Major Article

Evaluation of the predictive indices for candidemia in an adult intensive care unit

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ABSTRACT

Introduction: To evaluate predictive indices for candidemia in an adult intensive care unit (ICU) and to propose a new index. **Methods:** A prospective cohort study was conducted between January 2011 and December 2012. This study was performed in an ICU in a tertiary care hospital at a public university and included 114 patients staying in the adult ICU for at least 48 hours. The association of patient variables with candidemia was analyzed. **Results:** There were 18 (15.8%) proven cases of candidemia and 96 (84.2%) cases without candidemia. Univariate analysis revealed the following risk factors: parenteral nutrition, severe sepsis, surgical procedure, dialysis, pancreatitis, acute renal failure, and an APACHE II score higher than 20. For the *Candida* score index, the odds ratio was 8.50 (95% CI, 2.57 to 28.09); the sensitivity, specificity, positive predictive value, and negative predictive value were 0.78, 0.71, 0.33, and 0.94, respectively. With respect to the clinical predictor index, the odds ratio was 9.45 (95%CI, 2.06 to 43.39); the sensitivity, specificity, positive predictive value, and negative predictive value were 0.89, 0.54, 0.27, and 0.96, respectively. The proposed candidemia index cutoff was 8.5; the sensitivity, specificity, positive predictive value, and negative predictive value were 0.77, 0.70, 0.33, and 0.94, respectively. **Conclusions:** The *Candida* score and clinical predictor index excluded candidemia satisfactorily. The effectiveness of the candidemia index was comparable to that of the *Candida* score.

Keywords: Candidemia. Candidemia predictors. Risk factors. Bloodstream infection.

INTRODUCTION

In the United States, the incidence of fungal infections increased 207% between 1979 and 2000. *Candida* spp. is the most common causative agent of such infections, accounting for 80% of cases[1] Candidemia is considered to be the fifth to tenth most common cause of bloodstream infection in patients treated in intensive care units (ICUs)[2].

Colombo et al.[3] conducted a multicenter study in which the authors detected 712 cases of candidemia with an incidence density of 2.49 cases per 1,000 patients per day. Forty-six percent of the patients were staying in the ICU, whereas 39% were surgical patients. Compared with the United States, the incidence of candidemia in adult patients is higher in Brazil (0.46/1,000 versus 2.49/1,000, respectively). In both countries, candidemia represents the fourth most frequent cause of bloodstream infection[3]

Candidemia accounts for high mortality rates, typically when the onset of therapy is delayed for more than 48 hours[4] [5]. A positive blood culture for *Candida* spp. remains the gold standard for the diagnosis of candidemia[6]. However, this test cannot detect all cases of candidemia. Additionally, *Candida* spp. isolation may take too much time, thereby delaying effective antifungal therapy[7]. These difficulties have motivated the search for risk factors and candidemia-associated conditions that could help predict this opportunistic infection and design preemptive antifungal therapy.

One study analyzed 2,890 patients who remained in the ICU for at least four days in nine hospitals in the United States and Brazil. The authors proposed a clinical prediction rule for invasive candidiasis in the intensive care setting. The main risk factors were as follows: use of antibiotics, a central catheter, immunosuppressants or corticosteroids; previous surgery; pancreatitis; parenteral nutrition; and dialysis[8].

In 2009, León et al.[9] evaluated the use of the *Candida* score, an index that includes clinical data and multifocal colonization by *Candida* spp., to discriminate between *Candida* colonization and candidemia in non-neutropenic critically ill patients. The authors concluded that patients staying at the ICU for more than seven days but with a *Candida* score lower than 3 were at a 5% lower risk of candidemia[9].

Posteraro et al.[10] employed the beta-D glucan assay, colonization index, and *Candida* score to assess 377 patients

admitted to an ICU. The authors demonstrated that the *Candida* score provided the second best diagnostic yield: the negative predictive value was high (0.97), but the positive predictive value was low (0.57)[10].

The need for early therapy to treat invasive infection by *Candida* spp. motivated the present study. We investigated the risk factors for candidemia and evaluated the use of the two mentioned predictors of candidemia in an adult ICU setting in Brazil. In addition, we analyzed a new predictor, the candidemia index.

METHODS

Clinical setting, design, and study population

This prospective study aimed to compare a cohort of patients staying at the (ICU) of the University Hospital of the Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil (HC-FMRP-USP) for at least 48 hours. The study was conducted between January 2011 and December 2012.

The following data were collected for the participants: age, origin (clinical or surgical ward), underlying disease, central venous catheter, total parenteral nutrition, use of any type of dialysis, use of immunosuppressants (except corticosteroids), presence of neutropenia (<500 neutrophils/μL), previous surgery (any surgical procedure within the previous 30 days), presence of a site colonized by *Candida* (during ICU stay), intestinal perforation (up to seven days previously), APACHE II (Acute Physiology and Chronic Health Disease Classification System II) score higher than 20, and *Enterobacter* bacteremia (up to seven days previously).

The blood culture samples were processed on an automated BD® (Becton Dickinson, USA) system. The yeast isolated from the different samples was identified as *Candida* spp. by means of the standard procedures of a mycological laboratory and through the use of the VITEK 2® system (bioMérieux, France). The latter instrument was also employed to evaluate the *Candida* susceptibility to fluconazole.

The Ethics Committee of HC-FMRP-USP approved this study under Process number HCRP 6915/2010.

Definition of fungal colonization

Colonization was defined as *Candida* spp. isolation in some topography without causing disease in the host. We did not use active surveillance, but we evaluated the results obtained from cultures (urine, stool, tracheal secretion, and others) collected by an intensivist.

Calculation of the *Candida* score

The *Candida* score was calculated on the basis of the following score criteria: multifocal colonization (one score), surgery (one score), total parenteral nutrition (one score), and signs of severe sepsis (two scores), which amounted to five (5) scores[11].

Calculation of the clinical predictor index

The participants were classified as being at positive risk for candidemia when they were receiving systemic antibiotics or had a central venous catheter as well as at least two of the following risk factors: parenteral nutrition (minimum of three days), dialysis (minimum of three days), surgery (within seven days previously), pancreatitis (within seven days previously), corticosteroids (minimum of three days), and any other immunosuppressants (minimum of seven days). All of the patients were classified (positive or negative risk) according to these criteria[8].

Calculation of the candidemia index

This study evaluated an alternative criterion to predict candidemia using 16 factors assessed: each factor or condition that was present in the patient was awarded a score of one (total = 16). Patients were classified after 48 hours in the ICU. Only one classification was performed per patient according to the inclusion criteria. Patients were excluded if they had stayed at the ICU less than 48 hours or were hematological patients who had not developed neutropenia (<500 neutrophils/uL) during hospitalization. The risk factors analyzed may have first presented in the ICU or in the patient's original ward. More specifically, the following risk factors were analyzed: parenteral nutrition (minimum of three days), surgery (within the previous seven days), severe sepsis (with organ dysfunction), broad-spectrum antibiotics (previous use, up to 30 days, of fourth-generation cephalosporins, carbapenems or glycopeptides), central venous catheter (fitted during hospital stay), immunosuppressants (minimum of seven days), dialysis (minimum of three days), pancreatitis (within the previous seven days), corticosteroids (minimum of three days), acute renal failure (during hospital stay), intestinal perforation (during hospital stay), nosocomial infection (during hospital stay), APACHE score >20, *Enterobacter* bacteremia (during hospital stay), fungal colonization (evaluated during the ICU stay), and neutropenia (during the ICU stay). The receiver operating curves (ROC) was constructed to establish the best cutoff point for this index to predict candidemia.

Statistical analysis

To verify the association between the variables, the Fisher's exact test was employed. This procedure was conducted using the software SAS® 9.2 (Statistical Analysis System, USA) and PROC FREQ. Comparison between the *Candida* score groups and the candidemia index relied on the Mann-Whitney test for independent samples.

RESULTS

Participant characteristics

This study included 114 adult patients with a mean age of 57.8 years. Clinical patients represented 57.9% of the study population; the mean APACHE II score was 24.3, and the mean death risk was 49%. Blood culture revealed 18 cases of candidemia, whereas 96 patients did not present with this condition **(Table 1)**. The length of stay at the adult ICU was approximately the same for all the participants regardless of invasive infection by *Candida*, but the mortality was higher (61.1%) in the group with candidemia.

TABLE 1 - Clinical and demographic characteristics of the study population according to the presence or absence of candidemia among patients admitted to the adult intensive care unit.

Characteristics	Proven candidemia (n = 18)	No candidemia (n = 96)
Age	n	n
mean	55.7	58.3
maximum	89	94
minimum	21	16
Sex	n (%)	n (%)
female	7 (38.8)	55 (57.3)
male	11 (61.1)	41 (42.7)
Origin	n (%)	n (%)
clinical ward	11 (61.1)	55 (57.3)
surgical ward	7 (38.9)	41 (42.7)
APACHE II	Score	Score
mean	28.0	23.6
maximum	46	42
minimum	21	5

APACHE II: acute physiology and chronic health evaluation II.

TABLE 2 - Risk factors for candidemia in patients admitted to the adult intensive care unit.

Risk Factors	Proven candidemia (n = 18)		No candidemia (n = 96)		p-value
	n	%	n	%	
Parenteral nutrition	12	66.6	21	21.9	<0.01[+]
Surgery	9	50.0	45	46.9	0.01[+]
Severe sepsis*	18	100.0	52	54.2	<0.01[+]
Previous antibiotics	18	100.0	93	96.9	0.99
Central venous catheter	18	100.0	93	96.9	0.99
Immunosuppressor**	4	22.2	10	10.4	0.23
Dialysis	13	72.2	34	35.4	0.01[+]
Pancreatitis	2	11.1	0	0.0	0.02[+]
Corticosteroid	9	50.0	56	58.3	0.61
Renal failure	16	88.9	47	48.1	<0.01[+]
Neutropenia	2	11.1	1	1.0	0.41
Intestinal perforation	1	5.5	7	7.3	0.99
Hospital infection	17	94.4	70	72.9	0.07
APACHE II > 20	18	100.0	69	71.9	0,01[+]
Enterobacter bacteremia	5	27.8	29	30.2	0.99
Fungal colonization	11	61.1	39	40.6	0.13

APACHE II: acute physiology and chronic health evaluation II. *Defined as sepsis with organ dysfunction. **Excluding the use of corticosteroids. [+]Statistical significance at p < 0.05.

With respect to the underlying disease, 11 (61.1%) patients with candidemia had neoplasia. Six (54.5%) and five (45.5%) of the patients with candidemia had hematological and solid organ malignancies, respectively.

Microbiological data

Blood cultures isolated *Candida albicans* (n= 7; 36.8%), *Candida tropicalis* (n = 5; 26.3%), *Candida glabrata* (n = 3; 15.7%), *Candida krusei* (n = 1; 5.2%), *Candida parapsilosis* (n = 1; 5.2%), *Candida rugosa* (n = 1; 5.2%), and *Candida lipolytica* (n = 1; 5.2%).

With respect to sensitivity, all samples of *Candida albicans, Candida tropicalis,* and *Candida parapsilosis* were susceptible to fluconazole. However, 7 *Candida krusei* samples were resistant to fluconazole (63.6%): 3 urine culture samples, 2 tracheal secretion samples, 1 blood culture sample and 1 catheter tip sample. All of the samples of *Candida glabrata* were sensitive to fluconazole. The sensitivity and resistence to fluconazole were 94.34% and 5.66%, respectively.

Analysis of risk factors for candidemia

Univariate statistical analysis was used to evaluate whether the studied risk factors associated with candidemia were associated with parenteral nutrition (p < 0.01), surgical procedures (p = 0.01), severe sepsis (p < 0.01), dialysis (p = 0.01), pancreatitis (p = 0.02), acute renal failure (p < 0.01), or an APACHE II score higher than 20 (p = 0.01) (**Table 2**).

Performance of the *Candida* score and clinical predictor index

The incidence of invasive candidemia was 0%, 13% (four cases), 26% (six cases), 38.8% (seven cases), and 100% (one case) in patients with *Candida* scores of 0, 1, 2, 3, 4, and 5, respectively.

Table 3 lists the application of the *Candida* score and the clinical predictor index to all of the patients included in the study. The *Candida* score was statistically significant for the presumptive diagnosis of candidemia (p < 0.01), and the odds ratio was 8.50 [95% confidence interval (CI)], from 2.57 to 28.09); the sensitivity, specificity, positive predictive value, and negative predictive value were 0.78, 0.71, 0.33, and 0.94, respectively.

The clinical predictor index was also statistically significant for the presumptive diagnosis of candidemia (p < 0.01), and the odds ratio was 9.45 (95% CI, from 2.06 to 43.39); the sensitivity, specificity, positive predictive value, and negative predictive value were 0.89, 0.54, 0.27, and 0.96, respectively (**Table 3**).

Performance of candidemia index compared with the *Candida* score

The ROC curve (**Figure 1**) aided the estimation of the best cutoff point, 8.5, for the candidemia index. The sensitivity,

TABLE 3 - Prediction of candidemia by the *Candida* score and clinical predictor index in patients admitted to the adult intensive care unit.

Evaluated score	Proven candidemia (n = 18)		No candidemia (n = 96)		P-value	Odds ratio (CI = 95%)
	n	%	n	%		
Candida score						
Candida score ≥3	14	77.8	28	29.2	P < 0.01[+]	8.50 (2.57; 28.09)
Candida score <3	4	22.2	68	70.8		
Clinical predictor index						
positive	16	88.9	44	45.8	P < 0.01[+]	9.45 (2.06; 43.39)
negative	2	11.1	52	54.2		

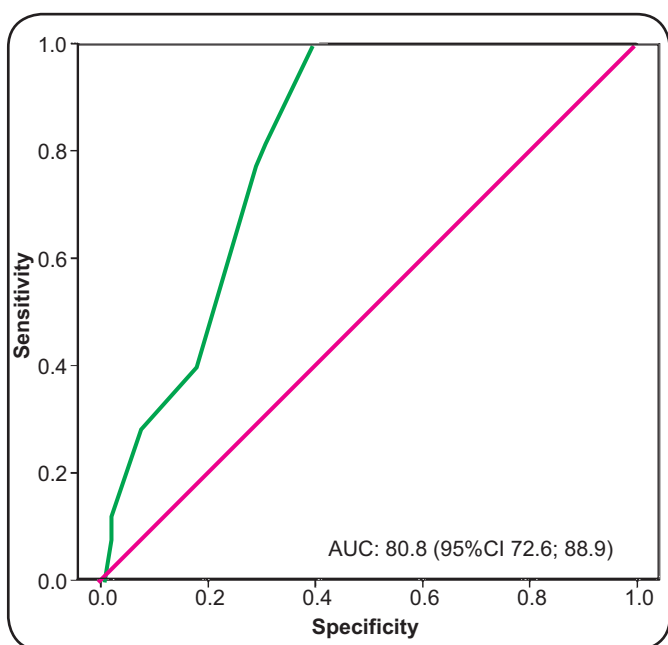**CI**: confidence interval. [+]Statistical significance at p < 0.05.

FIGURE 1 - ROC curve for the total score (candidemia index) obtained from the patients according to the number of risk factors for candidemia. **AUC:** area under the curve; **CI**: confidence interval; **ROC:** receiver operating curves. *Value with best sensitivity and specificity.

FIGURE 2 - *Box plot* of the relationship between the total score (candidemia index) and the candida score. [+]Statistical significance at p < 0.05.

specificity, positive predictive value, and negative predictive value were 0.77, 0.70, 0.33, and 0.94, respectively. The area under the curve (AUC) was 80.8, with a 95% confidence interval (72.6; 88.9). The total score statistically correlated (p < 0.01) with cutoff point 3 of the *Candida* score (**Figure 2**).

DISCUSSION

The main achievement of this study was to validate predictive indices that are particularly useful to exclude candidemia in patients admitted to the ICU of a tertiary hospital located in the interior of Brazil.
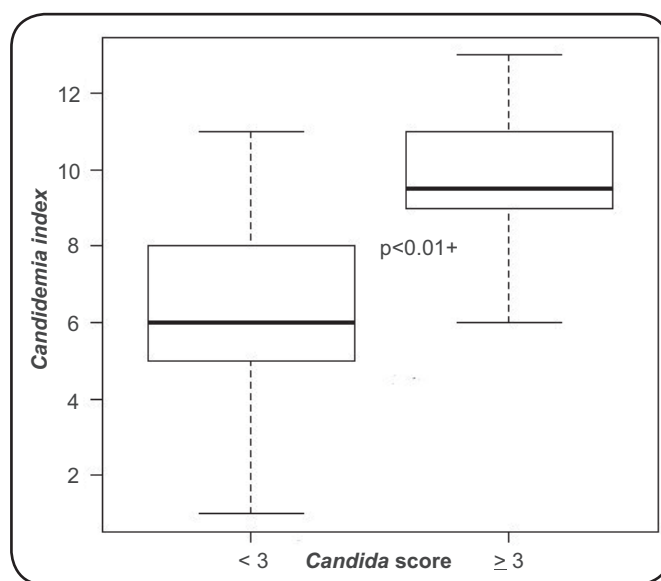
With respect to severity, the group with candidemia exhibited a higher mean APACHE II score than the group without candidemia. Therefore, patients who acquired candidemia exhibited more critical conditions, which could imply more interventions, such as the frequent use of invasive procedures. Fraser et al.[12] demonstrated that mortality in candidemia patients is directly related to the APACHE II score[12].

In the present study, neoplasia was the most prevalent underlying disease among patients with candidemia. Han et al.[13] reported similar findings, in which candidemia patients had more malignant neoplasms compared to non-candidemia patients[13]. When Ostrosky-Zeichner et al.[8] validated the clinical predictor index for candidemia, they also identified neoplasm as a risk factor[8].

Analysis of the patients' progression revealed a mortality of 61.1% among subjects with candidemia. Various studies have

also verified a general mean mortality rate and an attributed mortality rate of approximately 60% and 40%, respectively, among patients with candidemia[9][14].

Among the risk factors investigated in the present study, we found that parenteral nutrition, severe sepsis, surgical procedures, dialysis, pancreatitis, acute renal failure, and an APACHE II score higher than 20 were associated with candidemia (**Table 3**). Blumberg et al.[15] identified parenteral nutrition [relative risk (RR) = 3.6], acute renal failure (RR = 4.2), and previous surgical procedures (RR = 7.3) as risk factors for candidemia[15]. Cheng et al.[16] and Mokadas et al.[17] also demonstrated that renal failure was an independent risk factor for the onset of candidemia[16][17].

In a prospective cohor1t study, León et al.[11] also identified parenteral nutrition, severe sepsis, and multifocal *Candida* colonization as risk factors[9][11]. In 2009, this same team validated the *Candida* score and reported a relative risk of 5.9 for the occurrence of candidemia when the total score was equal to or higher than 3. Here, the *Candida* score provided similar results to those obtained in the validation conducted by those authors[9][11]: sensitivity 0.78 vs 0.77, specificity 0.71 vs 0.77, positive predictive value 0.33 vs 0.13, and negative predictive value 0.94 vs 0.97.

In the present study, the incidence of candidemia was low (5%) when the *Candida* score was less than 3 and 33% when the *Candida* score was equal to or higher than 3. Leroy et al.[18] reported incidences of candidemia of 0%, 17.6%, and 50% in patients with scores of 2 or 3, 4, and 5, respectively[18]. These data confirmed that the *Candida* score successfully excluded candidemia at the bedside.

Ostrosky-Zeichner et al.[8] described parenteral nutrition, pancreatitis, dialysis, previous surgery, and the use of antimicrobials, central venous catheters, immunosuppressants, or corticosteroids as risk factors for candidemia[8]. The clinical predictor index proposed by those authors was evaluated for the patients in the present study and provided increased sensitivity and reduced specificity. The parameters obtained by Ostrosky-Zeichner et al.[8] and this study for the clinical predictor index were sensitivity 0.43 vs 0.89, specificity 0.90 vs 0.54, positive predictive value 0.01 vs 0.27, and negative predictive value 0.97 vs 0.96, respectively.

We assessed a newly proposed index that considered the total score (candidemia index) of each patient included in the study; we adopted a cutoff point of 8.5. In these conditions, the candidemia prediction was similar to that achieved with the *Candida* score[9]. We verified a high correlation between the candidemia index proposed here and the *Candida* score. The candidemia index must be validated through studies involving a larger number of participants and evaluating different weights for each risk factor.

In conclusions, our data determined that the risk factors associated with candidemia were similar to those observed in hospitals of other geographic regions. The *Candida* score and the clinical predictor index performed well, which suggested that they might be useful in the clinical setting, especially to exclude candidemia. The candidemia index, a new predictive index for candidemia based on risk factors, was comparable to the *Candida* score.

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