Research Article

Evaluation of *Candida* Scoring Systems to Predict Early Candidemia: A Prospective and Observational Study at a Tertiary Care Hospital, Uttarakhand

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Abstract

Background: Candidemia in critically ill patients is usually a severe and life-threatening condition. Furthermore, due to its nonspecific presentation, it is difficult to diagnose leading to delayed treatment, prolonged hospitalization, and increased health-care costs with increase in morbidity and mortality. **Objectives:** In view of lack of data on "*Candida* scoring systems," this study was designed to evaluate the effectiveness of these scoring systems in predicting the development of candidemia among the Intensive Care Unit patients. **Materials and Methods:** The "*Candida* score" was calculated at the onset of systemic inflammatory response syndrome, sepsis, or shock. Various scoring systems were compared using the area under the receiver operating characteristic curve. **Results:** Among all three bedside risk scoring systems to predict candidemia both Leon score and Wenzel score offered significant discrimination between candidemic and noncandidemic patients with $P = 0.000$ and 0.001, respectively. The area under the curve for the scoring systems was 0.946 (95% confidence interval [CI] = 0.89–1) and 0.818 (95% CI = 0.687–0.949). **Conclusion:** Leon scoring system was found to have highest specificity, diagnostic accuracy, and positive likelihood ratio among all. Thus, we might conclude that a Leon score of ≥2.5 was most suitable for diagnosis of candidemia with significant accuracy and shortening of turnaround time when compared to the gold standard of blood culture. To the best of our knowledge, this is the first report on the subject.

Keywords: *Candida* scoring systems, candidemia, Intensive Care Unit

Introduction

Bloodstream infections (BSIs) caused by various *Candida* spp. have been reported from all over the world and are a significant cause of morbidity and mortality in hospitalized patients, especially those in critical care units. *Candida* spp. are the most common cause of invasive fungal infections, accounting for 70%–90% of all invasive mycoses.[1] Among the causes of nosocomial BSI, *Candida* spp. rank number four in the United States.[2]

The epidemiology of candidemia is complex and varies among the different patient care units. Its incidence varies between 0.5 and 1.4 per 10,000 patient-days in general wards and between 2 and 6.9 per 1,000 admissions in Intensive Care Units (ICUs).[3,4] Various logistic regression analyses of data from observational studies suggest that *Candida* infection is an independent predictor of mortality among ICU patients.[5,6]

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The incidence of candidemia in Asian countries is unclear due to the lack of multicentric studies. A study by Verma *et al*. from SGPGI, Lucknow, Uttar Pradesh, India, ranked *Candida* spp. eighth among all isolates from BSI.[7] There are a lot of differences among the prevalence and incidence reports available from different parts of India.

Early diagnosis of invasive candidiasis remains a challenge, and criteria for starting empirical antifungal therapy in ICU patients remain poorly defined. Although risk factors for invasive candidiasis are well identified, these are so numerous and nondiscriminatory that most ICU patients cannot be

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effectively identified for the early institution of prophylactic antifungal treatment.[2] Moreover, widespread administration of antifungal agents to ICU patients cannot be justified owing to the substantial increase in health-care costs, increased risk of the emergence of antimicrobial resistance in *Candida* spp., and occurrence of adverse drug reactions.[8]

In view of the importance of initiating early antifungal prophylaxis/therapy in high-risk patients, several authors have formulated clinical prediction rules or scoring systems to identify ICU patients at high risk of invasive candidiasis for whom initiation of empirical antifungal therapy could be justified.[9] These scoring systems could help overcome this dilemma.

Materials and Methods

The study was carried out on a total of 75 patients, admitted to ICU of a tertiary care hospital over a period of 12 months. Participants fulfilling the inclusion criteria of the study (mentioned below) were recruited. Written informed consent was obtained from nearby relatives of all recruited patients. Clinical and epidemiological information obtained from these patients was recorded, bedside scoring was done, and *Candida* isolates recovered from blood samples were analyzed.

Inclusion criteria

Patient admitted in ICU with the following:

- Admission for ≥2 days
- Systemic inflammatory response syndrome (SIRS): SIRS was defined as ≥2 findings with temperature >38°C or <36°C/heart rate >90/respiratory rate >20/total leukocyte count >12,000/mm^3 or < 4000/mm^3 or >10% bands.

Exclusion criteria

- Age <6 years
- Pregnant and nursing women.

Blood culture was performed for documenting evidence of candidemia. Candidemia was defined as documentation of one or more blood culture that yielded a *Candida* spp. in a patient with consistent clinical manifestations.[10] Unifocal colonization was defined as isolation of *Candida* from one focus, and multifocal colonization was defined as isolation of *Candida* from more than one noncontiguous foci, even with different *Candida* spp. Clinical sepsis was defined as features of SIRS along with source of infection. Bedside scoring was done for each patient. Each variable was given; 1 as present and 2 as clinical sepsis, and 0 as absent [Table 1]. Total risk score of each patient according to different scoring systems was calculated and further analyzed.

Results

The prevalence of candidemia among ICU patients with features of SIRS was 16% (n = 12) in our study [Figure 1]. Out of 75 patients, blood culture was positive in 28 (37.3%) patients

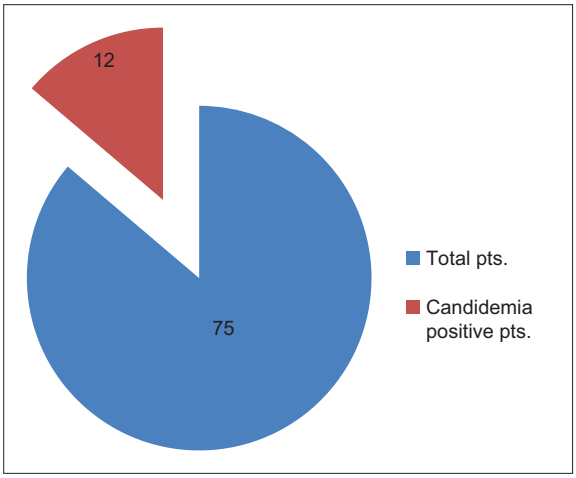

Figure 1: Prevalence of candidemia among total recruited patients

Table 1: Scorings for risk of candidemia

Candida scoring systems	*Candida* risk factors	Points Present (1)	Total score Absent (0)	Culture result (including speciation and sensitivity for culture-positive cases)
Leon *et al*.	Clinical sepsis			
	Surgery			
	Total parenteral nutrition			
	Multifocal colonization			
Wenzel *et al*.	Intravenous catheters			
	Hemodialysis			
	Antibiotic usage			
	Colonization with *Candida*			
Shorr *et al*.	Age <65 years			
	Temperature ≤98°F			
	Severe altered mental state			
	Cachexia			
	Previous hospitalization within 30 days			
	Admitted from other health-care facility			
	Need for mechanical ventilation at the time of admission			

and was thus confirmed as cases of clinical sepsis. Out of these 28 isolates, 12 (42.9%) were *Candida* species and 16 (57.1%) were aerobic bacterial pathogens. Thus, 12 out of 75 patients were found to be positive for candidemia with prevalence rate of 16%. *Candida albicans* was the most common species ($n = 6$, 50%) isolated from total candidemic patients ($n = 12$), followed by *Candida glabrata* ($n = 3$, 25%), *Candida krusei* ($n = 2$, 16.6%), and *Candida tropicalis* ($n = 1$, 8.3%). Majority of patients in the study group comprised of males ($n = 57$, 76%). The male-to-female ratio was 3.2:1. Out of 57 male patients, 7 (12.3%) had candidemia, whereas 5 (27.7%) out of 18 female patients had candidemia [Figure 2]; however, this difference was statistically insignificant ($P = 0.145$). In the present study, the age of recruited patients ranged from 20 to 88 years with maximum number of patients were in the age group of 60–69 years ($n = 17$, 22.6%), followed by patients ($n = 14$, 18.6%) in 40–49 years' age group.

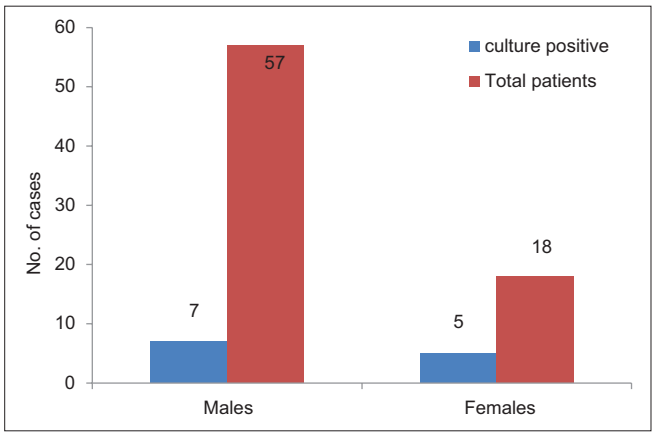

Figure 2: Comparison of gender-wise distribution among total and culture-positive patients

A total of 17 risk factors were identified among the recruited patients and analyzed for possible association with the development of candidemia. The maximum number of patients in our study group was on devices such as intravenous cannulae (82.6%), endotracheal or tracheal tubes (73.3%), and urinary catheters (69.3%). Patients on mechanical ventilation (41.3%) and those colonized by *Candida* at multifocal sites (34.6%) comprised the next highest group. There were 26 patients (34.6%) of clinical sepsis, 23 patients (30.6%) with previous history of hospitalization, and 16 patients (21.3%) each of prolonged ICU stay (>7 days) and prolonged antibiotic usage (>7 days) [Table 2]. Among these, six risk factors had a strong association with the occurrence of candidemia. Prolonged antibiotic usage was the most common risk factor associated with culture positivity for candidiasis ($P < 0.00001$, 95% confidence interval [CI] = 8.37–269. 46), followed by prolonged ICU stay ($P = 0.00024$, CI = 3.35–56.3), multifocal colonization ($P = 0.00025$, CI = 2.90–74.2), clinical sepsis ($P = 0.0024$, CI = 1.96–33.58), recent surgery ($P = 0.0194$, CI = 1.53–35.46), and previous hospitalization within 30 days ($P = 0.03$, CI = 1.14–14.79) [Figure 3].

We constructed receiver operating characteristic curves [Figure 4] using SPSS 21.0 software (Armonk, NY: IBM Corp) for the three scoring systems analyzed in this study and observed that both Leon score and Wenzel score offered significant discrimination between candidemic and noncandidemic study participants, with $P = 0.000$ and 0.001, respectively. The area under the curve (AUC) for the scoring systems was 0.946 (95% CI = 0.89–1) and 0.818 (95% CI = 0.687–0.949) [Table 3]. However, Shorr score did not deliver such significant discrimination in our study ($P = 0.398$; AUC = 0.577; 95% CI = 0.405–0.750).

We also attempted to analyze the most suitable diagnostic cutoff for the three scoring systems and observed that a cutoff

Table 2: Distribution of risk factors among recruited patients

Risk factor	Total patients ($n=75$)	*Candida* positive ($n=12$)	*P*	OR	0.95% CI
IV cannula	62	10	0.65	1.05	0.20-5.5
ET/TT	55	10	0.32	2	0.39-10.04
Urinary catheter	52	7	0.28	0.56	0.15-1.99
Mechanical ventilation	31	5	0.61	1.016	0.29-3.55
Multifocal colonization (colonization index ≥0.5)	26	10	0.00025	14.68	2.90-74.2
Clinical sepsis	26	9	0.0024	8.11	1.96-33.58
Previous hospitalization (within 30 days)	23	7	0.03	4.11	1.14-14.79
Cachexia	18	3	0.59	1.06	0.255-4.45
Prolonged ICU stay (≥7 days)	16	8	0.00024	13.35	3.35-56.3
Prolonged antibiotic usage (≥7 days)	16	10	<0.00001	47.5	8.37-269.46
TPN	15	3	0.44	1.41	0.33-6.04
CVP	14	3	0.39	1.57	0.36-6.7
Admitted from other health care	12	2	0.61	1.06	0.20-5.5
Steroid usage	10	3	0.19	2.66	0.58-12.2
Hemodialysis	10	3	0.19	2.66	0.58-12.2
Severe altered mental status	9	1	0.55	0.625	0.07-5.5
Recent surgery	8	4	0.0194	7.37	1.53-35.46

IV: Intravenous; ICU: Intensive Care Unit; TPN: Total parenteral nutrition; CVP: Central venous pressure; CI: Confidence interval; OR: Odds ratio; ET: Endotracheal tube; TT: Transtracheal tube

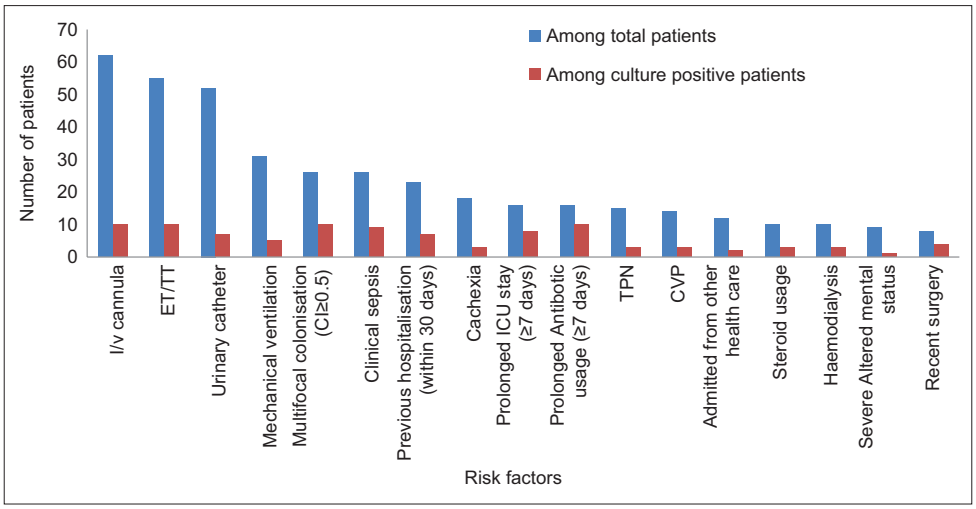

Figure 3: The most significant risk factors/predictive of candidemia

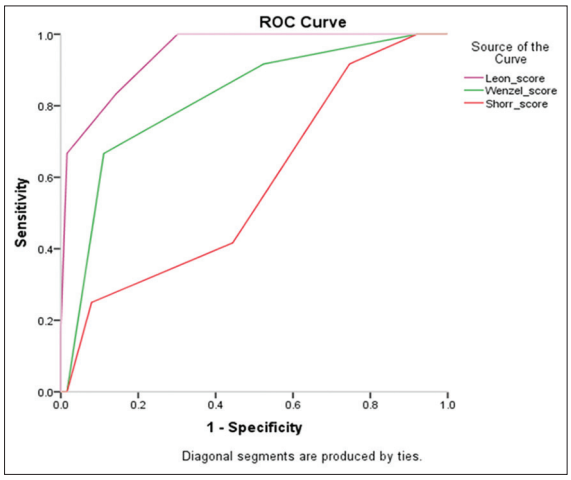

Figure 4: Receiver operating characteristic curve to compare between three risk scoring systems for candidemia

Table 3: Area under the curve for three scoring system

Test result variable(s)	Area	SE	*P*	Asymptotic 95% CI	
				Lower bound	Upper bound
Leon score	0.946	0.029	0.000	0.890	1.000
Wenzel score	0.818	0.067	0.001	0.687	0.949
Shorr score	0.577	0.088	0.398	0.405	0.750

CI: Confidence interval; SE: Standard error

of 2.5 and 1.5 for the Leon and Wenzel score, respectively, delivered the most favorable test characteristics using OpenEpi software (opensource.org/licenses)[11] [Table 3].

Discussion

Candidemia is the fourth most common cause of hospital-acquired BSI.[12] Prompt initiation of appropriate antifungal therapy is essential for managing invasive *Candida* infections; therefore, early diagnosis is a prerequisite for improving the prognosis of invasive candidiasis. However, timely laboratory confirmation of infection is often difficult; therefore, empirical antifungal therapy is often resorted to in ICU patients although the criteria for starting such therapy remain poorly defined.[13,14] The prevalence of candidemia was determined and its relationship with the value of *Candida* score was analyzed. The clinical and epidemiological information was obtained and "*Candida* score" was calculated for each patient. This study brought about many interesting findings strengthening the fact that "*Candida* score" is an interesting tool to predict the early onset of candidemia in ICU patients. The prevalence of candidemia in our study was 16%. In the present study, the age of recruited patients ranged from 20 to 88 years with maximum number of patients from 60 to 69 years (22.6%), followed by age groups 40–49 and 20–29 years. Candidemia is known to affect extremes of age due to building up of immune system in neonates and children and waning off immune response in elderly age group, but in our study, majority of patients were of middle-age group. The reason might be that these patients were admitted in ICU and were exposed to multiple risk factors, and neonates were not included in our study. The male outnumbered females in our study with male-to-female ratio being 3.1:1, which was similar to other studies by authors across the globe. Similar findings were reported by Leroy *et al*. and León *et al*. in their study.[10,13]

Among all three bedside risk scoring systems to predict candidemia, we found that both Leon score and Wenzel score offered significant discrimination between candidemic and noncandidemic patients. However, Shorr score did not deliver a similar significant discrimination in our study. We observed that a cutoff of 2.5 and 1.5 for the Leon and Wenzel score, respectively, gave the most suitable findings, and between these two scoring systems, Leon scoring system was found to have high specificity, diagnostic accuracy, and positive likelihood ratio [Table 4]. Although sensitivity and negative predictive value was lower than Wenzel, it was not statistically significant.

Like several other observers, the most significant independent risk factors associated with the occurrence of candidemia in our

Table 4: Comparison of Leon and Wenzel scoring system

Parameter	Leon score ≥2.5		Wenzel score ≥1.5	
	Estimate	Lower-upper (95% CIs)	Estimate	Lower-upper (95% CIs)
Sensitivity	83.33%	55.2-95.3	91.67%	64.61-98.51
Specificity	85.71%	75.03-92.3	47.62%	35.78-59.73
Positive predictive value	52.63%	31.71-72.67	25%	14.57-39.44
Negative predictive value	96.43%	87.88-99.02	96.77%	83.81-99.43
Diagnostic accuracy	85.33%	75.62-91.61	54.67%	43.45-65.43
Likelihood ratio of a positive test	5.833	4.511-7.543	1.75	1.623-1.887
Likelihood ratio of a negative test	0.1944	0.07254-0.5212	0.175	0.02294-1.335
Cohen's kappa (unweighted)	0.5586	0.3414-0.7758	0.1889	0.04273-0.3351

CIs: Confidence intervals

study were prolonged antibiotic usage ($P < 0.00001$), prolonged ICU stay ($P = 0.00024$), multifocal colonization ($P = 0.00025$), and recent surgery ($P = 0.0194$), clinical sepsis ($P = 0.0024$), and previous hospitalization within 30 days ($P = 0.03$).[15-18]

The use of broad-spectrum and prolonged antibiotic usage can lead to disruption of normal commensal flora of gut and cause colonization with *Candida*. Recent surgery, especially of gastrointestinal tract (GIT), was a common risk factor in our study and most of the other studies on candidemia since surgical procedures of the GIT might lead to mucosal disruption and cause seeding of the bloodstream by *Candida* spp. colonizing the gut.[19] Gonzalez *et al*., Leon *et al*., and Blumberg *et al*. reported total parenteral nutrition (TPN) and renal replacement therapy as clinically significant risk factors; however, the same was not observed in our study.[20] The reason can be due to relatively lower usage of TPN and less number of patients with chronic renal failure in ICU during our study period.

Conclusion

Thus, we might conclude that a Leon score of ≥2.5 is most suitable for ruling in the diagnosis of candidemia with significant accuracy and shortening of turnaround time when compared to blood culture. To the best of our knowledge, comparison between scoring systems has not been done, yet thus, our findings maybe of significance for physicians to predict candidemia and initiate antifungal therapy to improve the clinical outcome of critically ill patients admitted in ICUs.

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Conflicts of interest

There are no conflicts of interest.

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