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Prediction of candidemia in pediatric patients based on central venous catheter: Real world evidence to guide antifungal empirical prescription

Predição de candidemia em pacientes pediátricos baseada em cateter venoso central: Evidências do mundo real para orientar a prescrição empírica de antifúngicos

Predicción de candidemia en pacientes pediátricos basada en catéter venoso central: Evidencia del mundo real para guiar la prescripción empírica de antimicóticos

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Abstract
Background: Candida is one of the main etiological agents of bloodstream nosocomial infections, and is associated with high morbidity/mortality in children. High use of empirical antifungals incurs in higher health care costs and concerns on emergent resistant Candida spp. Therefore, a prediction model should optimize prescribing empirical antifungals in pediatrics. Objective: Based on real-world evidence data, we aimed at assessing how accurate is a regression model for predicting central venous catheter (CVC) candidemia in pediatric patients. We also explored how this prediction model might be useful for prescribing antifungals empirically. Methods: A case-control study was conducted based on 144 patients with positive and negative blood cultures for Candida spp.. A model for predicting Candida spp. was developed through univariate and multivariate analyses (logistic regression). Data were reported as odds ratio (OR) and p-value less than 0.05 was considered statistically significant. Results: Candidemia was predicted by the presence of CVC (OR 2.561, p=0.0042). For this model, an area under the curve (AUC) of 0.550 (p=0.314) was estimated, representing the Receiver Operating Characteristic curve of the present study, with a sensitivity of 86% and a specificity of 24%. Conclusion: Our study demonstrated that CVC is a fragile predictor for candidemia, however, its clinical significance and low specificity obtained in the ROC curve suggests that other covariates rather than those investigated should be considered to assess its impact on a prediction model for pediatric patients.
Keywords: Candidemia; Antifungal agents; Central venous catheterization; Hospitals, Pediatric.

Resumo
Introdução: A *Candida* é um dos principais agentes etiológicos das infecções nosocomiais da corrente sanguínea, estando associada a elevada morbimortalidade em crianças. O alto uso de antifúngicos empíricos incorre em custos altos de saúde e preocupações com *Candida spp* resistente emergente. Portanto, um modelo de predição deve otimizar a prescrição de antifúngicos empíricos em pediatria. Objetivo: Considerando dados de evidências do mundo real, objetivamos avaliar a precisão de um modelo de regressão para prever candidemia por cateter venoso central (CVC) em pediatria. Também exploramos como esse modelo pode ser útil para prescrever antifúngicos empiricamente. Métodos: Foi realizado um estudo caso-controle com 144 pacientes com hemoculturas positivas e negativas para *Candida spp*. Um modelo para prever *Candida spp*. foi desenvolvido por meio de análises univariadas e multivariadas

(regressão logística). Os dados foram relatados como odds ratio (OR) e valor de p inferior a 0,05 foi considerado estatisticamente significativo. Resultados: Candidemia foi predita pela presença de CVC (OR 2,561, p=0,0042). Para este modelo, estimou-se uma área sob a curva (AUC) de 0,550 (p=0,314), representando a curva Receiver Operating Characteristic do presente estudo, com sensibilidade de 86% e especificidade de 24%. Conclusão: Nosso estudo demonstrou que o CVC é um preditor frágil para candidemia, porém, sua significância clínica e baixa especificidade obtida na curva ROC sugere que outras covariáveis além das investigadas devem ser consideradas para avaliar seu impacto em um modelo de predição para pacientes pediátricos.
Palavras-chave: Candidemia; Antifúngicos; Cateterismo venoso central; Hospitais pediátricos.

Resumen
Introducción: *Candida* es uno de los principales agentes etiológicos de infecciones nosocomiales del corriente sanguínea, asociada con una elevada morbimortalidad en niños. El alto uso de antifúngicos empíricos conlleva costos elevados para la salud y preocupaciones sobre *Candida spp* resistente emergente. Por lo tanto, un modelo de predicción debería optimizar la prescripción de antifúngicos empíricos en pediatría. Objetivo: Considerando datos de evidencia del mundo real, nuestro objetivo es evaluar la precisión de un modelo de regresión para predecir candidemia por catéter venoso central (CVC) en pediatría. También exploramos cómo este modelo puede ser útil para prescribir antifúngicos empíricamente. Métodos: Se realizó un estudio de caso-control con 144 pacientes com hemocultivos positivos y negativos para *Candida spp.* Un modelo para predecir *Candida spp*. se desarrolló mediante análisis univariados y multivariados (regresión logística). Los datos se informaron como odds ratio (OR) y valor de p inferior a 0,05 se consideró estadísticamente significativo. Resultados: La candidemia fue predicha por la presencia de CVC (OR 2.561, p=0.0042). Para este modelo se estimó un área bajo la curva (AUC) de 0,550 (p=0,314), representando la curva de Característica Operativa del Receptor del presente estudio, con sensibilidad del 86% y especificidad del 24%. Conclusión: Nuestro estudio demostró que el CVC es un predictor frágil de candidemia, sin embargo, su significado clínico y la baja especificidad obtenida en la curva ROC sugieren que se deben considerar otras covariables además de las investigadas para evaluar su impacto en un modelo de predicción para pacientes pediátricos.
Palabras clave: Candidemia; Antifúngicos; Cateterismo venoso central; Hospitales pediátricos.

1. Introduction

Candida species are one of the main etiologic agents of nosocomial bloodstream infections and are associated with high morbidity and mortality in children and adults (Chakrabarti et al., 2020; Gebremicael et al., 2023; Motta et al., 2017). The overall incidence of candidemia in pediatrics is higher to the number seen in adults (40 vs 30 cases, respectively, per 100,000 admissions). More specifically, newborns are the most frequently affected population, with an incidence around four times greater than that observed in older children (Hope et al., 2012).

Despite *Candida albicans* has been considered the most common cause of fungal infection, the isolation of non-albicans *Candida* such as *Candida glabrata*, *Candida tropicalis, Candida parapsilosis*, and *Candida krusei* have been increasingly reported in the last years. Furthermore, resistance to fluconazole and other azoles, especially from non-albicans Candida, has become a challenge. This may be due to the increased empirical use of antifungal agents, mainly fluconazole (Behera et al., 2020; Reda et al., 2023).

There are guidelines that recommend the use of scoring tools, such as the Candida score, and biomarkers such as β-D-glucan; however, the criteria for indication and duration of empirical antifungal therapy remains undetermined. Identification of more accurate predictors can promote the more judicious use of empirical antifungals(Carr, Colley, Berhe, & Nguyen, 2018; Keighley et al., 2021).

This study is justified by the frequent empirical use of antifungals against candidemia, incurring in higher health care costs and concerns on emergent resistant *Candida spp*. Additionally, studies on pediatric patients in tropical countries are still scarce in literature. Thus, a case-control study was performed to evaluate the predictors that predict empirical use for candidemia in critical and non-critical pediatric patients and that can be applied in clinical practice to aid decision-making.

2. Methodology

This is a case-control stud, conducted according to Toassi (2021) (Toassi & Petry, 2021) y carried out in the largest exclusively pediatric hospital in Brazil, located in Curitiba, with 372 beds, 62 intensive care unit (ICU) beds and 32 pediatric specialties. The present study was approved by the Ethics Committee of the Pequeno Príncipe Hospital, Brazil (Protocol No. CAAE 39194420.1.0000.5580).

The study sample consisted of 144 participants admitted to the hospital, divided into 2 groups. Pediatric patients who presented candidemia (verified with positive blood cultures for Candida in samples collected from peripheral vein and/or catheter) were included in the case group, while, pediatric patients with negative blood cultures and in empirical use of micafungin, voriconazole, amphotericin B deoxycholate, liposomal amphotericin B and/or amphotericin B lipid complex were included in the control group.

2.1 Data collection

This retrospective, single-center, study was approved by the institutional review board (Protocol No. CAAE 39194420.1.0000.5580. Data were extracted during March 2014 to September 2017 and January to September 2020 from electronic health records.

The data collected for both groups were baseline variables (number of registers, initials of name, gender and age), laboratory results (neutrophil value and isolated fungus) and clinical data (ICU admission, length of stay, specialty, antimicrobials, corticosteroids, gastric protector, biofilm detection (only patients admitted after 2020, when biofilm evaluation was incorporated in institution), presence of central venous catheter, dialysis, total parenteral nutrition, mechanical ventilation, abdominal surgery and death) (see more in Table 1 and supplementary material).

Table 1 - Criteria for each variable included in the study.

Parameter	Criteria
Antimicrobial use	Greater or equal to 7 days of use of some antimicrobial, except prophylatics; whether there is an association with another antimicrobial; which day of treatment (if there is association – we considered the day of the antimicrobial that has been prescribed for the longest time) (ZAOUTIS; OPINION, 2010).
Broad-spectrum antimicrobial	According to the institution's clinical practice, the following drugs were classified as broad-spectrum antimicrobials: cefepime, ciprofloxacin, piperacillin+tazobactam, meropenem, vancomycin, linezolid and aztreonam. If there was at least one of these antimicrobials in the association, the combination was considered to have a broad spectrum.
Corticosteroid	Up to 15 days before confirmed candidemia or initiation of empirical antifungal; which day of corticosteroid use in relation to the day of confirmation of candidemia or initiation of the empirical antifungal (MOTTA et al., 2016; FRANÇA, RIBEIRO; QUEIROZ-TELLES, 2008; ZAOUTIS et al., 2004; ZAOUTIS et al., 2010).
Mechanical ventilation	At least within 24 hours up to 14 days before confirmation of candidemia or initiation of empirical antifungal (MOTTA et al., 2016; FRANÇA, RIBEIRO; QUEIROZ-TELLES, 2008).
Central venous catheter	At least within 24 hours up to 14 days before confirmation of candidemia or initiation of empirical antifungal (MOTTA et al., 2016; FRANÇA, RIBEIRO; QUEIROZ-TELLES, 2008).
Total parenteral nutrition	At least within 24 hours up to 14 days before confirmation of candidemia or initiation of empirical antifungal (MOTTA et al., 2016; FRANÇA, RIBEIRO; QUEIROZ-TELLES, 2008).
Gastric protection medication	Up to 15 days before confirmation of candidemia or initiation of empirical antifungal; day of use of the gastric protection medication in relation to the day of confirmation of candidemia or initiation of empirical antifungal agents.
Abdominal surgery	Up to 30 days prior to confirmed candidemia or initiation of empirical antifungal medication (ZAOUTIS et al., 2004).
Dialysis	At least 72 hours before, up to 15 days before the initial candidemia or initiation of empirical antifungal medication (FRANÇA, RIBEIRO; QUEIROZ-TELLES, 2008).
Neutrophil value	At least 72 hours before, up to 15 days before the initial candidemia or initiation of empirical antifungal medication (FRANÇA, RIBEIRO; QUEIROZ-TELLES, 2008). Neutropenia defined according to the reference value used in the laboratory of the hospital (varies with age group) and severe neutropenia when the number of neutrophils is less than $500/mm^3$.

Source: Produced by the authors (2020).

2.2 ***Data analysis***

After collecting the data, a descriptive analysis was conducted, in which categorical variables were presented as absolute and relative frequency, whilst, numeric variables were expressed, according to Kolmogorov-Smirnov normality test, as mean and standard deviation (SD) or median with interquartile interval (IQR 25%-75%).

Then, univariate analysis were carried out in order to correlate independent variables with candidemia. For this, chi-square test, t-test and Mann Whitney test were performed. Variables with a p-value less than 0.20 were included to multivariate analysis using logistic regression. Moreover, sensitivity analysis was conducted including some independent variables previously reported in other studies of literature.

Values of odds ratio (OR) superior to 1 demonstrate candidemia predisposition in uni and multivariate analysis. Furthermore, p<value inferior to 0.05 were considered as statistically significant.

In addition, Kaplan-Meier survival curve was plotted to compare groups, considering $p<0.05$ as significantly for Log Rank, Breslow and Tarone-Wave, and Receiver Operating Characteristic (ROC) curve was calculated to evaluate the sensitivity and specificity of the model. The ROC curve is used for evaluating the performance of binary classificiation algorithms and varied from 0 to 1. When $0.5<AUC<1$, there is a high chance that the classifier will be able to distinguish the positive class values from the negative class values.

All analysis were performed with IBM® Statistical Package for Social Sciences® software, SPSS® Statistics 20.0.

3. Results and Discussion

The sample was mainly composed by patients admitted with cancer or bone marrow transplant (BMT), having in average 2 years old (range 0 to 7 years), as demonstrated in Table 2. Still, 81 patients were admitted to the intensive care unit (ICU). Of these, 38 (52.8%) are patients with candidemia and 43 (59.7%) are patients using empirical antifungal agents. The median ICU stay for patients with confirmed candidemia was 18 days; while for patients without candidemia was 12 days.

Table 2 - Descriptive analysis of patient demographics.

Character	Case group (n=72)	Control group (n=72)
Basic characteristics		
Male	38 (52,8%)	36 (50,0%)
Age (years) (median)	1 (0-7)	2 (0-7)
Specialty		
Bone marrow transplant/Oncology	23 (44,2%)	29 (55,8%)
Cardiopulmonary	14 (19,4%)	21 (29,2%)
Neurology	12 (16,7%)	9 (12,5%)
Gastroenterology	10 (13,9%)	3 (4,2%)
Nephrology/Genitourinary tract	5 (6,9%)	5 (6,9%)
Infectious disease	2 (2,8%)	2 (2,8%)
Immunology	1 (1,4%)	2 (2,8%)
Prematurity	3 (4,2%)	-
Genetic	1 (1,4%)	-
Orthopedic	1 (1,4%)	-
Rheumatology	-	1 (1,4%)
Assistance characters		
Intensive care unit admission	38 (52,8%)	43 (59,7%)
Intensive care unit days (median)	18 (7-41)	12 (7-26)
Length of stay in hospitals	17 (6-42)	17 (9-32)
Central venous catheter (days)	62 (86,1%)	55 (76,4%)
Total parenteral nutrition (days)	15 (20,8%)	17 (23,6%)
Mechanical ventilation (days)	25 (34,7%)	32 (44,4%)
Abdominal surgery	9 (12,5%)	9 (12,5%)

Duration of antimicrobial therapy (days)	15 ± 11	12 ± 6
Antimicrobial association	14 (42,4%)	24 (51,1%)
Broad-spectrum antimicrobial	31 (43,0%)	32 (44,4%)
Corticosteroids	14 (19,4%)	15 (20,8%)
Duration of costicosteroids (days)	7 ± 6	10 ± 5
Dialysis	4 (5,6%)	9 (12,5%)
Duration of gastric protector (days)	40 (55,6%)	34 (47,2%)
Duration of gastric protector	9 ± 6	10 ± 5
Neutropenia	24 (33,3%)	20 (27,8%)
Severe neutropenia	16 (22,2%)	13 (18,1%)
Death	20 (27,8%)	21 (29,2%)

Source: Produced by the authors (2020).

The majority of included patients (n=117) was using central venous catheter (CVC), mainly for more than 7 days (case group: 90.3% and control group: 81.8%). Broad-spectrum antimicrobials was used in 43% of the case group and 44% of the control group, especially piperacillin+tazobactam (n=16, 15,4%), and meropenem (n=12, 11,5%).

Biofilm detection was indicated for 25 patients of case group, of which, 15 were positive for Candida spp.. Regarding the isolated *Candida* species, *C. parapsilosis* the most predominant (40.2%), followed by *C. albicans* (25%) and *C. tropicalis* (20,8%). The number identified for the other species is presented below: *C. glabrata* (4,2%), *C. haemulonii* (2,8%), *C. guilliermondii* (2,8%), *C. fabianii* (1,4%), *C. kefyr* (1,4%) and *C. lusitaniae* (1,4%).

The predictors associated with candidemia by univariate and multivariate analysis are demonstrated in Table 3. Predictors such as the presence of a CVC, association of antimicrobials and dialysis were eligible for multivariate analysis (they presented p-values<0.2).

Table 3 - Regression analysis for candidemia.

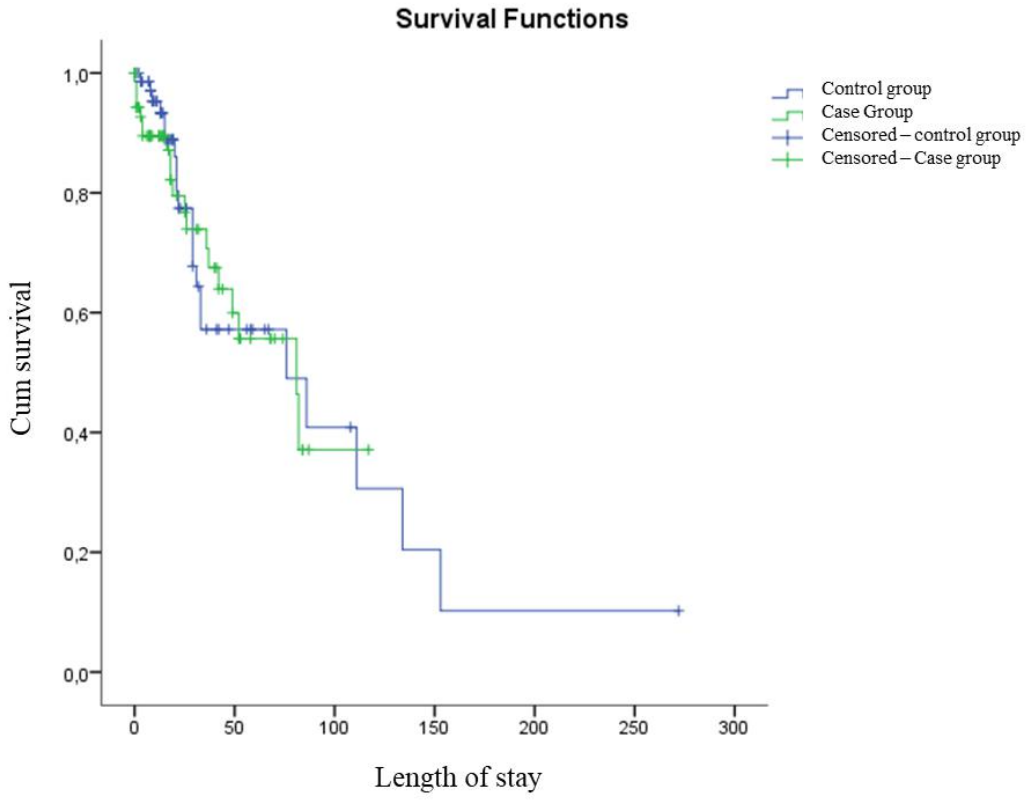
Classification	**N**	**Univariate analysis**			**Multivariate analysis**		
		OR	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
Male	74	1.1	0.6-2.1	0.739			
13 -18 years	20	—	—	0.345			
6 -12 years	23	0.8	0.2-2.6	0.697			
3 - 5 years	20	1.8	0.5-6.4	0.344			
29 days- 2 years	64	0.7	0.6-4.3	0.380			
0 - 28 days	17	0.8	0.2-2.5	0.550			
ICU admission	81	0.7	0.4-1.4	0.401			
Central venous catheter	117	1.9	0.8-4.5	**0.139**	2.6	1.0-6.3	**0.042**
Total parenteral nutrition	32	0.8	0.4-1.9	0.689			
Mechanical ventilation	57	1.5	0.8-2.9	0.234	0.6	0.3-1.3	0.227
Abdominal surgery	18	1.0	0.4-2.7	1.000			
Neutropenia	44	0.8	0.4-1.6	0.470	0.8	0.4-1.7	0.585
Antimicrobial association	38	1.8	0.8-3.8	**0.133**	2.1	0.9-4.7	0.071
Broad-spectrum antimicrobial	63	0.7	0.3-1.3	0.240			
Corticosteroids	29	0.9	0.4-2.1	0.835			
Dialysis	13	2.4	0.7-8.3	**0.156**	0.4	0.1-1.5	0.162
Gastric protector	70	1.4	0.7-2.7	0.318			
Prematurity comorbidity	3	0.5	0.1-5.6	0.567			
Infectious disease	4	1.0	0.1-7.3	1.000			
Nephrology/Genitourinary tract comorbidity	10	0.4	0.1-1.6	0.202			
Immunology comorbidity	3	0.5	0.1-5.6	0.567			
Neurology comorbidity	21	1.8	0.7-4.5	0.242			
Oncology/BMT comorbidity	52	1.0	0.5-2.0	1.000			
Gastroenterology comorbidity	12	0.7	0.2-2.3	0.548			
Cardiopulmonary comorbidity	35	1.3	0.6-2.7	0.560			

Note: OR, *odds ratio*; IC, confidence interval; ICU, intensive care unit; BMT, bone marrow transplant; In bold: p-value < 0,20. Source: Produced by the authors (2020).

Neutropenia and mechanical ventilation, even not being significant variables in the univariate analysis, were associated with the other variables in sensitivity analysis, based on clinical practice, and on other studies in the literature (Ahangarkani et al., 2020; Chakrabarti et al., 2020; Filioti et al., 2007; Lass-Flörl, 2010; Motta et al., 2017; T. Zaoutis, 2010; T. E. Zaoutis et al., 2004; T. E. Zaoutis et al., 2010). The multivariable regression suggested that presence of CVC was an independent predictor (OR 2.6, 95% CI 1.0-6.3, p-value=0.042) and was considered for building a ROC curve.

Furthermore, the Kaplan-Meier survival curve (Figure 1) demonstrated that there is no difference in survival between patients with or without candidemia (Log Rank: p=0.774, Breslow: p=0.393, Tarone-Ware: p=0.580). Based on the results of the logistic regression model, a ROC curve was performed considering CVC as factor. An area under curve of 0.55 was estimated (AUC=0.55, p = 0.314, 95% IC = 0.454-0.643), with 86% of sensitivity and 24% of specificity.

Figure 1 - Overall survival analysis case (green) and control group (blue).



Source: Produced by the authors (2020).

Our study demonstrated that CVC is a fragile predictor for candidemia, however, its clinical significance and low specificity obtained in the ROC curve suggests that other covariates rather than those investigated in the present study should be considered to assess its impact on a prediction model for pediatric patients.

4. Discussion

Our study showed that the CVC is fragile as a criterion to define risk for candidemia, although there are studies in the literature showing that the CVC is a good marker due to be an important port-site for microorganisms, mainly opportunists, and for patients who used antifungals, to be immunocompromised and critical (Alves et al., 2022). The ROC curve result

suggests that other covariates rather than those investigated in the present study should be considered to assess its impact on a prediction model for pediatric patients.

In a study carried out in a neonatal ICU in Italy, *C. parapsilosis* was also isolated more frequently (58.5%). In this same study, 65.9% of the episodes of candidemia were caused by Candida non-albicans, a result concordant with that obtained in our study, where 75% were non-albicans. In addition, 56.1% of the cases of candidemia in this study were related to the placement of an intravenous catheter, which is to be expected because Candida spp. it can adhere to platelets and fibrinogen on the surface of catheters and form biofilms, which can become a reservoir for systemic dissemination, very common with Candida parapsilosis (Caggiano et al., 2017). In addition, a study conducted in Turkey demonstrated similar rate of candidemia caused by *C. parapsilosis (*66.7%) and Candida non-albicans (58.3%)(Yılmaz-Ciftdoğan et al., 2021).

In another similar study, performed in a pediatric ICU in Philadelphia, suggested CVC is a significant source of candidemia and C. parapsilosis comprised 30% of all isolates, consistent with the role of catheters as a potential port-site, highlighting the importance of infection control practices, re-educating and training health professionals involved in the daily care of critically ill patients (Zaoutis, 2010; Zaoutis et al., 2010).

A study performed in Barcelona investigated the impact of immediate catheter removal (within 2 days of confirmed candidemia) in adult candidemia patient. This study reports that catheter removal is the standard of care, although this practice is not always possible. According to the statistical analyses performed in this study, the most predictive factor of in-hospital mortality among patients with candidemia with CVC was disease severity. These data suggest that the duration of CVC can be better determined after carefully considering the risks and benefits for individual patients (Rodriguez et al., 2007). Although in the present study the CVC was not evidenced as a good marker for candidemia, the time of use and the moment of remove the CVC are factors that can impact the disease.

Our death rate is very similar to the death rate in other studies. A study reports a mortality rate of 22% in neonates, 10.1% in children and 30.2% in adults. In this study, mechanical ventilation on the first day and admission to the ICU were independent predictors for death on day 30 in children(Blyth et al., 2009). Another study showed that 71 patients (28.6%) who developed candidemia died within 30 days after detection of Candida species (Karadag-Oncel et al., 2015).

Moreover, a study with an adult population achieved an AUC of 0.71 with TPN, severe sepsis, and multifocal Candida colonization as the significant predictors for their study center(Carr et al., 2018). However, the selection criteria for the control group in these studies are more comprehensive, considering only aspects such as length of stay (Zaoutis, 2010; Zaoutis et al., 2010) and including patients without evidence of fungal infection (Zaoutis et al., 2004). In the present study, the control group consisted of patients who had a clinical suspicion of fungal infection and who used antifungal drugs empirically. Thus, this control group is most similar to the case group, which justifies the smaller number of significant predictors found in this study.

The study is not without limitations. Among these, it stands out for being a retrospective study, making it difficult to collect data in medical records and the impossibility of intervention in clinical practices. Another important limitation of the study was related to the sensitivity of blood cultures. Despite blood culture is considered the gold standard method, blood culture has a low sensitivity that rarely exceeds 50% (Dinç et al., 2016), and in many cases may not isolate the microorganisms causing the infection. This low sensitivity can directly compromise the specificity of the ROC curve for CVC, as it decreases when false positive values (patients with CVC but without confirmed candidemia) increase and true negative values (patients without CVC and without confirmed candidemia) decrease. Although the study institution is the largest pediatric hospital in Brazil, these results may not be generalizable to other institutions, so the ideal would be new studies with multicenter collaboration. Future efforts should also focus on validating predictors for candidemia in the most critical areas and with specific hospital populations, for example, in each ICU and in oncology/hematology, in addition to focusing on interventions

to prevent candidemia in children seriously ill. Our controls were not randomly chosen based on propensity scores techniques or other method to reduce bias. However, it is important to note that all cases with suspected candidemia and negative blood culture confirmation were included.

As few studies in the field of antifungals, with adequate relevance, have been carried out in children, pediatricians based on data from adults when planning a therapy. Therefore, there is a need for new studies involving this target population, as well as there are the necessity to improve an antifungal management program, with antifungal stewardship. With this program, the prescriptions can be improved and costs and hospitalizations can be reduced.

5. Conclusion

Our study demonstrated that CVC is a fragile predictor for candidemia due to the low specificity obtained in the ROC curve. However, more studies are essentials to confirm these results, mainly considering contradictory results obtained in previous studies of literature. Based on these results, there are an important opportunity to improve the empirical prescription of antifungal agent, in order to decrease possible inadequate antifungal exposure, species resistance and associated costs.

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