

ORIGINAL ARTICLE

THE USE OF CANDIDA SCORING AS A PREDICTOR FOR CANDIDA INFECTION IN PATIENTS ADMITTED IN THE INTENSIVE CARE UNITS OF A TERTIARY MEDICAL CENTER

Hazel Anne Buctuanon, MD, Cleo Ann Marie D. Pasco, MD, FPPS, FPIDSP
Vicente Sotto Memorial Medical Center, B. Rodriguez St, Cebu City

ABSTRACT

Background: Candida infections range from oral candidiasis to candida endophthalmitis, peritonitis and candidemia. Invasive fungal disease or disseminated candidiasis is highly fatal among children. There are no studies done in the pediatric population to detect early candida infection to help identify those who will benefit from early and prompt medical treatment.

Objective: This study determined the value of Candida scoring (CS) as a predictive tool for invasive candidiasis among pediatric patients admitted in the intensive care units of a tertiary referral center.

Methods: This was a retrospective cross sectional study where 4184 charts of pediatric patients and admitted in the ICU between January 2018 to December 2020 were reviewed. Patients were scored upon admission, after 3 days, after 1 week and weekly thereafter until discharge or demise. The scoring tool used was developed by Leon et al., and uses four variables: presence of sepsis, use of total parenteral nutrition (TPN), presence of multifocal colonization and presence of surgery. Data collected for Candida scores were presented as frequencies and percentages.

Results: There were 396 patients enrolled in this study and 25.7% were treated for candida infection. Majority were newborns where 78.7% had a CS >3, which is statistically significant, $p = < 0.001$. Most patients with severe sepsis/septic shock (85%) had a CS of >3 which is statistically significant. Among intubated patients, 84% had a CS of >3 and all patients on TPN had a CS of >3, both of which are significant. CS could correctly predict 64.6% of patients who will likely have candida infection.

Conclusion: Candida scoring is a tool that can be used in patients at high risk of developing Candida infection. In this study, a CS of >3 can be used to predict Candida infection in the ICU.

KEYWORDS: Candidemia, Candida scoring, Invasive candidiasis

Correspondence:

Dr. Hazel Anne Buctuanon

Email: hangeel.anne@gmail.com

The author declares that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by the author, and that the author has met the requirements for authorship.

INTRODUCTION

Candidemia refers to the presence of *Candida* species in the bloodstream. It is the fourth most common bloodstream infection seen in the intensive care unit (ICU) and is in fact the most common fungal bloodstream infection.¹ Candidemia, the most common form of invasive candidiasis, causes high mortality rates. Candidiasis manifests clinically as a mild infection to invasive and disseminated forms. Bloodstream infection (BSI) due to *Candida* species (spp.) in the neonatal intensive care unit (NICU) is less frequent than that due to Gram-positive or Gram-negative bacteria but has high morbidity and mortality rates. Newborns who survive frequently have long-term neurological impairment, including cerebral palsy, blindness, hearing impairment, cognitive deficits, and periventricular leukomalacia.²

In the Philippines, candidiasis comprised about 80.40% of total fungal infections in 2016.³ The Philippine Pediatric Society, Inc. Registry listed 393 cases of candida infection since 2015. The incidence of candida infection is increasing and antifungal drug choices are limited. Identifying patients who should be started on antifungal medications and appropriate timing for initiating antifungal agents to prevent drug resistance is important, however, lack of feasible, rapid, and accurate diagnostic tools often lead to delayed initiation of antifungal agents, and a worse prognosis. The goal of every intensive care unit is to provide a management plan from admission to discharge through the use of standard tools for evaluating patients. To our knowledge, there is currently no assessment tool being used in the Philippines and in our institution, that can be utilized to identify patients with a high probability of developing candidiasis. Leon et al.⁴ developed a scoring tool, the "Candida score", to aid clinicians in identifying patients who will benefit from early antifungal treatment. This study was done on adult patients in medical-surgical ICUs in 70 tertiary care hospitals in Spain. This tool looked into four main

variables: (1) sepsis, (2) use of total parenteral nutrition (TPN), (3) multifocal colonization and (4) surgery. It is critical to assess the effectiveness of a tool to be used in the PICU and NICU to guide clinicians in the early administration of antifungal medications. Risandy et al., used the same tool in patients 1 month to 18 years old admitted in the PICU in Yogyakarta Indonesia. It was observed from these studies that patients with a Candida score of >3 was significantly associated with candida infection and a Candida score of >3 can be used as a predictor for developing candida infection in the PICU.⁵ An external validation study of candida scoring systems, namely, that of Leon et al., Wenzel et al., and Shore et al. showed that the Candida score by Leon et al., had the best discriminatory power for invasive candidiasis.⁶

The objective of this study is to determine the clinical profile of patients admitted to the ICUs according to the following: sex, age, mean length of ICU stay, reason/s for admission (surgical, medical, trauma), clinical condition at the time of ICU admission (no sepsis, severe sepsis, septic shock), comorbidities, length of use of mechanical ventilator, use of inotropes, presence of central venous access (e.g.umbilical catheter), use of total parenteral nutrition, duration of use of broad-spectrum antibiotics, blood culture report and presence of fungal growth and candida score. This study also determined the mean candida score of patients admitted to the PICU and NICU, determine the proportion of patients admitted at the ICUs with a mean candida score of > 3 and determine the sensitivity, specificity, negative and positive predictive values of the candida scoring tool. Results from this study may assist with antimicrobial stewardship programs and help promote rational use of antifungal agents while minimizing healthcare costs, preserving the effectiveness of antifungal agents, and optimizing patient outcomes.

MATERIALS AND METHODS

Study Design

The study was a retrospective review of charts of patients admitted to the PICU and NICU of Vicente Sotto Memorial Medical Center, Philippines for the period of January 2018 to December 2020.

Methodology

Candida scoring was done on admission, after 3 days and 7 days of hospitalization, and weekly thereafter, to assess if the Candida Scoring by Leon, et al., can be utilized as a predictor of invasive candidiasis in the PICU and NICU.

The scoring tool used four main variables: (1) presence of sepsis (2) use of total parenteral nutrition (TPN), (3) presence of multifocal colonization (defined as the isolation of Candida from three or more samples from the same or different sites in a patient) and (4) presence of surgery prior to PICU or NICU admission.

Variables for Candida Score	Score if present	Score if absent
Clinical Sepsis	2	0
Use of Total Parenteral Nutrition	1	0
Multifocal Colonization	1	0
Surgery	1	0

In the Candida Score Tool by Leon et al, clinical sepsis was given a score of 2 if present and 0 if absent. All other variables were given a score of 1 if present and 0 if absent.

Setting

This study was conducted at the Vicente Sotto Memorial Medical Center (VSMMC), a tertiary medical center and training facility owned by the Philippine government, and located in Cebu City, Philippines.

Population and Sampling Technique

This study included 4184 patients admitted at the PICU and NICU of VSMMC from January 2018 to December 2020. Medical records of patients who met the inclusion criteria were reviewed which

included (1) age 0 to 18 years old (2) admission to the ICU for any illness whether medical or surgical in nature and (3) final diagnosis of sepsis. Excluded were (1) post-arrest patients (2) patients who stayed at the ICU for only 24 hours and (3) patients who died within 8 hours of PICU and NICU admission.

A sample size of 449 was computed using the web calculator based on Buderer's formula for sample size calculation of diagnostic accuracy studies as shown below.

Data Collection Procedure

The study commenced after obtaining approval from the Hospital Research Ethics Committee. Data was collected by chart review which was done at the Records Section of VSMMC. The data collection form for Candida scores was filled up by the researcher. Candida Scoring was done as follows: 2 points was given for presence of clinical severe sepsis, 1 point was given for use of total parenteral nutrition, 1 point was given for presence of candida colonization in more than one site, and 1 point was given for presence of surgery during the current admission. Aside from the variables used for Candida Scoring, additional data collected were age, sex, comorbidities, use of mechanical ventilator, use of inotropes, and presence of sepsis whether prior to or during ICU admission. The Candida score was taken on the day of admission, on the third day, on the 7th day, and weekly thereafter until the 4th week or until the patient's demise. These scores were then recorded and mean scores were computed.

Data Processing and Analysis

Encoding and Data Cleaning Procedures

All data collected were encoded by the researcher with the use of a Microsoft Excel spreadsheet. This was followed by data validation, data coding, input, and analysis with SPSS version 26.

Data Analysis

Descriptive statistics such as mean (or median for non-normal data) and standard deviation (or range) were used to describe continuous variables.

Categorical data were summarized and presented as frequencies and percentages. Association of categorical data was determined with the use of chi-square test of independence to determine if there was an association between Candida score and the occurrence of invasive candida infection and all-cause mortality. Area Under Receiver Operating Characteristic curve was used to determine the diagnostic ability of the Candida Score in predicting septic shock and mortality. P values <0.05 was considered statistically significant.

Ethical Consideration

This study was approved by the Research Committee of the Medical Center. Data gathered were kept confidential. Only the researcher and statistician had access to the data and subjects were assigned codes and deidentified.

RESULTS

Only 411 pediatric admission records from January 1, 2018 to December 31, 2020 met the inclusion criteria and of these, 396 (96.4%) had complete demographic data and 101 or 25.7% were treated for candida infection. Majority of patients were newborns (88.4%), and the rest were less than one year old (9.6%) or older (2.0%). There were more males (60.6%) than females (39.4%) but this was not statistically significant ($p = .535$) with respect to the Candida Score.

Table 1 Clinical Profile of Pediatric Patients and Candida Scores

Profile	Candida score <3 (n = 246)	Candida Score >3 (n = 150)	Total (n = 396)	p-values
Age				
Newborn	232 (94.3)	118 (78.7)	350 (88.4)	.000
Less than one year	12 (4.9)	26 (17.3)	38 (9.6)	
One year or older	2 (0.8)	6 (4.0)	8 (2.0)	
Gender				
Male	149 (60.6)	91 (60.7)	240 (60.6)	.535
Female	97 (39.4)	59 (39.3)	156 (39.4)	
Average ICU Stay, days	20.63 ± 12.0	16.59 ± 13.8	19.1 ± 12.88	.002
Comorbidities				
With	113 (47.3)	69 (46.9)	182 (47.2)	.516
Without	126 (52.7)	78 (53.1)	204 (52.8)	
Reasons for admission				
Surgical	4 (1.6)	15 (10.1)	19 (4.9)	.000
Medical	239 (98.4)	133 (89.9)	372 (95.1)	
(missing)	(3)	(2)		

A significant number of patients had comorbidities (47.2%) such as prematurity and low birthweight. Majority of cases were admitted in the ICU for medical reasons and among them, 35% had a Candida score >3. Among surgical cases, 78% had a Candida score of >3, which is statistically significant. Medical reasons for admission (95.1%) were Neonatal Sepsis, Pediatric Community Acquired Pneumonia – High Risk, and Hospital Acquired Pneumonia. Surgical indications comprised 4.9%.

Table 2 shows that majority of patients in the PICU and NICU had no infection upon ICU admission (60.6%). However, there were 99 (66%) patients with severe sepsis and 38 (9.6%) patients in septic shock with a CS>3. Most patients with severe sepsis and septic shock had a CS score of >3 which was statistically significant at $p=.000$. Out of 411 patients, 35% were on mechanical ventilator for 7 days or more. Of these, 126 or 84% have a Candida score >3, x^2 , $p=.000$ which is statistically significant.

Table 2 Clinical Condition of Pediatric Patients at ICU

Profile	Candida score <3 (n = 246)	Candida Score >3 (n = 150)	Total (n = 396)	p-values
Upon admission				
Aseptic	228 (92.7)	12 (8.0)	240 (60.6)	.000
Severe sepsis	18 (7.3)	99 (66.0)	117 (29.5)	
Septic shock	0 (0.0)	38 (25.3)	38 (9.6)	
Use of mechanical ventilator				
No	233 (94.7)	24 (16.0)	257 (64.9)	.000
Yes (7 days or more)	13 (5.3)	126 (84.0)	139 (35.1)	
Use of inotrope				
No	245 (99.6)	92 (61.3)	337 (85.1)	.000
Yes	1 (0.4)	58 (38.7)	59 (14.9)	
Use of umbilical catheter tip				
No	244 (99.2)	103 (68.7)	347 (87.6)	.000
Yes	2 (0.8)	47 (31.1)	49 (12.4)	
Use of parenteral nutrition				
No	246 (100.0)	18 (12.0)	264 (66.7)	.000
Yes	0 (0.0)	132 (88.0)	132 (33.3)	
Blood culture with fungal growth				
No	246 (100.0)	145 (96.7)	391 (98.7)	.000

Only 59 (14.9%) patients received inotropes, however 58 of these patients had CS >3 which is statistically significant $\chi^2, (1) = 107.580, p = .000$. Majority of patients had no umbilical catheter, but among those with umbilical catheter 47 (31.1%) had a CS >3.

A total of 132 (33%) patients were on parenteral nutrition and all had a CS of >3, which is statistically significant $p = .000$.

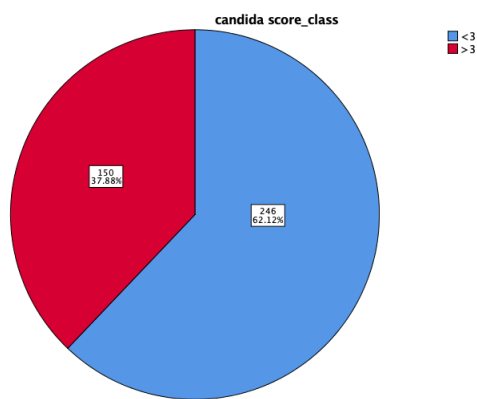


Figure 1. Proportion of ICU Patients based on Candida Score

Most pediatric patients admitted at the ICU had candida scores of <3 (62.12%) while 37.88% had candida scores >3. Mean candida score is 0.76, with standard deviation of 1.0.

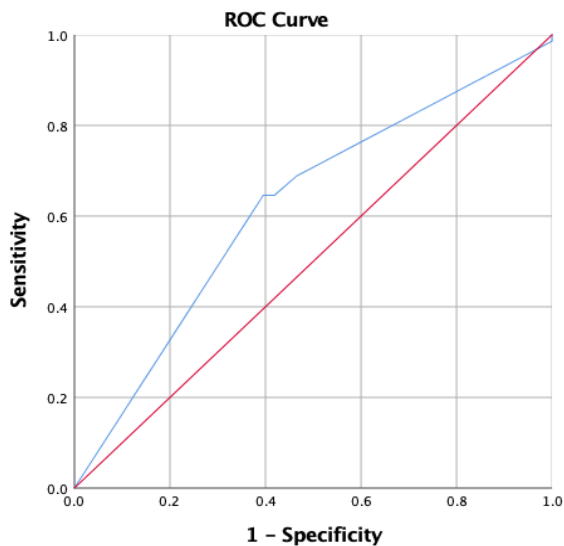


Figure 2. ROC Curve of Candida Score

The Receiver Operating Characteristic curve was used to test the sensitivity of the candida score and the area under the curve (AUC) obtained was 0.621, which is statistically significant, $p = .009$, 95% CI [0.533, 0.710].

The table below shows that a cut-off score of 3.0570 could correctly predict 64.6% of hospitalized pediatric patients who are likely to have candida infection with a 41.9% possibility of a false positive candida infection.

Table 3. Coordinates of the Curve

Positive if Less Than or Equal To	Sensitivity	1 - Specificity (False Positive)
-1.0000	.000	.000
1.0190	.646	.395
3.0570	.646	.419
4.5300	.688	.465
5.4380	.986	1.000
5.9365	.989	1.000
6.0385	.994	1.000
7.1950	.997	1.000
9.2940	1.000	1.000

DISCUSSION

Managing critically ill children is immensely challenging and identification of high-risk groups that can benefit from timely drug initiation is essential. By assessing the patient's candida risk through a scoring system, pediatricians can anticipate those who are likely to develop fungal infection in critical care units. Earlier research done in several countries suggest that a Candida score ≥ 3 can be used to predict candida infection in intensive care units and thus guide pediatricians with the use of antifungal medications.

Majority of patients in this study were newborns and had a Candida score >3 which is statistically significant ($p < 0.00$). Presence of comorbidities amongst patients however was not statistically significant. It was noted that the average length of stay among those with CS >3 is 14 days, which was longer compared to patients with CS <3. This is supported by a previous study by Zhang et

al., which showed a median length of ICU stay of ≤ 10 days both in medical and surgical ICUs prior to the onset of Candida infection.⁷

Majority of cases admitted in the ICU were due to medical reasons. Of these 35% had a Candida score >3 , and among surgical cases 78% had a Candida score of >3 , which is statistically significant. This finding is similar to a study done by Blumberg et al., where majority of SICU patients had significantly higher rates of Candida bloodstream infection compared to those who did not undergo surgery.⁸ Surgical patients tend to stay longer in ICUs, with use of broad spectrum antibiotics, total parenteral nutrition, and use of central lines all of which are associated with increased risk for Candida infection.

Most patients have sepsis on admission, with 35% in septic shock. Of these, 92% had a CS >3 . It is established in many studies that sepsis can lead to immunosuppression. The body is unable to ward off existing infections which put patients at increased risk for acquiring hospital-acquired infections. A study conducted by Chakraborti et al. in India⁹ showed that candidemia was seen in about 10% of patients by day 7 of mechanical ventilation. Fungal invasion of the lung as documented by culture-positive transbronchial lung biopsy specimens were seen in 17% of patients in their study. Factors contributing to Candida Infection in patients on prolonged ventilation are length of ICU admission, use of broad spectrum antibiotics and immunocompromised state.

Most patients in this study were not given inotropes. Only 15% of patients in our study were on cardiac support and among those patients 98% of them had a CS >3 .

Most patients (87.6%) have no umbilical catheter, only 12.4% have indwelling UVC but among those, 95% had a CS >3 , the presence of which was associated with candida infection, similar to previous studies. A cross sectional study by Yamin et al. in Malaysia from January 2006 to December 2018 among children and adult patients who tested positive for *C. parapsilosis*, showed that the presence

of a central venous catheter is correlated with candida infection due to the ability of surface receptors in candida species to adhere to the thrombin biofilm on catheters.¹⁰ These biofilms can evade host defenses and increase the risk for infection.

Use of parenteral nutrition has long been associated with risk for fungal infection. About 33% of enrolled patients received total parenteral nutrition during their admission, and most were neonates. All of them had a CS >3 . In a case-control study by Luzzati et al. done in Italy among adult patients, Candidemia was strongly associated with duration of total (duration >7 days: OR = 20.09; 95% CI: 3.44–117.52) and peripheral parenteral nutrition (duration >7 days: OR = 26.83; 95% CI: 6.54–110.17).¹¹

The receiver operating characteristic curve was used to test for sensitivity and yielded similar results when compared with existing literature. It showed that the candida score can differentiate between ICU patients with hospital-acquired severe sepsis or septic shock who would benefit from early antifungal treatment (score >3) and those in whom invasive candidiasis is highly improbable (score ≤ 3). This study found a significant relationship between Candida score and Candida infection which is most likely expected as the Candida score reaches 3.

There were several limitations in our study. It focused mainly on pediatric patients aged 18 years & 364 days and below who were admitted to the ICU for any cause and critical but stable at the time of admission. Also, as a retrospective single center study, the clinical status and scoring of patients were done based on available data in the charts.

Due to the above limitations, the real value of Candida scoring might be miscalculated in predicting Candida infection in patients with a Candida score of 3 or more. We recommend a larger population with a control group and a multicenter study is also recommended in future studies.

CONCLUSION

This study determined the value of Candida scoring (CS) as a predictive tool for invasive candidiasis among pediatric patients admitted in the intensive care units of a tertiary referral center. Candida scoring is a simple tool that can be used in critically ill patients at high risk of candida infection where it becomes likely as the candida score reaches 3 or more. Age, clinical status on admission, use of mechanical ventilator, and total parenteral nutrition are associated with candida infection.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Mora Carpio AL, Climaco A. Fungemia Candidiasis [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2020. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK436012/>
2. Caggiano G, Lovero G, De Giglio O, Barbuti G, Montagna O, Laforgia N, et al. Candidemia in the Neonatal Intensive Care Unit: A Retrospective, Observational Survey and Analysis of Literature Data. *BioMed Research International*. 2017;2017:1–12.
3. Alain C J, Joseph Peter T L, Zeith Ceve B de los R, Mary Dane B T, Zia Isabel P B, Jan Frances Nichole V G, et al. Antifungal Resistance of Candida Species in Bacolod City, Philippines. *Journal of Infectious Diseases and Epidemiology* [Internet]. 2019 Apr 5;5(2). Available from: <https://clinmedjournals.org/articles/jide/journal-of-infectious-diseases-and-epidemiology-jide-5-076.pdf>
4. León C, Ruiz-Santana S, Saavedra P, Galván B, Blanco A, Castro C, et al. (PDF) Usefulness of the “Candida score” for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: A prospective multicenter study. www.researchgate.net.
5. Risandy DA, Rusmawatiningtyas D, Makrufardi F, Herini ES, Nurnaningsih. Predicting Candida Infection in Pediatric Intensive Care Unit using Candida Score in a Low-Resource Setting. *Global Pediatric Health*. 2021 Jan;8:2333794X2199915.
6. Ahmed A, Baronia AK, Azim A, Marak RSK, Yadav R, Sharma P, Gurjar M, Poddar B, Singh RK. External Validation of Risk Prediction Scores for Invasive Candidiasis in a Medical/Surgical Intensive Care Unit: An Observational Study. *Indian J Crit Care Med*. 2017 Aug;21(8):514-520. doi: 10.4103/ijccm.IJCCM_33_17. PMID: 28904481; PMCID: PMC5588486
7. Zhang Z, Zhu R, Luan Z, Ma X. Risk of invasive candidiasis with prolonged duration of ICU stay: a systematic review and meta-analysis. *BMJ Open*. 2020 Jul;10(7):e036452.
8. Blumberg Henry M, Jarvis William R, Soucie J Michael, Edwards Jack E, Patterson Jan E, Pfaller Michael A, et al. Risk Factors for Candidal Bloodstream Infections in Surgical Intensive Care Unit Patients: The NEMIS Prospective Multicenter Study. *Clinical Infectious Diseases*. 2001 Jul 15;33(2):177–86
9. Chakraborti A, Jaiswal A, Verma PK, Singhal R. A Prospective Study of Fungal Colonization and Invasive Fungal Disease in Long-Term Mechanically Ventilated Patients in a Respiratory Intensive Care Unit. *Indian Journal of Critical Care Medicine : Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine* [Internet]. 2018 Aug 1;22(8):597–601. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6108304/>
10. Yamin DH, Husin A, Harun A. Risk Factors of Candida parapsilosis Catheter-Related Bloodstream Infection. *Frontiers in Public Health*. 2021 Aug 12;9.
11. Luzzati R, Cavinato S, Giangreco M, Granà G, Centonze S, Deiana ML, et al. Peripheral and total parenteral nutrition as the strongest risk factors for nosocomial candidemia in elderly patients: a matched case-control study. *Mycoses*. 2013 May 16;56(6):664–71.