Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2023, Vol. 51(1) 1–7

DOI: 10.1177/03000605221131122
journals.sagepub.com/home/imr
SAGE

Characteristics, risk factors, and outcomes of bloodstream *Candida* infections in the intensive care unit: a retrospective cohort study

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Abstract

Objective: The main objective was to assess the clinical characteristics, associated factors, and outcomes of patients admitted to the ICU for candidemia. The secondary objective was to examine the relationship of candidemia with the length of stay and mortality.

Methods: The analysis was a retrospective single-center cohort study addressing the effect of invasive candidemia on outcomes. This study was performed in a medical-surgical ICU located in a tertiary private hospital in São Paulo, Brazil. Data was collected through the review of the hospital database.

Results: In total, 18,442 patients were included in our study, including 22 patients with candidemia. The median age was similar in patients with and without candidemia [67 (56–84) vs. 67 (51–80)]. Most patients were male, and the proportion of men was higher among patients with candidemia (77% vs. 55.3%). The rates of renal replacement therapy (40.9% vs. 3.3%), mechanical ventilation (63.6% vs. 29.6%), and parenteral nutrition (40.9% vs. 4.8%) were higher in patients

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with candidemia than in those without candidemia. The mortality rate (77.3% vs. 11.9%) and length of hospital stay [42 days (23.0–78.8) vs. 8 days (5.0–17.0)] were significantly higher in patients with candidemia.

Conclusions: Patients with candidemia are prone to longer hospital stay and mortality. In addition, we found associations of candidemia with the use of invasive mechanical ventilation, renal replacement therapy, and parenteral nutrition.

Keywords

Infection, candidemia, invasive candidiasis, critical care, mechanical ventilation, renal replacement therapy, parenteral nutrition

Date received: 27 June 2022; accepted: 20 September 2022

Introduction

The prevalence of invasive fungal infections in the intensive care setting has increased significantly over time.[1–3] Previous studies suggested that broad-spectrum antibiotics, immunosuppression, central venous catheter placement, and parenteral nutrition were possible risk factors for this infection.[4,5]

Among the causative pathogens, *Candida* and *Aspergillus* species are the most prevalent, and the incidence of non-albicans *Candida*, especially *C. glabrata*, has increased in recent years.[6–9] Other causes include *Cryptococcus*, *Pneumocystis jirovecii*, *Penicillium marneffei*, *Zygomycetes*, *Fusarium*, and *Scedosporium*, but these pathogens mainly affect immunosuppressed patients.[10]

The mortality rates associated with candidemia remain above 40% despite advances in therapy.[10] In addition, candidemia is associated with an increase in the length of stay and consequently in treatment costs.[9,11–15] The high mortality might be associated with both resistance to azoles and echinocandin antifungal agents and diagnostic delays because culture has low sensitivity and usually requires more than 24 hours of incubation for positivity to be observed.[8,16–19]

Candidemia is a serious pathology, and its diagnosis is typically late because of the limitations of the diagnostic methods in addition to the risk factors for candidemia being extremely prevalent in critically ill patients. Therefore, the objective of this study was to describe the characteristics of this population in our service and compare these data with the available literature.

Materials and methods

Study design

This was a retrospective, single-center cohort that evaluated patients diagnosed with candidemia and correlated their characteristics with primary and secondary outcomes. The Local Ethics Committee at Hospital Israelita Albert Einstein approved the study protocol (CAAE: 20712919.9.0000.0071), and the need for informed consent from patients for publishing the study was waived as no patient data were being exposed.

For the present study, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed as recommended by the Equator Network for case–control studies.[20]

Setting

The study was conducted at a tertiary-level private hospital comprising 662 inpatient beds located in São Paulo, SP, Brazil. The intensive care unit (ICU), which follows an open model of patient care, features 49 beds and 91 step-down unit beds.

Patients

All consecutive patients aged 18 years or older who were admitted to the ICU with or without a diagnosis of candidemia between 1 January 2012 and 30 June 2019 were included in the analysis. There were no exclusion criteria; however, if any patient data were incomplete, then the affected variables were excluded.

Data collection and study variables

All data collected from the study were taken from the Epimed Monitor System® (Epimed Solutions, Rio de Janeiro, Brazil) which is an electronic data platform in which patient data are prospectively recorded by trained ICU personnel. All patient details were deidentified

The variables collected included age; gender; patient category (clinical or surgical); associated comorbidities; reason for ICU admission; patient origin (location of patient prior to ICU admission); Simplified Acute Physiology Score (SAPS) III at ICU admission; Sequential Organ Failure Assessment score; receipt of renal replacement therapy (RRT), mechanical ventilation (MV), and total parenteral nutrition (TPN); destination at ICU discharge; destination at hospital discharge, ICU mortality; in-hospital mortality; 28-day mortality; and length of stay in the ICU and hospital.

Definitions

Candidemia is diagnosed by isolating *Candida* species in the blood cultures of patients without clinical and laboratory evidence of secondary viscera foci.[21]

The diagnosis of catheter-related bloodstream infection requires a positive culture of blood from a peripheral vein and the catheter as the source. Diagnosis also requires a positive semi-quantitative (>15 CFU/catheter segment) or quantitative ($>10^3$ CFU/catheter segment) catheter tip culture and isolation of the same organism (species and antibiogram) from the catheter segment and peripheral blood culture.[22] Simultaneous quantitative paired blood cultures with a ratio exceeding 5:1 between the central vein catheter culture and peripheral blood culture or a differences in time to positivity whereby a non-quantitative blood culture drawn from the central vein catheter becomes positive at least 2 hours earlier than the peripheral blood culture are other diagnostic criteria.[22]

Microbiological methods

The culture medium used for *Candida* spp. in the institution was chromogenic and Sabouraud agar. Its identification was performed by MALDI-TOF (Bruker, Billerica, MA, USA; BioMérieux, Marcy-l'Étoile, France), and its sensitivity to antifungals was tested by microdilution in broth.

Statistical analysis

Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented as the median and interquartile range. Normality was assessed by the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-squared test or Fisher's exact test. Continuous variables were compared using the independent-samples *t*-test or Mann–Whitney U test in case of non-normal distribution.

Statistical tests were two-sided. $P < 0.05$ was considered statistically significant.

Statistical analyses were performed using R ver. 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 18,442 patients were included in our study, including 22 patients with invasive candidiasis (Figure 1). Concerning the distribution of *Candida*, we found *C. parapsilosis* (7/22; 31.8%), *C. albicans* (7/22; 31.8%), *C. glabrata* (4/22; 18.1%), *C. krusei* (1/22; 4.5%), *C. tropicalis* (1/22; 4.5%), *C. famata* associated with *C. parapsilosis* (1/22; 4.5%), and *C. glabrata* associated with *C. parapsilosis* (1/22; 4.5%). The median age was similar between patients with and without candidemia [67 years (56–84) vs. 67 years (51–80); $P = 0.14$]. Most patients included in both groups were male, but the proportion of men was higher in patients with candidemia ([17 (77%) vs. 10,181 (55.3%); $P = 0.63$]). SAPS III was clearly higher in patients with fungal infection ([64 (53–75) vs. 43 (33–55); $P < 0.01$]). In both groups, the admission was primarily for clinical reasons ([17 (77%) vs. 10,709 (58%); $P = 0.11$]).

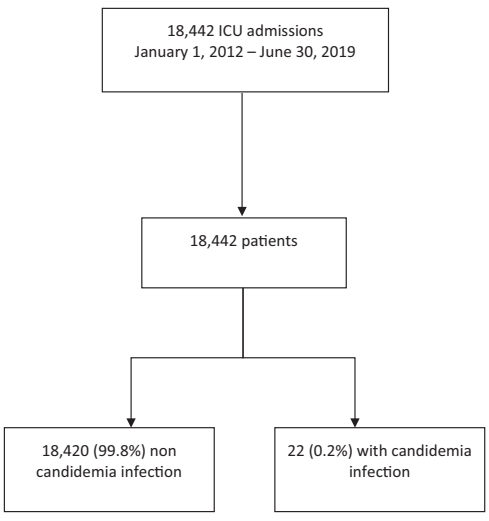

Figure 1. Patient details.

The rates of diabetes mellitus [6 (30%) vs. 5181 (32%); $P > 0.999$], hematologic malignancy [2 (10%) vs. 662 (4.1%); $P = 0.198$], and COPD [4 (20%) vs. 1570 (9%); $P = 0.123$] did not differ between the groups.

The rates of RRT [9 (40.9%) vs. 612 (3.3%); $P < 0.01$], MV [14 (63.6%) vs. 3617 (29.6%); $P < 0.01$], and TPN [9 (40.9%) vs. 893 (4.8%); $P < 0.01$] were higher in patients with candidemia. The rate of immunosuppression did not differ between the groups [5 (25.0%) vs. 2590 (16.0%); $P = 0.353$]. The characteristics of study participants are presented in Table 1.

Clinical outcomes are presented in Table 2. The mortality rate [17 (77.3%) vs. 2186 (11.9%); $P < 0.01$] and length of hospital stay [42 days (23.0–78.8) vs. 8 days (5.0–17.0); $P < 0.01$] were significantly higher in patients with candidemia.

Discussion

In this paper, the main finding was the marked association between candidemia and increased mortality risks. Other interesting findings were the longer length of stay; larger SAPS III; and associations of RRT, MV, and TPN with candidemia. Regarding the detected *Candida* specimens, our results agreed with previous findings of the high prevalence of *C. parapsilosis* in Brazil.[23]

Concerning mortality, in line with our findings, prior studies recorded invasive candidiasis rates of 40% to 60%.[24–27] Our findings regarding SAPS III were corroborated by Poissy *et al.*[28] Regarding risk factors, Wey *et al.* in 1989 and Poissy *et al.* in 2020 reported associations of candidemia with the use of TPN, MV, and RRT.[29,30] Along the same lines, Blumberg *et al.* observed that the use of TPN and RRT was associated with candidemia.[28]

Table 1. Characteristics of the study participants.

Characteristics	All patients n = 18,442	Candidemia n = 22	Non-candidemia infection n = 18,420	*P**
Age, years	67 (51–80)	67 (56–84)	67 (51–80)	0.14[a]
Men	10,198 (55.3%)	17 (77%)	10,181 (55.3%)	0.63[b]
SAPS III[§]	43 (33–55)	64 (53–75)	43 (33–55)	<0.01[a]
Reason for ICU admission				0.11[c]
Medical	10,726 (58%)	17 (77.3%)	10,709 (58%)	
Surgical	7710 (42%)	5 (22.7%)	7705 (42%)	
Underlying disease				
Diabetes mellitus	5187/16,164 (32%)	6/20 (30%)	5181/16,144 (32%)	>0.999[c]
Hematologic malignancy	664/16,164 (4.1%)	2/20 (10.0%)	662/16,144 (4.1%)	0.198[c]
COPD	1574/16,164 (9.7%)	4/20 (20.0%)	1,570/16,144 (9.7%)	0.123[c]
Support on ICU admission				
Renal replacement therapy	621/18,440 (3.4%)	9/22 (40.9%)	612/18,418 (3.3%)	<0.001[c]
Mechanical ventilation	3631/18,440 (19.7%)	14/22 (63.6%)	3617/18,418 (19.6%)	<0.001[b]
Parenteral nutrition	902/18,440 (4.9%)	9/22 (40.9%)	893/18,418 (4.8%)	<0.001[c]
Immunosuppression	2595/16,164 (16.1)	5/20 (25.0%)	2590/16,144 (16.0%)	0.353[c]

Data are presented as the median (interquartile range) or n (%). §: SAPS III ranges from 0 to 217, with higher scores indicating more severe illness and a higher risk of death* *P* was calculated using (a) an independent-samples *t*-test, (b) the chi-square test, or (c) Fisher's exact test.
SAPS III, Simplified Acute Physiology Score III; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.

Table 2. Clinical outcomes.

Characteristics	All patients 18,442 (100%)	Candidemia 22 (0.2%)	Non-candidemia infection 18,420 (99.8%)	*P**
Hospital mortality	2203/18,364 (12.0%)	17/22 (77.3%)	2186/18,342 (11.9%)	<0.001[a]
Length of hospital stay (days)	8.0 (5.0–17.0)	42.0 (23.0–78.8)	8.0 (5.0–17.0)	<0.001[b]

Data are presented as the median (interquartile range) or n (%).* *P* was calculated using the (a) chi-squared test or (b) Mann–Whitney *U* test.

Given the findings in both our study and the literature, the availability of commercial diagnostic methods providing the etiological diagnosis of *Candida* spp. and effective antifungal agents is essential because, as previously mentioned, one factor limiting treatment efficacy is the late diagnosis of candidemia, which in combination with the inherent severity of the fungal infection could result in greater mortality.

Finally, although the number of patients included is considerable, our study was limited by its retrospective protocol with a records review. Given the constant efforts to prevent bloodstream infections, it is possible, or even likely, that the findings reflect the actual clinical situation in our institution, although the need for prospective studies remains.

Conclusions

Fungal bloodstream infection might be associated with longer hospital stays as well as increased mortality. Among the risk factors, we found associations with the use of MV, RRT, and TPN.

Authors' contributions

FBH, RCFC, and TDC conceived the study hypothesis and design. FBH and RCFC collected and analyzed the data. FBH and RCFC wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript and assumed responsibility for the integrity of the data and the accuracy of the data analysis.

Availability of data and material

The datasets generated during and/or analyzed during the current study are not publicly available due to the risk of breach of patient data privacy but are available from the corresponding author on reasonable request.

Declaration of conflicting interests

The authors declare that they have no competing interests.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Resources for statistical analysis, impressions, and other costs were provided by the authors themselves.

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