, n (%)	85 (52.5)	32 (51.6)	48 (52.7)	.89
BMI (kg/m^2), mean (SD)	29.3 (11.5)	30.0 (14.2)	29.0 (9.6)	.60
Location before ICU admission, n (%)				
Emergency department	82 (50.6)	29 (46.8)	48 (52.7)	
Ward	66 (40.7)	29 (46.8)	35 (38.5)	
Other hospital	14 (8.6)	4 (6.5)	8 (8.8)	.57
APACHE II score, mean (SD)	24.1 (8.4)	23.7 (8.5)	24.8 (8.4)	.47
SOFA score, mean (SD)	12.1 (3.9)	12.0 (4.1)	11.9 (3.7)	.83
Candida score, mean (SD)	1.97 (1.17)	1.58 (1.23)	2.23 (1.06)	.01
Chronic illnesses, n (%)				
Cardiac	17/111 (15.3)	9/46 (19.6)	8/60 (13.3)	.39
Respiratory	28/111 (25.2)	12/46 (26.1)	14/60 (23.3)	.74
Renal with dialysis	55/161 (34.2)	22/62 (35.5)	30/90 (33.2)	.78
Hepatic	17/111 (15.3)	6/46 (13.0)	11/60 (18.3)	.53
Diabetes, n (%)	107 (66.0)	40 (64.5)	59 (64.8)	.99
Insulin treated	48 (29.6)	24 (38.7)	21 (23.1)	.04
Active cancer, n (%)	15/114 (13.2)	8/46 (17.4)	6/63 (9.5)	.23
Immunosuppression, n (%)	12/160 (7.5)	4/62 (6.5)	6/89 (6.7)	.94
Corticosteroids in the previous 2 weeks, n (%)	5/160 (3.1)	2/62 (3.2)	3/89 (3.4)	.96
Recent neutropenia, n (%)	27/159 (17.0)	8/61 (13.1)	17/89 (19.1)	.33
Surgery in the preceding 3 months, n (%)	17/161 (10.6)	7 (11.3)	10 (11.1)	.97
Abdominal	8/161 (5.0)	3 (4.8)	5 (5.5)	
Total parenteral nutrition, n (%)	17/160 (10.6)	5/62 (8.1)	9/89 (10.1)	.67
Antibiotics in the preceding 5 days, n (%)	59 (36.4)	15 (24.2)	39 (42.9)	.02
Recent antifungal therapy, n (%)	19/160 (11.9)	2/62 (3.2)	15/89 (16.9)	.01
Azole	11/160 (6.9)	1 (1.6)	8 (16.9)	
Echinocandin	7/160 (4.4)	1 (1.6)	6 (6.7)	
Previous culture of *Candida* in the previous 2 weeks, n (%)	15 (9.3)	6 (9.7)	9 (9.9)	.26
Reason for ICU admission, n (%)				.67
Medical	133 (82.1)	52 (83.8)	78 (85.7)	
Cardiovascular	11 (6.8)	3 (4.8)	7 (7.7)	
Septic shock	28 (17.3)	13 (21.0)	14 (15.4)	
Respiratory	39 (24.1)	20 (32.3)	16 (17.6)	
Gastrointestinal	11 (6.8)	4 (6.5)	7 (7.7)	
Neurological	5 (3.1)	2 (3.2)	3 (3.3)	
Nonoperative trauma	5 (3.1)	1 (1.6)	3 (3.3)	
Postoperative	21 (13.0)	9 (14.5)	10 (11.0)	
Abdominal	8 (4.9)	4 (6.5)	4 (4.4)	
Invasive candidiasis				.29
Led/contributed to ICU admission	57/152 (37.5)	24/56 (42.9)	30/88 (34.1)	
Developed during ICU stay	95/152 (62.5)	32/56 (57.1)	58 /88 (65.9)	
Source of *Candida* in definite cases, n (%)				
Blood	108 (66.7)	26 (41.9)	81 (89.0)	<.001
Sterile fluid	5 (3.1)	2 (3.2)	1 (1.1)	.57
Tissue	4 (2.5)	2 (3.2)	2 (2.2)	1.0
Vital signs on diagnosis day				
Heart rate (beats/min), mean (SD)	100 (28)	98 (29)	100 (27)	.61
Temperature (°C), mean (SD)	37.0 (1.1)	36. 9 (1.2)	37.0 (1.1)	.53
Arterial catheter	69 (42.6)	30 (48.4)	35 (38.5)	.22
Central venous catheter, n (%)	70 (43.2)	29 (46.8)	38 (41.8)	.54
Urinary catheter, n (%)	97 (59.9)	40 (64.5)	52 (57.1)	.36
Mechanical ventilation, n (%)	125 (77.2)	45 (72.6)	71 (78.0)	.44
Laboratory findings on diagnosis day				
Blood urea nitrogen (mmol/L), mean (SD)	14.8 (13.6)	12.4 (9.1)	16.9 (16.1)	.05
Creatinine (μmol/L),[b] mean (SD)	155.3 (116.9)	153.7 (119.7)	161.8 (118.8)	.68
Lactate (mmol/L),[b] mean (SD)	3.3 (3.2)	3.4 (3.3)	3.4 (3.3)	.74
White blood cell count (10^9/L), mean (SD)	17.3 (17.3)	18.4 (19.4)	16.6 (14.2)	.53

(continued)

Table 1. (continued)

	All Patients, N = 162	*Albicans*,[a] n = 62	Non-*albicans*,[a] n = 91	*P* Value
Hemoglobin (g/dL), mean (SD)	9.0 (1.8)	9.1 (1.8)	8.8 (1.7)	.28
Platelet count (10^9/L), mean (SD)	192 (151)	203 (140)	191 (161)	.64
INR, mean (SD)	1.6 (1.0)	1.6 (1.3)	1.5 (0.8)	.46
Partial thromboplastin time (seconds), mean (SD)	49.3 (34.0)	51.2 (32.1)	47.6 (36.3)	.54
Alanine aminotransferase (U/L), mean (SD)	108.6 (282.3)	104.9 (288.5)	96.5 (266.3)	.87

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index, ICU, intensive care unit; INR, international normalized ratio; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.
[a]Nine patients had *Candida* species not identified.
[b]To convert creatinine to mg/dL divide by 88.4, lactate to mg/dL divide by 0.111.

mechanical ventilation); clinical features on the day of positive *Candida* culture, antifungal therapy including timing of administration; and other treatment modifications and interventions. The primary outcome was hospital mortality. Other assessed outcomes were 28-day and ICU mortality, length of stay in the ICU and hospital, and duration of mechanical ventilation. We also noted changes in code status during ICU stay.

Statistical Methods

Frequencies and percentages were presented for categorical variables. Means with standard deviations or medians with the 25th and 75th percentiles were presented for continuous variables. The χ^2 test or Fisher exact test was used to evaluate differences between categorical variables and the *t* test to evaluate differences between continuous variables. Multivariable logistic regression analyses were performed to identify the independent predictors of non-*albicans* versus *albicans* infection and hospital mortality. Potential risk factors included in these models were clinically significant or had *P* value < .1 in the univariate analyses. For the predictors of non-*albicans* versus *albicans* infection, the following variables were entered in the model: KAMC versus KFMC, medical versus nonmedical admission, Candida score, APACHE II score, SOFA score on diagnosis day, insulin-treated diabetes, hemodialysis, history of recent surgery, prior antibacterial and antifungal therapy, and recent neutropenia. The hospital mortality rates were compared in certain subgroups, which were selected based on clinical relevance. For the higher versus lower age, APACHE II score, and SOFA score, categorization was based on the median values. For the predictors of hospital mortality, the following variables were entered in the model: KAMC versus KFMC, invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness, Candida score, age, APACHE II score, SOFA on diagnosis day, empirical antifungal therapy versus treatment, and renal replacement therapy after invasive candidiasis diagnosis. The results were presented as odds ratio (OR) with 95% confidence interval (CI). A $P < .05$ was considered statistically significant. Data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois).

Results

Characteristics of Patients

We enrolled 162 patients with invasive candidiasis: 120 from KAMC and 42 from KFMC at a rate of 2.6 cases per 100 ICU admissions. The diagnosis was definite in 119 (73.5%), probable in 3 (1.9%), and possible in 40 (24.7%). Invasive candidiasis occurred on a median of 5 days after ICU admission (25th and 75th percentiles = 1 and 8 days, respectively) and 18 days after hospital admission (25th and 75th percentiles = 8 and 44.5 days, respectively). Most (62.5%) of the cases developed invasive candidiasis during the course of their critical illness in the ICU. Candidemia occurred in 107 patients.

The cohort characteristics are described in Table 1 and included age (58.4 ± 18.9 years), 52.5% were males, APACHE II score = 24.1 ± 8.4, and Candida score = 1.97 ± 1.17. Invasive candidiasis risk factors included diabetes (66.0%), chronic kidney disease requiring hemodialysis (34.2%), active cancer (13.2%), recent neutropenia (17.0%), recent surgery (10.6%), total parenteral nutrition (10.6%), recent antibacterial therapy (36.4%), and recent antifungal therapy (11.9%). Hypothermia (<35°C) was present in 6.8% of patients on the diagnosis day and hyperthermia (>38°C) in 10.1%. Compared with those from KFMC, KAMC patients were generally older (60.0 ± 17.5 vs 53.5 ± 22.0 years; $P = .09$) with higher APACHE II scores (25.5 ± 8.3 vs 19.8 ± 7.0; $P < .001$).

Epidemiology

In our cohort, *Candida* non-*albicans* accounted for the majority of species causing invasive candidiasis (56.2% of all cases) as described in Figure 1A. The most frequent species were *albicans* (n = 62, 38.3%), *tropicalis* (n = 27, 16.7%), *glabrata* (n = 26, 16%), and *parapsilosis* (n = 22, 13.6%). In patients with candidemia, non-*albicans* species were more prevalent (74.1%; Figure 1B). *Candida* non-*albicans* was more common in KAMC compared with KFMC (77/114 [67.5%] vs 14/39 [35.9%] of *Candida*; $P = .001$).

Table 1 also describes the characteristics of *albicans* and non-*albicans* cases. The non-*albicans* group had higher

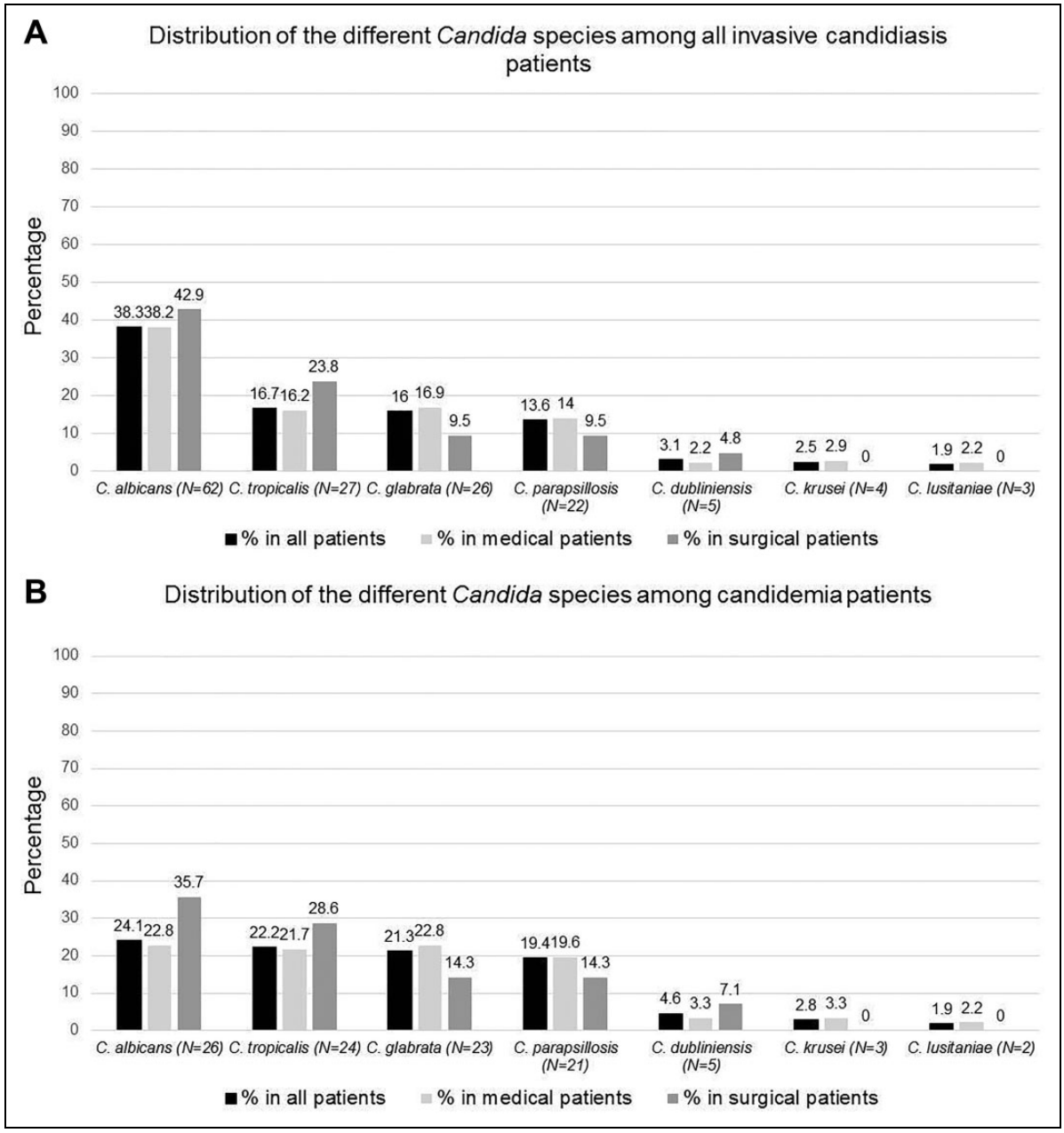

Figure 1. Order rank of the different species of *Candida* causing invasive candidiasis (A) and candidemia (B) in all medical and surgical patients.

Candida score, more insulin-treated diabetics, and more patients with prior recent antibacterial and antifungal treatment.

On multivariable logistic regression analysis, only candidemia was independently associated with non-*albicans* infection (OR: 6.74; 95% CI: 2.41-18.91).

Table 2 also describes the susceptibility of *Candida* to antifungal agents. Resistance to fluconazole was present in 31 (27.9%) of 111 patients (5/30 [16.7%] *albicans*, 11/19 [57.9%] *parapsilosis*, 8/24 [33.3%] *glabrata*, and 3/3 [100%] *krusei*), resistance to voriconazole in 9/99 (8.1%; 4/29 [13.8%] *albicans*, 2/19 [10.5%] *glabrata*, 1/21 [4.8%] *tropicalis*, 1/19 [5.3%] *parapsilosis*, and 3/3 [100%] *krusei*), resistance to caspofungin in 3/102 (2.9%; 1/28 [3.6%] *albicans*, 1/22 [4.5%] *glabrata* and one-fourth [25%] *dubliniensis*), and resistance to amphotericin B in 3/96 (3.1%; 2/28 [7.1%] *albicans* and ½ [50%] *lusitaniae*). There was no difference in fluconazole resistance between KAMC and KFMC (29.0% and 22.2%, respectively; $P = .35$). All fluconazole-resistant *Candida parapsilosis* (n = 11) occurred at KAMC.

Management of Invasive Candidiasis

Table 3 describes certain management elements of invasive candidiasis. Antifungal therapy was empirical in 42.9%

Table 2. Antifungal Susceptibility and Minimal Inhibitory Concentrations for Isolated *Candida*.

	All Patients, N = 162	*Albicans*,[a] n = 62	Non-*albicans*,[a] n = 91	*P* Value
Susceptibility to antifungal agents, n (%)				
Amphotericin B	93/96 (96.9)	26/28 (92.9)	67/68 (98.5)	.20
Caspofungin	99/102 (97.0)	27/28 (96.4)	72/74 (95.9)	1.0
Anidulafungin	4/4 (100)	1/1 (100)	3/3 (100)	-
5-Flucytosine	85/104 (81.7)	24/30 (80.0)	61/73 (83.6)	.67
Fluconazole	80/111 (72.1)	25/30 (83.3)	55/81 (67.9)	.15
Itraconazole	60/93 (64.5)	21/26 (80.8)	39/67 (58.2)	.04
Voriconazole	91/99 (91.9)	25/29 (86.2)	66/70 (94.3)	.23
Minimal inhibitory concentration, median (25th and 75th percentiles)				
Amphotericin B	0.5 (0.41 and 1.00)	0.50 (0.25 and 1.00)	0.50 (0.47 and 1.00)	.83[b]
Caspofungin	0.06 (0.03 and 0.50)	0.03 (0.03 and 0.11)	0.12 (0.053 and 0.50)	.04[b]
Anidulafungin	Not available	Not available	Not available	
5-Flucytosine	0.06 (.006 and 0.153)	0.09 (0.06 and 0.12)	0.06 (0.06 and 0.25)	.94[b]
Fluconazole	16.00 (1.00 and 80.00)	0.75 (0.25 and 97.25)	28.00 (7.00 and 80.00)	.099[b]
Itraconazole	0.25 (0.12 and 0.75)	0.06 (0.04 and 12.02)	0.50 (0.25 and 0.75)	.045[b]
Voriconazole	0.25 (0.08 and 1.00)	0.06 (0.01 and 6.03)	0.50 (0.25 and 1.00)	.047[b]

[a]9 patients had candida species not identified.
[b]Mann-Whitney *U* test.

Table 3. Management of Invasive Candidiasis.

	All Patients, N = 162	*Albicans*,[a] n = 62	Non-*albicans*,[a] n = 91	*P* Value
First antifungal agent, n (%)				
Empirical	62/152 (40.8)	21/56 (37.5)	40/88 (45.5)	.35
Therapeutic	90/152 (59.2)	35/56 (62.5)	48/88 (54.5)	
Amphotericin B	7/148 (4.7)	1/52 (1.9)	5/88 (5.7)	.06
Caspofungin	103/148 (69.6)	30/52 (57.7)	66/88 (75.0)	
Anidulafungin	18/148 (12.2)	10/52 (19.2)	8/88 (9.1)	
Fluconazole	19/148 (12.8)	11/52 (21.2)	8/88 (9.1)	
Voriconazole	1/148 (0.7)	0/52 (0)	1/88 (1.1)	
Timing of antifungal therapy (hours),[b] median (25th and 75th percentiles)	1.0 (−35.0 and 13.0)	3.5 (−29.8 and 11.0)	1.0 (−43.0 and 15.5)	.57[c]
Initiation interval of antifungal therapy,[b] N (%)				
>24 hour before culture result	28/99 (28.3)	6/24 (25.0)	22/74 (28.6)	.31
0-24 hours before culture result	12/99 (12.1)	3/24 (12.5)	9/74 (12.2)	
0-24 hours after culture result	36/99 (36.4)	12/24 (50.0)	23/74 (35.7)	
>24 hour after culture result	23/99 (23.2)	3/24 (12.5)	20/74 (23.5)	
First antifungal changed during therapy course	34/148 (23.0)	14/53 (26.4)	20/88 (22.7)	.62
Antifungal therapy clinical effectiveness,[d] n (%)	76/108 (70.4)	12/18 (66.7)	39/56 (69.6)	.81
Other management interventions, N (%)				
Vasopressors	76/107 (71.0)	44/62 (71.0)	67/90 (74.4)	.64
Central venous catheter removed/changed	28/111 (25.2)	12/46 (26.1)	16/60 (26.7)	.95
Arterial line removed	12/111 (10.8)	8/46 (17.4)	2/60 (3.3)	.02
Urinary catheter removed/changed	23/111 (20.7)	9/46 (19.6)	14/60 (23.3)	.64

[a]Nine patients had *Candida* species not identified.
[b]For patients with candidemia.
[c]Mann-Whitney *U* test.
[d]Antifungal therapy was considered completely effective when all symptoms and radiologic and nonradiologic signs caused by invasive candidiasis disappeared.

(46% for candidemia cases) with caspofungin being the most commonly used agent. When caspofungin was used as empirical therapy, it was appropriate in 34 (97.1%) of 35 patients. When fluconazole was used, it was appropriate in 2 (50%) of 4 patients. Combination antifungal therapy was used in only 1 patient. In patients with candidemia, antifungal therapy was started −1 hour (median, 25th and 75th percentiles = −35 and 13 hours) before culture result was known (59.6% of therapy was initiated after knowing the culture result).

Antifungal agents were changed in 34 patients: amphotericin B in 4 to caspofungin (n = 3) and fluconazole (n = 1); caspofungin in 19 to anidulafungin (n = 4), fluconazole (n = 11), and voriconazole (n = 1); anidulafungin in 2 to fluconazole (n = 2); and fluconazole in 9 to anidulafungin

Table 4. Outcomes of Invasive Candidiasis.

	All Patients, N = 162	*Albicans*,[a] n = 62	Non-*albicans*,[a] n = 91	*P* Value
Hospital mortality, n (%)	95 (58.6)	38 (61.3)	50 (54.9)	.44
ICU mortality, n (%)	83 (51.2)	32 (51.6)	44 (48.4)	.69
28-Day mortality, n (%)	92 (57.1)	33 (54.1)	52 (57.1)	.71
New RRT after invasive candidiasis, n (%)	60 (37.5)	19/62 (30.6)	39/89 (43.8)	.10
No code	52/160 (32.5)	17/61 (27.9)	31/90 (34.4)	.40
Mechanical ventilation duration (days), mean (SD)	25.5 (27.9)	22.4 (24.4)	27.6 (30.4)	.39
ICU LOS (days), mean (SD)	42.4 (54.2)	40.2 (61.4)	43.8 (50.9)	.69
Hospital LOS (days), mean (SD)	88.8 (87.2)	86.2 (90.8)	92.1 (88.0)	.67

Abbreviations: RRT, renal replacement therapy; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.
[a]Nine patients had candida species not identified.

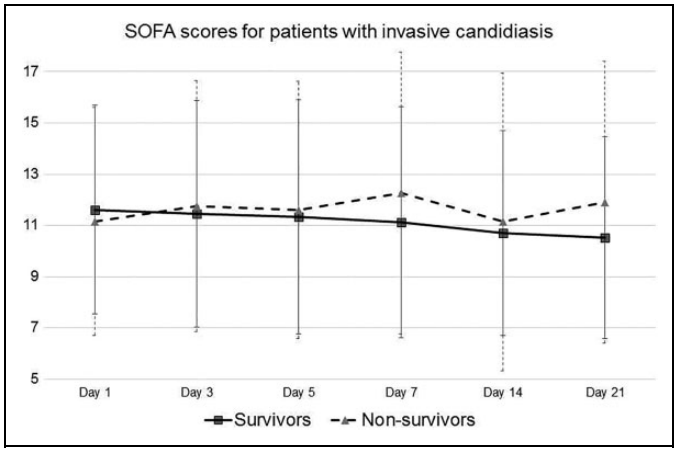

Figure 2. Serial Sequential Organ Failure Assessment Scores in survivors and nonsurvivors of patients with invasive candidiasis; *P* values were > .05 at all points.

(n = 2) and caspofungin (n = 7). *Candida* susceptibility was the most common reason for changing antifungal therapy (n = 15) followed by inadequate clinical response (n = 9).

Table 3 also describes nonantibiotic interventions for invasive candidiasis. Of note, the central venous catheter was removed/changed in 30% of candidemia cases and the urinary catheter in 75% when candiduria was present.

Outcomes

Table 4 describes the various outcomes of our cohort. Invasive candidiasis was associated with high hospital mortality (58.6%), prolonged stay on mechanical ventilation, and in the ICU and hospital. Figure 2 shows the progression of SOFA score, which did not differ between survivors and nonsurvivors. The mortality rates according to the *Candida* species are described in Figure 3A for all patients with invasive candidiasis and in Figure 3B for patients with candidemia.

Table 5 shows the hospital mortality in selected subgroups. The hospital mortality was higher in KAMC compared with KFMC, when invasive candidiasis led/contributed to ICU admission compared when it developed during critical illness, in patients with Candida score ≥ 2 compared with <2 (Candida score was 1.74 ± 1.23 in survivors and 2.14 ± 1.10 in nonsurvivors; $P = .03$).

On multivariable logistic regression analysis, the predictors of mortality were renal replacement therapy after invasive candidiasis diagnosis (OR: 5.42; 95% CI: 2.16-13.56) and invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness (OR: 2.87; 95% CI: 1.22-6.74).

Discussion

In this study, we found that invasive candidiasis was mostly due to non-*albicans* species and was associated with high mortality; there was no significant outcome difference between *albicans* and non-*albicans* infections; invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness and requirement for renal replacement therapy were predictors of hospital mortality; and resistance to amphotericin B and echinocandins was rare.

It is estimated that 15% of health-care-associated infections are caused by fungi, and *Candida* species account for 70% to 90% of all invasive infections.[28] *Candida* is responsible for 8% to 10% of bloodstream infections in the United States[29] and is ranked seventh in both a large prevalence survey of health-care-associated infections from 183 geographically diverse acute-care hospitals in the United States[30] and a multicenter surveillance study in 16 Brazilian hospitals.[31] While in Europe, *Candida* species account for 2% to 3% of bloodstream infections and are ranked sixth to tenth among health-care-associated infections.[32] At least 15 distinct *Candida* species that produce disease in humans, but >90% of invasive infections are caused by 5 common pathogens: *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei.*[33] *Candida albicans* was previously the dominant species in invasive candidiasis, accounting for 65% to 70% of the total number of *Candida* isolates; however, in recent years, non-*albicans* species has been responsible for about 50% of cases in some centers.[32] Additionally, several studies have reported increasing significant variation in the distribution of *albicans* and non-*albicans* causing invasive candidiasis in ICUs between health-care facilities.[34,35] In the Prospective Antifungal Therapy Alliance registry (United States and Canada), non-*albicans* species accounted for >50% of all cases of invasive candidiasis in 15 (62.5%) of the 24

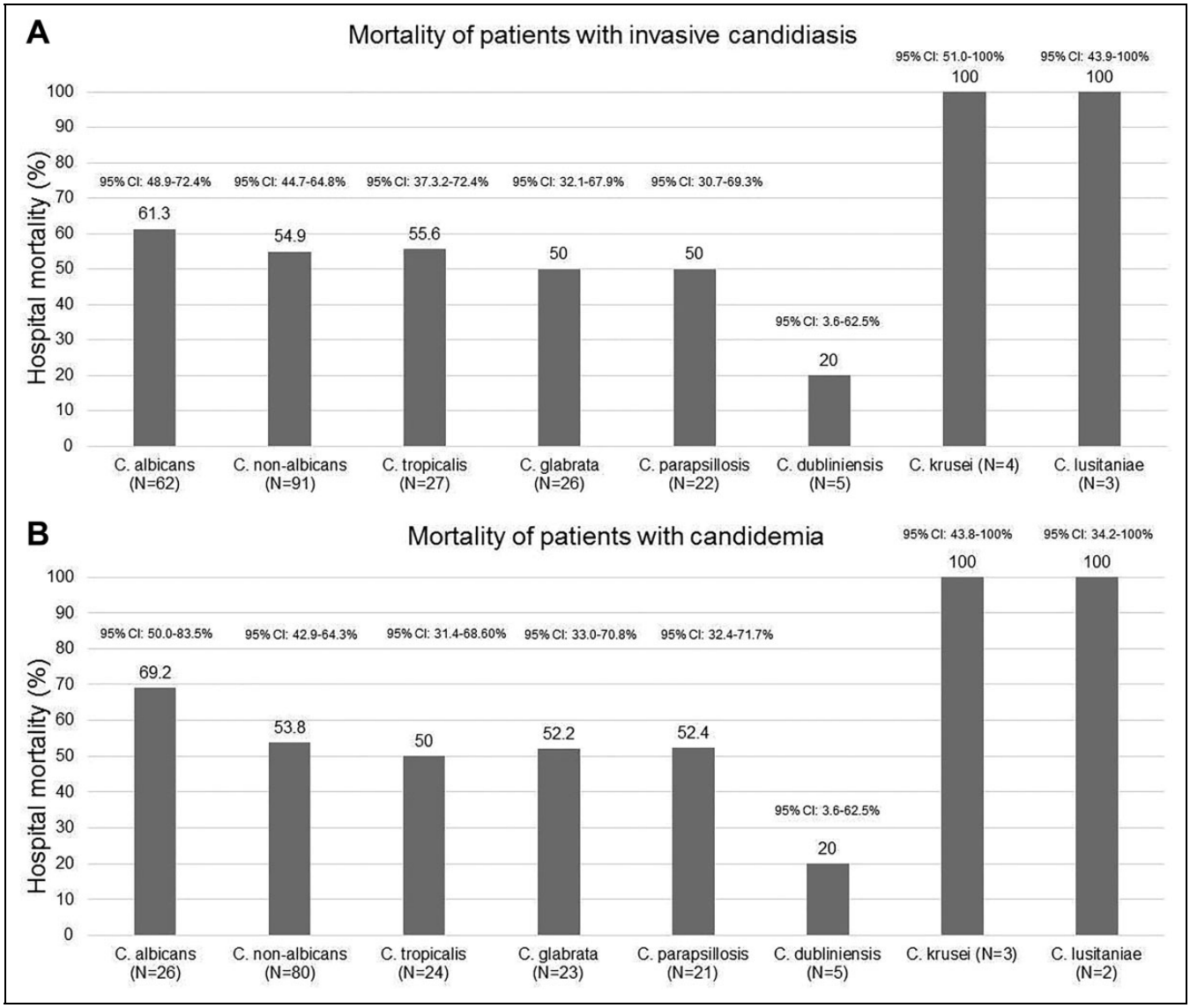

Figure 3. Mortality according to the *Candida* species causing invasive candidiasis (A) and candidemia (B) in all medical and surgical patients.

participating sites.[36] Historical data indicated that factors associated with increased non-*albicans* risk were major postoperative cases, gastrointestinal procedure, enteric bacteremia, hemodialysis days, total parenteral nutrition, and number of red blood cell transfusions.[6,37] Other studies found that cancer, chemotherapy, traumatic brain injury, bacterial sepsis, and previous use of fluconazole may increase the risk of these infections.[38-40] We found a significant variation in the distribution of *albicans* and non-*albicans* in the 2 participating hospitals. This may be related to differences in patient populations and antifungal practices. Additionally, we found that the only independent predictor of non-*albicans* infection was the presence of candidemia.

Non-*albicans*species have reduced susceptibilities or even intrinsic resistance to azoles and sometimes echinocandins.[41] Pfaller et al tested 197 619 clinical *Candida* isolates from 41 countries (1997-2007) and found that 90.2% of *Candida* isolates were susceptible to fluconazole; however, 13 of the 31 species exhibited <75% susceptibility.[5] Further, an increase in fluconazole resistance for *Candida parapsilosis*, *Candida guilliermondii*, *Candida lusitaniae*, *Candida sake*, and *Candida pelliculosa* was observed over time.[5] Recent data indicated that globally the resistance to fluconazole for the most common non-*albicans* were 1.2% to 5.2% for *Candida parapsilosis*, 5.1% to 15% for *Candida glabrata*, and 2.3% to 24.2% for *C tropicalis*.[42-44] In the current study, we observed higher fluconazole resistance (16.7% for *C albicans*, 57.9% for *Candida parapsilosis*, and 33.3% for *Candida glabrata*). Fluconazole resistance has been increasing over time.[5] The high prevalence of fluconazole-resistant *Candida parapsilosis* at KAMC may be related to antifungal treatment practices and may represent an ongoing outbreak.

Invasive candidiasis is associated with high mortality rate.[31,32,45] In an Australian nationwide study of mortality determinants in non-neutropenic ICU patients, the overall

Table 5. Hospital Mortality in Subgroups of Patients.

Subgroup	Mortality, n/N (%)	Relative risk (95% confidence interval)	*P* Value
Definite invasive candidiasis	68/119 (57.1)	0.840 (0.493-1.432)	.52
Possible/probable invasive candidiasis	27/43 (62.8)	Reference	
Invasive candidiasis led/contributed to ICU admission	41/57 (71.9)	1.383 (1.088-1.759)	.01
Invasive candidiasis occurred during ICU stay	48/95 (50.5)	Reference	
Candidemia	32/54 (59.3)	1.013 (0.812-1.263)	.91
Invasive candidiasis without candidemia	63/108 (58.3)	Reference	
Albicans	38/62 (61.3)	1.110 (0.856-1.440)	.44
Non-*albicans*	50/91 (54.9)	Reference	
KAMC	76/120 (63.3)	1.716 (1.019-2.890)	.04
KFMC	19/42 (45.2)	Reference	
Age < 62 years	46/79 (58.2)	0.984 (0.725-1.336)	.92
Age $\geq$ 62 years	49/83 (59.0)	Reference	
Medical	78/136 (57.4)	0.751 (0.356-1.581)	.45
Trauma/postoperative	17/26 (65.4)	Reference	
Diabetes	61/107 (57.0)	0.876 (0.561-1.367)	.56
No diabetes	34/55 (61.8)	Reference	
APACHE II score on ICU admission < 24	44/73 (60.3)	1.053 (0.771-1.437)	.75
APACHE II score on ICU admission $\geq$ 24	45/78 (57.7)	Reference	
SOFA on invasive candidiasis diagnosis day < 12	29/53 (54.7)	1.059 (0.742-1.511)	.75
SOFA on invasive candidiasis diagnosis day $\geq$ 12	30/58 (51.7)	Reference	
Candida score < 2	15/34 (44.1)	0.844 (0.705-1.010)	.049
Candida score $\geq$ 2	78/124 (62.9)	Reference	
Empirical antifungal agents	39/62 (62.9)	1.171 (0.902-1.521)	.24
Therapeutic antifungal agents	42/90 (53.3)	Reference	
>24 hours before culture result	19/32 (59.4)	1.200 (0.753-1.912)	.88
0-24 hours before culture result	7/14 (50.0)	1.000 (0.696-1.438)	
0-24 hours after culture result	22/41 (53.7)	1.083 (0.659-1.780)	
>24 hours after culture result	17/34 (50.0)	Reference	
Echinocandin (caspofungin/anidulafungin)	68/121 (56.2)	0.942 (0.404-2.198)	.89
Fluconazole	11/19 (57.9)	Reference	
Vasopressors	70/118 (59.3)	1.111 (0.664-1.857)	.69
No vasopressors	24/43 (55.8)	Reference	
Mechanical ventilation	74/125 (59.2)	1.080 (0.611-1.911)	.79
No mechanical ventilation	21/37 (56.8)	Reference	
Central venous catheter removed/changed[a]	14/23 (60.9)	1.103 (0.822-1.480)	.52
Central catheter not removed/changed	28/53 (52.8)	Reference	

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; KAMC, King Abdulaziz Medical City; KFMC, King Fahad Medical City; SOFA, Sequential Organ Failure Assessment.
[a]Analysis restricted for candidemia.

mortality was 52% with a median time to death of 7 days after candidemia.[45] In a large Brazilian study, the crude mortality associated with candidemia was 72.2%.[31] A systematic review of 7 matched cohort and case-control studies found that the mortality attributed to candidemia ranged from 5% to 71%.[13]

Factors that influence outcomes may include the virulence of the infecting organism, severity of the underlying illness, and the appropriateness and timing of antifungal treatment. One study found that host factors independently associated with mortality were older age, ICU admission diagnosis other than polytrauma, and mechanical ventilation at time of candidemia.[45] We did not find significant difference in mortality between *albicans* and non-*albicans* infections. *Candida parapsilosis* has been associated with lower mortality rate in other studies.[35] This was not observed in our study, possibly because of high rate of antifungal resistance. In the current study, invasive candidiasis leading/contributing to ICU admission versus occurring during critical illness was an independent predictor of mortality. This may suggest that the underlying illness is an important mortality determinant. The Candida score, which was suggested to guide empirical antifungal therapy, was higher in nonsurvivors but was not an independent predictor of mortality.

Antifungal therapy timing and source control have been associated with improved outcomes in *Candida* infections in multiple[46-47] but not all studies.[45] Parkins et al studied 199 patients with invasive candidiasis and found that only 26% received adequate empirical therapy, which was associated with lower mortality (27% vs 46%; risk ratio: 0.60; 95% CI: 0.37-0.96).[46] After adjusting for age and ICU admission, adequate empirical therapy was independently associated with lower mortality risk (OR: 0.46; 95% CI: 0.22-1.00).[46] Morrell

et al also demonstrated that delayed administration of antifungal treatment >12 hours after a positive blood culture was an independent mortality predictor (adjusted OR: 2.09; 95% CI: 1.53-2.84).[47] Another study showed a significant mortality benefit to receiving antifungal treatment within 72 hours of a positive blood culture (30-day mortality for early treatment: 27% vs 40%; $P = .004$; hazard ratio: 1.41; 95% CI: 1.01-1.98).[48] However, the Australian Candidemia Study group found that antifungal therapy, but not the timing or choice of antifungal agent, was significantly associated with survival on multivariable logistic regression analysis.[45] A recent observational study found that both hospital mortality and ICU mortality were significantly lower in patients treated with an echinocandin compared with fluconazole, voriconazole, or itraconazole.[49] In our study, the mortality associated with invasive candidiasis was high (59%). Reasons could be delay in antifungal therapy and inadequate source control as we observed that empirical therapy was provided in 40.8% of our patients, and the central venous catheter was removed in 30% of candidemia cases. Catheter removal may have an additive beneficial effect to adequate empirical therapy in candidemia.[50] On the other hand, invasive candidiasis may be a sign of severe illness and treatment may not change illness course in many patients. Nevertheless, earlier appropriate antifungal therapy and removal of contaminated central venous catheters or drainage of infected material are advocated.[33]

The study should be interpreted taking into accounts its strengths and limitations. The strength included the prospective and wide range of data collection, the adjudication of infection by 2 intensivists, and the availability of susceptibility data on majority of patients. The limitations include that it was performed at only 2 centers in 1 city. We used the definitions created by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) for invasive fungal diseases, which were made for research purposes and apply to immunocompromised patients but not necessarily to critically ill patients. Moreover, the lack of susceptibility data on some patients limited our analysis for the association of resistance on outcome.

In conclusion, *Candida* non-*albicans* was responsible for most cases of invasive candidiasis but with significant variation between the 2 hospitals where the study was conducted. Hence, hospital epidemiologic data are important in management. Fluconazole resistance was common (28%), but resistance to amphotericin B and caspofungin was rare. Antifungal therapy was initiated after culture results in >50% of cases suggesting low clinical suspicion. Invasive candidiasis was associated with high mortality, which may reflect the severity of underlying illness.

Authors' Note

Ethics approval was obtained from the institutional review boards of King Abdullah International Medical Research Center and King Fahad Medical City (Protocol RC11/096). Informed consents were obtained from enrolled patients. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Hasan M. Al-Dorzi made substantial contributions to conception and design, acquisition, analysis, and interpretation of data; drafted the manuscript, and revised it critically for important intellectual content. Hussam Sakkijha made substantial contributions to acquisition and interpretation of data and revised the manuscript for important intellectual content. Raymond Khan made substantial contributions to design, acquisition, and interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. Tarek Aldabbagh made substantial contributions to design, acquisition, and interpretation of data and revised the manuscript critically for important intellectual content. Aron Toledo made substantial contributions to acquisition of data and revised the manuscript for important intellectual content. Pendo Ntinika made substantial contributions to acquisition of data and revised the manuscript for important intellectual content. Sameera M. Al Johani made substantial contributions to acquisition and interpretation of data and contributed to manuscript drafting and revised it critically for important intellectual content. Yaseen M. Arabi made substantial contributions to design and interpretation of data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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