Predicting Candida Infection in Pediatric Intensive Care Unit using Candida Score in a Low-Resource Setting

Dicky Ari Risandy, MD[1]**, Desy Rusmawatiningtyas, MD**[1] **ⓘD,
Firdian Makrufardi, MD**[1]**, Elisabeth Siti Herini, MD, PhD**[1]**,
and Nurnaningsih, MD**[1] **ⓘD**

Abstract

Candida infection was previously thought to be rare in intensive care. With the increased use of broad-spectrum antibiotics, the incidence of candida infection increased significantly. Case-control study was done in patients ≤18 years of age treated for 3 days or more in Pediatric Intensive Care Unit (PICU) Dr. Sardjito General Hospital, Yogyakarta from January 2014 to December 2016. Overall, 43 children were included in this study as a case group with positive candida culture and 43 children as a control group with no candida culture. Cut off point of candida score is ≥3 from our subjects. The area under curve (AUC) value for cut off ≥3 was moderate (0,72). Candida score ≥3 has an odd ratio (OR) 6.8 (95% CI 2.4-18.6) with $P < .05$. All of confounding factors in candida infection have no association with $P > .05$. Candida score can be used as predictor of candida infection in PICU.

Keywords

candida score, candida infection, critically ill children, pediatric intensive care unit, predictor factor

Received October 27, 2020. Accepted for publication February 8, 2021.

Introduction

WHO study showed that the prevalence of the Pediatric Intensive Care Unit (PICU) infection is the highest in the hospital, around 20% to 25% of patients were infected.[1] Candida infection was previously thought to be rare in the intensive care, but along with increased use of broad-spectrum antibiotics and increased knowledge of fungal infections, the incidence of candida infection increased significantly. Candida albicans is responsible for the majority of fungal infections caused within the Genus Candida. The incidence of candida infections accounted for 8% of the overall causes of nosocomial infection in hospital setting.[2] In the last 20 years, there was an increase in nosocomial infections caused by fungus of the genus candida and mainly infect the urinary tract.[3] This candida infection leads to prolonged antibiotic therapy, increasing length and cost of hospitalization, increasing morbidity, and mortality.[4]

Candida is a commensal flora on the body, but on the other hand, Candida albicans are a species that the majority found on preparations culture. In candida infection, there is a transition from a commensal state to a pathogenic state. This transition is influenced by the level of virulence. Some of the virulence factors that occur are the production of proteolytic, lipolytic, and hemolytic enzymes. The most significant virulence is the production of hemolysin. This enzyme degrades erythrocytes resulting in the use of iron (Fe) for candida growth in an invasive candida state. The majority of fungi are dominated by the genus Candida, 58% have the possibility of candida infection become invasive candida due to the existence of the hemolytic enzyme.[5]

[1]Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

Corresponding Author:
Desy Rusmawatiningtyas, Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Jalan Kesehatan No. 1, Sinduadi, Mlati, Sleman, Yogyakarta 55281, Indonesia.
Email: desy_rusma@yahoo.co.id

The IDSA (Infectious Diseases Society of America) recommends that empirical antifungal therapy should be considered in critical patients with risk factors for candida infection and unknown causes of fever, but excessive antifungal use may increase health costs and resistance.[6] Diagnosis of candida infection by tissue culture takes a long time and must be done by experienced workers. Detection of antigens such as galactomannan and anti-mycelium antibodies require time and expensive.[5]

The use of candida scores in children is still rarely used especially in low-resource PICU settings. A study showed the sensitivity and specificity for candidiasis were 81% and 74%.[7] A previous study stated that antibiotics treatment had a significant value on the occurrence of candida infection.[8] In a prospective cohort study, Candida scores consist of 4 significant variables, including severe sepsis, total parenteral nutrition (TPN), multifocal colonization, and surgery as a predictor of invasive candida incidence.[7] A study revealed as much as 58% of candida infections could develop into invasive candida.[9] This score is particularly useful for stratifying the proven risk factors for candida infection, identifying patients who will give early antifungal therapy, and to be a caution for the physician that their patients could develop to invasive candida.[10]

Studies on the role of candida scores in children treated at PICU to be a predictor of proven candida infection has not been widely practiced in Indonesia. Furthermore, the candida score has not been routinely used to predict the possibility of candida infection in our unit. The new implementation of universal health coverage adds some more complexities in the procedures for admission and treatment of critically ill children, which often may have an implication on the care of children with candida infection in our setting. This study is aimed to predict candida infection in critically ill children and its associated factors.

Materials and Methods

Study Design and Population

This study was a case-control study of patients ≤18 years of age treated for 3 days or more in Pediatric Intensive Care Unit (PICU) Dr. Sardjito General Hospital, Yogyakarta, Indonesia from January 2014 to December 2016.

The definition of candidiasis was determined by positive result in 1 of blood, urine, pus, sputum, and CVC culture that yielded Candida species in a patient admitted to the PICU. Case patients were identified through the records of the clinical microbiology laboratory at Dr. Sardjito General Hospital. If multiple candidiasis occured in the same patient during the study period, then the patient was included as a study participant using only the first episode of candida infection.

Patients with incomplete data in their medical records and who discovered fungi on culture examination before day 3 of treatment, neutropenia laboratory results, and malignant diagnosis were excluded from this study.

Selection of Control Patients

This study needed 43 cases of candida infection and 43 control without candida infection. Study control patients were selected by use of unit-spesific patient admission databases. To increase statistical efficiency, incidence density sampling was used to match control patients to case patients with respect to time at risk for developing infection. Time at risk is an important confounding variable because it represents the opportunity for both exposures (example: antibiotics) and development of candidiasis. For example, a patient who develops candidemia on day 10 of his or her PICU stay becomes a case patient, and the potential control patients are patients who have been in the PICU for at least 10 days and have not developed candidemia by day 10 their stay.

Data Collection

We recorded all demographic and clinical data of all patients during their admission in PICU. The demographic data that we evaluated were age and gender, while the clinical data include nutritional status, morbidity, length of treatment, and the need of invasive device.

Candida score components consist of multifocal Candida colonization, surgical or non-surgical history before being admitted to the PICU, total parenteral nutrition use, and cilinical signs of severe sepsis/septic shock.[7]

Comorbidity was defined as any chronic condition that has been diagnosed and treated before the patient was admitted to the PICU, such as infection, surgery, and others. Patient's nutritional status was classified according to the WHO growth charts: Weight-for-Height curve for children younger than 5 years old or BMI-for-age curve for children 5 years old or older. Children were categorized into having good nutritional status ($-2 < z < 2$ SD), being under-nourished ($z < -2$ SD) or overweight ($z > 2$ SD).

We defined the length of treatment as the length of time a patient stays in the PICU until the patient was discharged with any conditions. Patients were classified as using the invasive device if whether ventilator, CVC, and drain were applied during admission in PICU.

Table 1. Characteristics of Research Subjects.

Variables	Case group, candida culture (+), (%), (n = 43)	Control group, candida culture (−), (%), (n = 43)
Age in months, mean (%)		
Age 1 month-1 year	14 (32.5)	16 (37.2)
Age 1-18 years	29 (67.5)	27 (62.8)
Median (min–max)	1.6 (0.1-15.9)	2 (0.1-14.9)
Sex, n (%):		
Male	26 (60.5)	24 (55.8)
Female	17 (39.5)	19 (44.2)
Nutritional status*, n (%):		
Overweight	1 (2.3)	2 (4.6)
Good nutritional status	33 (76.7)	32 (74.4)
Under nourished	9 (20.6)	9 (20.8)
Length of treatment (days):		
Median	13.0	10.0
Mean	19.4	12.9
SD	17.5	8.8
Giving antibiotics:		
Mean	3.4	2.5
Amount ≤2, n (%)	18 (41.8)	23 (53.4)
Number of ≥3, n (%)	25 (58.1)	20 (46.5)
Other therapies, n (%):		
Corticosteroids	1 (2.3)	2 (4.6)
Urine catheter	31 (72)	31 (72)
NGT	29 (67.4)	26 (60.4)
Invasive device, n (%):		
Ventilator	30 (69.7)	21 (48.8)
CVC	21 (48)	14 (32)
Drain	8 (18.6)	7 (16.2)
Number of basic diseases:		
Infection	22 (51.1)	24 (55.8)
Surgery	20 (46.5)	14 (32.5)
Others	1 (2.3)	5 (11.6)
Candidemia	7 (16.2)	0 (0)

Abbreviations: NGT, nasogastric tube; SD, standard deviation.
*Nutritional status was categorized based on WHO weight-for-height growth chart for <5 years old and BMI-for-age growth age for ≥5 years old.

Data Analysis

Data were analyzed using IBM SPSS Statistics 23rd version. Continuous data were presented as mean and standard deviation (SD) for normally distributed data or median and quartiles (Q) $Q1$ and $Q3$ for skewed data. Categorical variables are presented as counts and percentages. Normality of variables was checked using Kolmogorov-Smirnoff test. The significance for variables was assessed using the Chi-squared test and $P < .05$ was considered to indicate statistical significance.

Ethical Approval and Informed Consent

This study approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia (KE/FK/0786/EC/2017). As the patients in this study were less than 19 years of age, the patients' mother and/or guardian provided written consent.

Results

Patients Characteristics

Characteristics of the patients are shown in Table 1. Overall, from 86 children admitted to the PICU during the study period, 43 children were included in this study as a case group with positive candida culture and 43 children as a control group with no candida culture.

Confounding Variables in Candida Infections

Univariate analysis of confounding variables on candida infections are shown in Table 2. Using data analysis

Table 2. Univariate Analysis of Confounding Variables on Candida Infections.

Variables	OR	95% CI	P
Lenght of stay in PICU			
≥14 days	1.9	0.8-4.7	.12
Antibiotics, amount			
2	0.6	0.27-1.61	.37
≥3	1.5	0.68-3.74	.28
CVC	1.9	0.8-4.7	.12
Ventilator	1.9	0.69-5.68	.19
Drain	1.3	0.45-4.06	.58
Corticosteroids	1.0	0.13-7.44	1.00
Urine catheter	0.8	0.34-1.95	.65
Invasive device, amount			
2	1.5	0.61-3.68	.36
3	2.2	0.78-6.29	.13
Case of infection	1.1	0.4-3.3	.85
Malnutrition	1.1	0.36-3.91	.76

Abbreviations: TPN, total parenteral nutrition; CVC, central venous catheter; PICU, pediatric intensive care unit; OR, odds ratio.

Table 3. Bivariate Analysis of Confounding Variables on Candida Infections.

Variables	OR	95% CI	P
Lenght of stay in PICU			
≥14 days	1.97	0.8-4.7	.12
CVC	1.97	0.8-4.7	.12
Ventilator	1.99	0.69-5.68	.19
Invasive device, amount			
3	2.2	0.78-6.29	.13

Abbreviations: TPN, total parenteral nutrition; CVC, central venous catheter; PICU, pediatric intensive care unit; OR, odds ratio.

Table 4. Multivariate Analysis of Candida Infection.

Variables	β	OR	95% CI	P
Ventilator	.21	1.2	0.34-4.48	.74
CVC	.68	1.9	0.64-5.75	.23
Lenght of stay in PICU				
≥14 days	.74	2.1	0.75-2.88	.15
Invasive device, amount				
3	−.75	0.39	0.08-2.63	.39

Abbreviations: CVC, central venous catheter; PICU, pediatric intensive care unit; OR, odds ratio.

Table 5. The Cutoff Point of the Candida Score against Candida Infection.

	Candida infection	
Cut off value	P value	AUC
<3	<.01	0.27
≥3	<.01	0.72
≥4	.01	0.65
≥5	.09	0.60

Abbreviation: AUC, area under curve.

Cutoff Point of the Candida Score against Candida Infection

Table 5 showed that the candida score with a cut of value ≥3 had a significance association with candida infection ($P < .01$). The AUC value for cut off ≥3 was moderate (0.72). Cut off value <3 has an association with candida infection ($P < .01$) but the AUC value showed low statistical size (.27)

The Effect of Candida Score on Candida Infection

We analyzed candida score with diagnostic result of candida infection (Table 6). Our study found significance association with candida infection ($P < .01$).

Discussion

We found that in pediatric patients treated in PICU with candida score ≥3 had a significance association with candida infection ($P < .01$) and moderate AUC value. Candida score ≥3 has an odds ratio (OR) of 6.8 (95% CI 2.4-18.6).

This study was conducted in 1 of the university-based referral hospitals in mainland Indonesia, equipped with

software, we showed risk of candida infection might increase with following factors: length of stay in PICU ≥14 days, antibiotics ≥3, CVC, mechanical ventilator, drain, 2 invasive devices, 3 invasive devices (OR 2.2, 95% CI 0.78-6.29), but all of them have no association ($P > .05$).

While using bivariate analysis (Table 3), we found candida infections might increase with following factors: length of stay in PICU ≥14 days, CVC, mechanical ventilator, 3 invasive devices. Using bivariate analysis we found no association with $P > .05$.

We analyzed using multivariate analysis (Table 4), we found candida infections might increase with following factors: mechanical ventilator, CVC, and length of stay in PICU ≥14 days. No association was found in multivariate analysis with $P > .05$.

Table 6. Diagnostic Test Results and OR of Candida Score Category ≥3.

Candida score	Positive candida	Negative candida	OR (95% CI)	*P* value
Positive (≥3)	33	14	6.8 (2.4-18.6)	<.01

Abbreviation: OR, odds ratio.

a tertiary-PICU facility that might represent pediatric patients treated in the PICU facility, especially in the Central Java region. There were also some limitations in our study. First, the retrospective retrieval of research subjects by the case-control method. One disadvantage in the case-control method is that it is difficult to get the appropriate case and control group. The reason is that the small sample of the study due to culture examination proving the presence of candida infection is quite rare and not following the standard sampling culture that exists to influence the selection bias. We confirmed the culture examination results in the Microbiology Department of Dr. Sardjito General Hospital to minimize the bias that might occur. The scoring calculation in this study was obtained from the medical record, thus the score that we obtained was not as accurate as of the patients' condition at the time of treatment, but we tried to minimize this by adding a second data collector who validated the data input processes. This study is also a single-center study, which might not reflect the overall situation of pediatric patients where candida infection in Indonesia.

Our study found that the median age of the patients was 1.7 years. A previous study has revealed similar findings with the median age of patients was 12.8 months. This study showed the gender of pediatric patients with positive candida cultures dominate males (60.5%) than females (39.5%). This was the same data with the results of the previous study which showed that males were more dominant (54%) in the case group.[11] The most common category of nutritional status of patients treated in PICU was good nutritional status (76.7%) followed by under nourished patients (20.8%). A previous study has the same characteristics of nutritional status which showed most patients had a good nutritional status.[12]

The use of 3 invasive devices have a higher incidence of candida infection. Previous study proved that use of invasive device had a higher candidiasis incidence in pediatric patients.[13] The results of univariate, bivariate, and multivariate analysis in this study showed the length of stay ≥14 days increase the risk for candida infection. A study in the Indian population showed the median length of stay in PICU before developed candida infection was 16 days.[14] Candida colonization occurred in pediatric patients after a median stay of 25 days.[15] This result can be explained by horizontal transmission of

Candida parapsilosis that might be occurred from patient to patient, and from the hands of healthcare workers to patients. A longer duration of stay would have a higher probability of candida infection.[16]

The presence of a central venous catheter has been reported to have an association with candida infection in previous study (OR 13.4, 95% CI 4.80-37.42).[13] Our univariate and bivariate analysis was found similar results. That result might be correlated with the ability of surface receptors in the candida species that can adhere to the thrombin biofilm and forms on the catheter.[17] The internal surface of the catheter may be contaminated by the migration of bacteria or fungi as a result of the use of the hub.[18]

The use of a mechanical ventilator was increased in the risk of candidiasis in our study. The most common facilitating factor in the previous study was the use of mechanical ventilator support with all patients and required mechanical ventilators were 89 (87.3%).[16] The same results were revealed in infant patients that persistent candidemia also had a higher incidence of mechanical ventilation (85.7% vs 50.0%; *P* < .001) and mechanical ventilation had a significantly increased risk of developing into persistent candidemia (OR 5.72, 95% CI 1.05-31.25).[19] Even after prompt removal of infected medical appliances, the residual fungal deposit might exist because Candida species has an ability to adhere to foreign material.[20]

We found candida score has a value of Odds Ratio about 6.8. This value means that patients has a risk of 6.8 times for candida infection when the candida score is positive. The value of candida score in this study with a score ≥3 has AUC 0.72. In a prospective cohort study candida score consists of 4 significant variables: severe sepsis, total parenteral nutrition, multifocal colonization, and surgery, having RR 5.98 with 95% CI 3.28-10.92; *P* < .05 as a predictor of invasive candida with an AUC value of 0.77.[7] Patient with candida infection, 58% could develop invasive candida.[9]

Our study can provide data to physicians, especially pediatric intensivists, regarding the incidence of candida infection and its associated factors. This study also suggests that giving antibiotics and immunosuppressive agents is a risk factor for candida infection. Antibiotics and immunosuppressants need to be considered to suppress the occurrence of candida infection. We also

suggest further research methods using a prospective cohort to improve our results.

Conclusions

Candida score ≥3 can be used as a predictor for candida infection in PICU. Candida cases in pediatric patients in PICU are very high, requiring extra caution and careful monitoring of the signs and symptoms of candida in children. Implementation of the scoring system is quite important because a physician can know the right time to start antifungal therapy. Antibiotic treatment can also increase the incidence of candidiasis, therefore precise treatment is fundamental in treating critically ill patients especially in children with a candida infection. A further prospective cohort with a larger number of cases and multicenter study is needed to validate the candida score.

Author Contributions

DAR: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. DR: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. FM: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. ESH: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. N: Contributed to conception and design; contributed to acquisition, analysis, or interpretation of data; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iDs

Desy Rusmawatiningtyas (iD) https://orcid.org/0000-0002-1643-0887

Nurnaningsih (iD) https://orcid.org/0000-0001-9365-1790

References

1. Sande AS, Kapusnik-Uner JE, Mandell GL. *Antimicrobial Agents, General Considerations. Goodman and Gilman's the Pharmacological Basis of Therapeutics*. 8th ed. Pergamon Press; 1990: 1018–1046.
2. Baharuntan A, Rares FE, Soeliogan S. Pola bakteri penyebab infeksi nosokomial pada ruang perawatan intensif anak di Rsup Prof. Dr. R. D. Kandou Manado. *eBm*. 2015; 1:412-419. doi:10.35790/ebm.3.1.2015.7417
3. Silva S, Negri M, Henriques M, Oliveira R, Williams DW, Azeredo J. Candida glabrata, candida parapsilosis and candida tropicalis: biology, epidemiology, pathogenicity and antifungal resistance. *FEMS Microbiol Rev*. 2012;36:288-305. doi:10.1111/j.1574-6976.2011.00278.x
4. el-Ebiary M, Torres A, Fàbregas N, et al. Significance of the isolation of candida species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. *Am J Respir Crit Care Med*. 1997;156:583-590. doi:10.1164/ajrccm .156.2.9612023
5. Cuenca-Estrella M, Bernal-Martinez L, Buitrago MJ, et al. Update on the epidemiology and diagnosis of invasive fungal infection. *Int J Antimicrob Agents*. 2008;32:S143-S147. doi:10.1016/S0924-8579(08)70016-5
6. Leroy G, Lambiotte F, Thévenin D, et al. Evaluation of "candida score" in critically ill patients: a prospective, multicenter, observational, cohort study. *Ann Intensive Care*. 2011;1:50. doi:10.1186/2110-5820-1-50
7. León C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system ("candida score") for early antifungal treatment in nonneutropenic critically ill patients with candida colonization. *Crit Care Med*. 2006;34:730-737. doi:10.1097/01.CCM.0000202208.37364.7D
8. Peres-Bota D, Rodriguez-Villalobos H, Dimopoulos G, Melot C, Vincent JL. Potential risk factors for infection with candida spp. in critically ill patients. *Clin Microbiol Infect*. 2004;10:550-555.
9. Rossoni RD, Barbosa JO, Vilela SF, Jorge AO, Junqueira JC. Comparison of the hemolytic activity between c. albicans and non-albicans candida species. *Braz Oral Res*. 2013;27:484-489. doi:10.1590/S1806-83242013000 600007
10. Njoto EN. Peranan candida score untuk deteksi infeksi fungal invasif di ruang intensif. *CDK*. 2014;41:70-71.
11. Paganini H, Rodriguez Brieshcke T, Santos P, Seú S, Rosanova MT. Risk factors for nosocomial candidaemia: a case-control study in children. *J Hosp Infect*. 2002;50: 304-308. doi:10.1053/jhin.2002.1169
12. Indrawan IGD, Pudjiadi AH, Latief A. Insidens infeksi kandida di paediatric intensive care unit rumah sakit Dr. Cipto Mangunkusumo. *Sari Pediatri*. 2016;18:182-186. doi:10.14238/sp18.3.2016.182-6

13. Zaoutis TE, Prasad PA, Localio AR, et al. Risk factors and predictors for candidemia in pediatric intensive care unit patients: implications for prevention. *Clin Infect Dis*. 2010;51:e38-e45. doi:10.1086/655698

14. Singhi S, Rao DS, Chakrabarti A. Candida colonization and candidemia in a pediatric intensive care unit. *Pediatr Crit Care Med*. 2008;9:91-95. doi:10.1097/01. PCC.0000298643.48547.83

15. MacDonald L, Baker C, Chenoweth C. Risk factors for candidemia in a children's hospital. *Clin Infect Dis*. 1998;26:642-645. doi:10.1086/514580

16. Filioti J, Spiroglou K, Roilides E. Invasive candidiasis in pediatric intensive care patients: epidemiology, risk factors, management, and outcome. *Intensive Care Med*. 2007;33:1272-1283. doi:10.1007/s00134-007-0672-5

17. Donlan RM, Costerton JW. Biofilms: survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev*. 2002;15:167-193. doi:10.1128/cmr.15.2.167-193.2002

18. Anaissie E, Samonis G., Kontoyiannis D., et al. Role of catheter colonization and infrequent hematogenous seeding in catheter-related infections. *Eur J Clin Microbiol Infect Dis*. 1995;14:134-137. doi:10.1007/BF02111873

19. Fu J, Ding Y, Jiang Y, Mo S, Xu S, Qin P. Persistent candidemia in very low birth weight neonates: risk factors and clinical significance. *BMC Infect Dis*. 2018;18:558. doi:10.1186/s12879-018-3487-9

20. Chapman RL, Faix RG. Persistently positive cultures and outcome in invasive neonatal candidiasis. *Pediatr Infect Dis J*. 2000;19:822-827. doi:10.1097/00006454-200009000-00003