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ORIGINAL ARTICLE

Central venous catheter unrelated candidemia influences the outcome of infection in patients with solid tumors

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Abstract

Systemic infections due to *Candida* spp. is common among immunocompromised patients, including those with solid tumors (ST). Clinical characteristics of candidemia in 114 patients with ST were compared with those of 249 candidemic patients without ST (non-ST). Patients with ST were more likely to be hospitalized in medical departments, to have a significantly higher Charlson's score and to undergo a significantly later central venous catheter (CVC) removal ($P < 0.001$). Similarly, the use of total parenteral nutrition was more common in ST patients ($P = 0.026$). Although there was a trend toward a more appropriate use of antifungal therapy in ST (60%) than in non-ST patients (49%), the difference was not statistically significant ($P = 0.059$). Thirty-day mortality was significantly higher in ST (49%) than in non-ST patients (36%, $P = 0.016$). Multivariate analysis showed that either higher age or septic shock was an independent risk factor for mortality in both groups of patients. Conversely, a CVC-unrelated candidemia represented an independent risk factor for mortality in ST patients (HR 3.581 [CI 95% 1.412–9.087, $P = 0.007$]). Overall, these data show that candidemia in ST patients is characterized by an extremely high mortality rate.

Keywords Candidemia · Solid tumors · Antifungal therapy · Central catheters

Introduction

Bloodstream infections due to *Candida* species occur frequently in immunocompromised patients and are characterized by a high mortality rate despite recent advances in diagnosis and therapeutic approaches [1]. Cancer patients are among those at risk for developing this infection. Although either hematologic or solid malignancies are reported as predictors for candidemia, yet the epidemiology of fungemia in the latter group of patients has not been fully elucidated [2–5].

Therefore, in this study, we compared the epidemiology and all-cause mortality associated with candidemia in patients with solid tumors to those without solid tumors hospitalized in a tertiary referral hospital of Ancona, Italy, during a 7-year period.

Patients and methods

Study population, data collection, and definition A retrospective observational study of all cases of candidemia was carried out from January 1, 2010, to December 31, 2016, in a single 980-bedded referral University Hospital in Ancona, Italy. A case of *Candida* bloodstream infection (BSI) was defined as a peripheral isolation of *Candida* species from blood culture in a patient with temporally related clinical signs and symptoms of infection. All *Candida* BSIs were identified through the microbiological laboratory database. Data regarding demographic characteristics and clinical risk factors were collected from the patients' medical records.

Elena Orsetti and Lucia Brescini contributed equally to this work.

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Appropriate antifungal therapy was considered when an appropriate drug (based on subsequent in vitro susceptibility testing results) with adequate dosage was started within 72 h from the first blood culture performed. Adequate dosage of an antifungal agent was defined according to IDSA 2009–2016 guidelines [6, 7]. Early central venous catheter (CVC) removal was defined a

Table 1 Demographics and clinical characteristics of 363 patients with BSIs due to *Candida* species considered in this study

Characteristics	All patients ($n = 363$)	Solid tumors ($n = 114$)	No solid tumors ($n = 249$)	P value[a]
Male sex, *n* (%)	230 (63)	73 (64)	157 (63)	0.788
Age, median (IQR)[b]	71 (60–78)	71 (62–78)	69 (58–77)	0.152
Ward				
Internal medicine, *n* (%)	148 (41)	57 (50)	91 (36)	< 0.001
Surgery, *n* (%)	87 (24)	38 (33)	49 (20)	
Intensive care unit, *n* (%)	128 (35)	19 (17)	109 (44)	
Chronic comorbidities	340 (94)	114 (100)	226 (91)	
Chronic pulmonary diseases, *n* (%)[c]	53 (15)	16 (14)	37 (15)	0.836
Hematological malignancy, *n* (%)	15 (4)	1 (1)	14 (6)	0.085
Cardiovascular diseases, *n* (%)[d]	203 (56)	51 (45)	152 (61)	0.004
Neurological diseases, *n* (%)[e]	71 (19)	12 (10)	59 (24)	0.003
Gastrointestinal diseases, *n* (%)[f]	99 (27)	36 (31)	63 (25)	0.213
Diabetes mellitus, *n* (%)	70 (19)	16 (14)	54 (22)	0.086
Chronic renal failure, *n* (%)	52 (14)	13 (11)	39 (22)	0.282
Charlson's score, median (IQR)	6 (4–7)	7 (6–8)	6 (5–7)	< 0.001
Previous surgery (< 30 days), *n* (%)	190 (52)	64 (56)	126 (51)	0.327
Central venous catheter, *n* (%)	320 (88)	101 (89)	219 (88)	0.860
Central venous catheter-related BSIs, *n* (%)[g]	236 (74)	76 (67)	160 (64)	0.612
Early central venous catheter removal, *n* (%)[h]	125 (34)	12 (11)	113 (45)	< 0.001
Other devices, *n* (%)[i]	330 (91)	100 (88)	230 (92)	0.153
Previous invasive procedures (< 72 h), *n* (%)[j]	111 (30)	38 (33)	73 (29)	0.410
Parenteral nutrition, *n* (%)	241 (66)	85 (74)	156 (63)	0.026
Steroid therapy, *n* (%)	108 (30)	39 (34)	69 (28)	0.209
Neutropenia, *n* (%)	8 (2)	3 (3)	5 (2)	0.707
Septic shock, *n* (%)	56 (15)	15 (13)	41 (16)	0.418
Acute kidney failure, *n* (%)	30 (8)	6 (5)	24 (10)	0.159
Concomitant bacteremia, *n* (%)	133 (37)	42 (37)	91 (36)	0.978
Candida species				
Candida albicans, *n* (%)	187 (51)	63 (55)	124 (50)	0.862
Candida parapsilosis, *n* (%)	86 (24)	24 (21)	62 (25)	
Candida tropicalis, *n* (%)	39 (11)	11 (10)	28 (11)	
Candida glabrata, *n* (%)	33 (9)	11 (10)	22 (9)	
Other *Candida* species, *n* (%)[k]	18 (5)	5 (4)	13 (5)	
Appropriate antifungal therapy, *n* (%)[l]	190 (52)	68 (60)	122 (49)	0.059
Primary antifungal therapy				
Azoles, *n* (%)	172 (47)	61 (53)	111 (44)	0.165
Echinocandins, *n* (%)	98 (27)	30 (26)	68 (27)	
Polyenes, *n* (%)	6 (2)	0 (0)	6 (2)	
No treatment, *n* (%)	87 (24)	23 (20)	64 (26)	
30-day mortality, *n* (%)	145 (40)	56 (49)	89 (36)	0.016

[a] Comparisons between groups were performed using Mann-Whitney *U* test for quantitative variables and chi-square test (or Fisher's exact test when expected frequencies were less than five) for qualitative variables

[b] IQR, interquartile range

[c] Chronic pulmonary diseases include asthma, chronic bronchitis, emphysema, and lung fibrosis

[d] Cardiovascular diseases include heart failure, ischemic heart disease, endocarditis, and arrhythmia

[e] Neurological diseases include Parkinson's disease, Alzheimer's disease, and paralysis

[f] Gastrointestinal diseases include Crohn's disease, ulcerative colitis, chronic pancreatitis, and gallbladder stones

[g] A catheter-related candidemia was defined according to ref. 8 and 9

[h] Early central venous catheter removal was considered occurring within 48 h from blood cultures drawing

[i] Other devices include urinary catheter, surgical drainage, cutaneous gastrostomy, and tracheostomy tube

[j] Previous invasive procedures include endoscopy and positioning of any device

[k] Other *Candida* species included *Candida guilliermondii* ($n = 6$), *Candida krusei* ($n = 4$), *Candida lusitaniae* ($n = 3$), *Candida dubliniensis* ($n = 2$), *Candida norvegensis* ($n = 1$), *Candida pelliculosa* ($n = 1$), and *Candida utilis* ($n = 1$)

[l] Appropriate antifungal therapy was considered when the appropriate drug with adequate dosage was started within 72 h the first blood culture performed

removal of the line within 48 h from drawing blood culture. Proven catheter-related candidemia was defined as follows: evidence of catheter exit site exudate with the same *Candida* spp. that was isolated from the bloodstream; semiquantitative culture of the catheter tip yielded > 15 CFU of the same *Candida* spp.; simultaneously quantitative cultures of blood samples showing a ratio of 3:1 of CFU between blood samples obtained through the catheter and a peripheral vein or the differential time to positivity was ≥ 2 h for non-*glabrata Candida* BSI [8, 9]. Mortality was calculated after 30 days from the occurrence of the episode of *Candida* BSI. To ascertain the outcome, we considered only those patients from which clinical information was included in the regional health surveillance system. The present research was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The Institutional Review Board of the Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I°-Lancisi-Salesi granted retrospective access to the data without the need for individual informed consent. The consent was not given since the data were analyzed anonymously.

Microbiology Candida species were isolated from blood samples using BacT/ALERT (bioMérieux) and identified with the MALDI-TOF Biotyper™ (Brucker Daltonics, Germany). Antifungal susceptibility testing was performed using the SensitreYeastOne colorimetric plate (Trek Diagnostic System) and MIC results were interpreted according to latest species-specific clinical breakpoints (CBPs) as established by the Clinical and Laboratory Standards Institute (CLSI) [10].

Statistical analysis Patients with candidemia and solid tumors (ST, study group) were compared to candidemic patients without ST (non-ST, control). Quantitative data are depicted as median with interquartile (Q1–Q3) ranges and compared by Mann-Whitney *U* test. Qualitative variables were expressed as absolute and relative frequencies. Categorical variables were compared using the χ^2 test with Yates' correction or Fisher's exact test when appropriate. The factors associated with mortality were analyzed by using a stepwise binary logistic regression model in which variables found to be significant at the univariate level (*P* value < 0.05) were introduced. Statistical analysis was performed using SPSS software, version 20 (Statistical Package for Social Sciences Inc., Chicago, IL).

Results

A total of 363 patients with candidemia were considered. There were 114 and 249 ST and non-ST patients, respectively (Table 1). ST were as follows: gastrointestinal tract (47%), urogenital tract (19%), lung and respiratory tract (17%), other tumors (17%). ST patients were more likely to be hospitalized either in internal medicine or surgery wards than in intensive care units. Both cardiovascular and neurological diseases were more common in non-ST than in ST patients. ST patients had higher Charlson's score, they had less likely an early CVC removal, and they were undergoing a parenteral nutrition more frequently. Although there was a trend toward a more appropriate use of antifungal therapy in ST (60%) than in non-ST patients (49%), the difference was not statistically significant ($P = 0.059$). The type of primary antifungal therapy did not differ between groups with fluconazole being the most common used antifungal agent. Of note, 24% of the overall patients were not treated. Thirty-day crude mortality accounted for 40% of the overall population being significantly higher in ST (49%) than in non-ST patients (36%). Kaplan-Meier survival curves of the two patients' populations confirmed a significant difference between groups (Fig. 1).

The specific risk factors significantly more common in ST patients who died within 30 days were the following: higher age, being hospitalized in ICU rather than in other wards, suffering from chronic pulmonary diseases, the occurrence of a CVC-unrelated candidemia, and the presence of septic shock (Table 2). The specific risk factors significantly more common in non-ST patients who died within 30 days were the following: higher age, being hospitalized in ICU rather than in other wards, suffering from chronic pulmonary diseases, hematological malignancies, diabetes mellitus, chronic renal failure, having a higher Charlson's score, the presence of neutropenia, septic shock, acute kidney failure, the type of *Candida* spp., and the type of primary antifungal treatment (i.e., the lack of any antifungal therapy, Table 3). Multivariate analysis showed that either higher age or septic shock was an independent risk factor for mortality in both groups of patients (Table 4). Conversely, a CVC-unrelated candidemia represented an independent risk

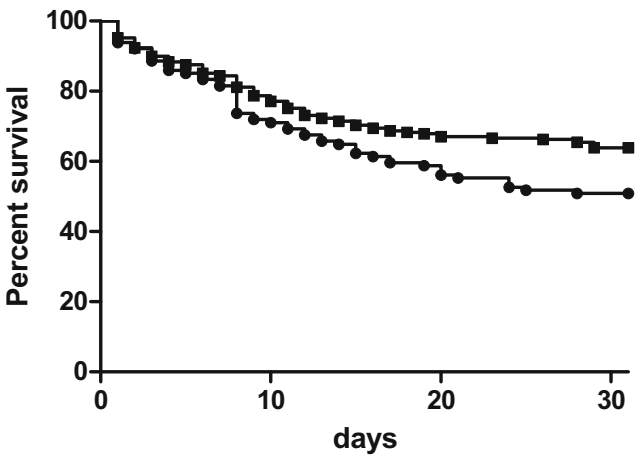

Fig. 1 Kaplan-Meier survival curves of the two patients population: patients with solid tumors (circles) and patients without solid tumors (squares), $P = 0.025$

Table 2 Outcome of 114 patients with solid tumors and BSIs due to *Candida* species considered in this study

Characteristics	30-day outcome		
	Survival ($n = 58$)	Death ($n = 56$)	P value[a]
Male sex, *n* (%)	37 (64)	36 (64)	0.956
Age, median (IQR)[b]	67 (58–77)	73 (69–80)	0.012
Ward			
Internal medicine, *n* (%)	32 (55)	25 (45)	< 0.001
Surgery, *n* (%)	24 (41)	14 (25)	
Intensive care unit, *n* (%)	2 (3)	17 (30)	
Chronic comorbidities	58 (100)	56 (100)	
Chronic pulmonary diseases, *n* (%)[c]	4 (7)	12 (21)	0.026
Hematological malignancy, *n* (%)	1 (2)	0 (0)	0.324
Cardiovascular diseases, *n* (%)[d]	21(36)	30 (53)	0.062
Neurological diseases, *n* (%)[e]	4 (7)	8 (14)	0.199
Gastrointestinal diseases, *n* (%)[f]	17 (29)	19 (34)	0.596
Diabetes mellitus, *n* (%)	7 (12)	9 (16)	0.539
Chronic renal failure, *n* (%)	6 (10)	7 (12)	0.717
Charlson's score, median (IQR)	7 (5–8)	7 (6–8)	0.468
Previous surgery (< 30 days), *n* (%)	37 (64)	27 (48)	0.094
Central venous catheter, *n* (%)	53 (91)	48 (86)	0.341
Central venous catheter-related BSIs, *n* (%)[g]	44 (76)	32 (57)	0.023
Early central venous catheter removal, *n* (%)[h]	6 (10)	6 (11)	0.949
Other devices, *n* (%)[i]	49 (84)	51 (91)	0.284
Previous invasive procedures (< 72 h), *n* (%)[j]	17 (29)	21 (37)	0.318
Parenteral nutrition, *n* (%)	41 (71)	44 (78)	0.334
Steroid therapy, *n* (%)	19 (53)	20 (36)	0.739
Neutropenia, *n* (%)	0 (0)	3 (5)	0.074
Septic shock, *n* (%)	2 (3)	13 (23)	0.002
Acute kidney failure, *n* (%)	3 (5)	3 (5)	0.964
Concomitant bacteremia, *n* (%)	22 (38)	20 (36)	0.806
Candida species			
Candida albicans, *n* (%)	29 (50)	34 (61)	0.334
Candida parapsilosis, *n* (%)	15 (26)	9 (16)	
Candida tropicalis, *n* (%)	6 (10)	5 (9)	
Candida glabrata, *n* (%)	4 (7)	7 (12)	
Other Candida species, *n* (%)[k]	4 (7)	1 (2)	
Appropriate antifungal therapy, *n* (%)[l]	31 (56)	37 (66)	0.170
Primary antifungal therapy			
Azoles, *n* (%)	27 (46)	34 (61)	0.307
Echinocandins, *n* (%)	18 (31)	12 (21)	
Polyenes, *n* (%)	0 (0)	0 (0)	
No treatment, *n* (%)	13 (22)	10 (18)	

[a] Comparisons between groups were performed using Mann-Whitney *U* test for quantitative variables and chi-square test (or Fisher's exact test when expected frequencies were less than five) for qualitative variables

[b] IQR, interquartile range

[c] Chronic pulmonary diseases include asthma, chronic bronchitis, emphysema, and lung fibrosis

[d] Cardiovascular diseases include heart failure, ischemic heart disease, endocarditis, and arrhythmia

[e] Neurological diseases include Parkinson's disease, Alzheimer's disease, and paralysis

[f] Gastrointestinal diseases include Crohn's disease, ulcerative colitis, chronic pancreatitis, and gallbladder stones

[g] A catheter-related candidemia was defined according to ref. 8 and 9

[h] Early central venous catheter removal was considered occurring within 48 h from blood cultures drawing

[i] Other devices include urinary catheter, surgical drainage, cutaneous gastrostomy, and tracheostomy tube

[j] Previous invasive procedures include endoscopy and positioning of any device

[k] Other *Candida* species included *Candida krusei* ($n = 2$), *Candida guilliermondii* ($n = 1$), *Candida lusitaniae* ($n = 1$), and *Candida norvegensis* ($n = 1$)

[l] Appropriate antifungal therapy was considered when the appropriate drug with adequate dosage was started within 72 h the first blood culture performed

factor for mortality in ST patients (HR 3.581 [CI 95% 1.412–9.087], $P = 0.007$) while acute kidney failure represented an independent risk factor for mortality in non-ST patients (HR 4.030 [CI 95% 1.379–11.773], $P = 0.011$).

Discussion

In this study, we characterized *Candida* BSIs in patients with ST. Although malignancy is identified as a major

Table 3 Outcome of 249 patients without solid tumors and BSIs due to *Candida* species considered in this study

Characteristics	30-day outcome		
	Survival ($n = 162$)	Death ($n = 87$)	P value[a]
Male sex, *n* (%)	100 (62)	57 (66)	0.381
Age, median (IQR)[b]	67 (54–76)	74 (65–79)	< 0.001
Ward			
Internal medicine, *n* (%)	64 (39)	27 (31)	< 0.001
Surgery, *n* (%)	43 (26)	6 (7)	
Intensive care unit, *n* (%)	53 (33)	56 (64)	
Chronic comorbidities	144 (89)	82 (94)	
Chronic pulmonary diseases, *n* (%)[c]	17 (10)	20 (23)	0.012
Hematological malignancy, *n* (%)	5 (3)	9 (10)	0.028
Cardiovascular diseases, *n* (%)[d]	93 (57)	59 (68)	0.205
Neurological diseases, *n* (%)[e]	38 (23)	21 (24)	0.978
Gastrointestinal diseases, *n* (%)[f]	40 (25)	23 (26)	0.833
Diabetes mellitus, *n* (%)	28 (17)	26 (30)	0.032
Chronic renal failure, *n* (%)	19 (12)	20 (23)	0.027
Charlon's score, median (IQR)	5 (3–6)	6 (5–7)	0.001
Previous surgery (< 30 days), *n* (%)	81 (50)	45 (52)	0.992
Central venous catheter, *n* (%)	137 (84)	82 (94)	0.130
Central venous catheter-related BSIs, *n* (%)[g]	99 (61)	61 (70)	0.322
Early central venous catheter removal, *n* (%)[h]	66 (41)	47 (54)	0.095
Other devices, *n* (%)[i]	145 (89)	85 (98)	0.164
Previous invasive procedures (< 72 h), *n* (%)[j]	46 (28)	27 (31)	0.792
Parenteral nutrition, *n* (%)	97 (60)	59 (68)	0.376
Steroid therapy, *n* (%)	40 (25)	29 (33)	0.200
Neutropenia, *n* (%)	1 (1)	4 (4)	0.037
Septic shock, *n* (%)	11 (7)	30 (34)	< 0.001
Acute kidney failure, *n* (%)	8 (5)	16 (18)	< 0.001
Concomitant bacteremia, *n* (%)	62 (38)	29 (33)	0.315
Candida species			
Candida albicans, *n* (%)	73 (45)	51 (59)	0.037
Candida parapsilosis, *n* (%)	45 (28)	17 (19)	
Candida tropicalis, *n* (%)	22 (13)	6 (7)	
Candida glabrata, *n* (%)	10 (6)	12 (14)	
Other Candida species, *n* (%)[k]	10 (6)	3 (3)	
Appropriate antifungal therapy, *n* (%)[l]	85 (52)	37 (42)	0.081
Primary antifungal therapy			
Azoles, *n* (%)	79 (49)	32 (37)	0.028
Echinocandins, *n* (%)	40 (25)	28 (32)	
Polyenes, *n* (%)	6 (4)	0 (0)	
No treatment, *n* (%)	35 (22)	29 (33)	

[a] Comparisons between groups were performed using Mann-Whitney *U* test for quantitative variables and chi-square test (or Fisher's exact test when expected frequencies were less than five) for qualitative variables

[b] IQR, interquartile range

[c] Chronic pulmonary diseases include asthma, chronic bronchitis, emphysema, and lung fibrosis

[d] Cardiovascular diseases include heart failure, ischemic heart disease, endocarditis, and arrhythmia

[e] Neurological diseases include Parkinson's disease, Alzheimer's disease, and paralysis

[f] Gastrointestinal diseases include Crohn's disease, ulcerative colitis, chronic pancreatitis, and gallbladder stones

[g] A catheter-related candidemia was defined according to ref. 8 and 9

[h] Early central venous catheter removal was considered occurring within 48 h from blood cultures drawing

[i] Other devices include urinary catheter, surgical drainage, cutaneous gastrostomy, and tracheostomy tube

[j] Previous invasive procedures include endoscopy and positioning of any device

[k] Other *Candida* species included *Candida guilliermondii* ($n = 5$), *Candida dubliniensis* ($n = 2$), *Candida krusei* ($n = 2$), *Candida lusitaniae* ($n = 2$), *Candida pelliculosa* (1), and *Candida utilis* ($n = 1$)

[l] Appropriate antifungal therapy was considered when the appropriate drug with adequate dosage was started within 72 h the first blood culture performed

underlying disease in candidemic patients, data available in the literature are limited in patients with ST compared to other settings of patients [3–5, 11–13].

We found several differences between ST- and non-ST patients. First, ST patients were hospitalized more frequently in internal medicine or surgery wards than in ICUs. Our results

Table 4 Multivariate analysis of risk factors for 30-day mortality in the study cohort

Risk factors	Hazard ratio	CI 95%		*P* value
		Lower limit	Upper limit	
Solid tumors				
Age	1.055	1.013	1.098	0.009
Septic shock	7.790	1.485	40.784	0.015
CVC-unrelated BSI	3.581	1.412	9.087	0.007
No solid tumors				
Age	1.040	1.010	1.070	0.008
Septic shock	6.595	2.810	15.475	< 0.001
Acute kidney failure	4.030	1.379	11.773	0.011

are in line with those reported by others [14, 15]. Recently, one study showed that the majority of BSIs due to *Candida* spp. occurred in patients hospitalized outside the ICU or the hematologic departments [15]. Despite this, a prospective multicentric study on oncologic patients with candidemia showed that hospitalization in ICU increased the mortality rate [4]. Overall, these data show that, regardless the patient's underlying disease, a low clinical performance status, as that observed in ICU patients, makes a difference on survival.

Second, ST patients removed the CVC later than other patients. Guidelines strongly recommend an early removal of CVC in the treatment of candidemia [8]. Several studies, including those conducted in patients with ST, showed an improvement of survival following an adequate control of the infection source [8, 16]. It must be noted however that in some circumstances, the central access is difficult to remove early due either to current chemotherapy or possible complications (i.e., thrombosis or risk of bleeding) which are not uncommon in these patients. It should be emphasized that in cases in which CVC removal is not feasible, an antifungal agent with good penetration into the biofilm is mandatory. One study evaluated two randomized clinical trials of patients with candidemia treated with echinocandins or liposomal amphotericin B and showed that early CVC removal was not associate with any clinical benefit [17].

Third, total parenteral nutrition (TPN) was more common in ST than in non-ST patients. A similar finding was reported by Puig-Asensio et al., in a prospective, population-based surveillance study of *Candida* BSI, in which ST patients were compared to hematologic patients [18]. It is interesting to note that TPN, which is mandatory in some types of patients, causes per se an increased risk for candidemia.

Fourth, there was a trend, although not statistically significant, of a more frequent use of appropriate therapy in ST patients. For this study, we defined drug appropriateness by considering only two characteristics: timing (drug given within 72 h from the first blood culture performed) and dosages, while we did not consider the type of antifungal utilized. In our series, fluconazole was the most used drug. Apparently, our therapeutic management did not strictly follow the current guidelines in which an echinocandin should be the preferred regimen in critical patients [6, 7]. One study analyzes risk factors and clinical outcome of candidemia in 3417 patients based on underlying malignancy and found that ST patients were treated mainly with fluconazole, similarly to candidemic patients without malignancy. On the opposite, the echinocandins were mainly used in hematological patients [4]. Overall, these data indicate that patients with ST are often considered not critical compared to hematological or ICU patients.

In this study, 30-day mortality was 49% in patients with ST and it was significantly higher than that reported in patients without ST. This finding is similar to previous studies, which found mortality rates in this population ranging from 30 to 50% [1, 4, 12, 18].

We observed two variables which were independently associated with mortality in the overall population: higher age and septic shock. Several studies have found that either advanced age or septic shock are often associated with increased mortality of candidemic patients including those with cancer [14, 19]. Interestingly, we found that a CVC-unrelated candidemia was an independent risk factor for mortality only in ST patients. This finding would suggest that primary infection in this type of patients influences heavily the outcome thereby suggesting either a more aggressive therapeutic approach in terms of drug timing (i.e., very early introduction), dosing (i.e., maximize the doses), and molecules (i.e., fungicidal vs fungistatic drugs) or a less time-consuming diagnostic work up (i.e., the use of antigens or DNA detection). Recently, Wu et al. analyzed the epidemiology of candidemia due to *Candida* species other than *C. albicans* in 346 subjects and found that patients with primary infection had higher mortality rate (47%) with respect to those with CVC-related candidemia (21%) [5]. Arias et al. compared mortality and epidemiology in patients with candidemia which was both related and unrelated to the CVC. In this study, patient survival remains poor after the removal of the CVC, probably because this population of patients was more seriously ill [20].

Our study has several limitations. First, since this was a retrospective and monocentric study, the conclusions may not be relevant to other patient populations. Second, although we have made every attempt to collect and analyze as many clinical data as possible to reveal useful information for the patient management, some variables could not be explored because of missing data. In this regard, it should be emphasized that data on involvement of target organs (i.e., eye and heart) were often difficult to identify from medical records and therefore, they were not considered in this study. Additionally, control blood cultures were not always performed after antifungal initiation thereby making

data on early clearance of *Candida* spp. from the blood lacking. Third, being a study encompassing several departments and medical disciplines over a 7-year period, there was not a univocal management of each individual case in terms of treatment.

In conclusion, we found that mortality due to candidemia is significantly higher in ST than in non-ST patients. Multivariate analysis confirmed that either higher age or septic shock was an independent risk factor for mortality in both groups of patients. Conversely, a CVC-unrelated candidemia represents an independent risk factor for mortality in ST patients. Overall, these data show that candidemia in ST patients is characterized by extremely high mortality rate and distinctive features.

Compliance with ethical standards

Ethical approval and informed consent The present research was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The Institutional Review Board of the Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I°-Lancisi-Salesi granted retrospective access to the data without the need for individual informed consent. The consent was not given since the data were analyzed anonymously.

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