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The Importance of Scoring Systems in Patients with Candidemia

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Abstract

Background: Candidemias are becoming a growing problem for reasons such as the increasing need for both broad spectrum antibiotic use and total parenteral nutrition and the prolongation of life spans of patients with malignancies. The fact that, despite all the technological advances that have been made, *Candida spp*. are seen in 50% of blood cultures shows that the problem is more serious than previously thought. The purpose of our study was to evaluate patients with candidemia and determine the importance of scoring systems.

Methods: Patients with *Candida spp*. growth in blood cultures between 2009-2014 were investigated retrospectively. Patients' demographic and clinical characteristics, laboratory results, time to start of appropriate treatment, Charlson comorbidity index (CCI), SOFA and Pitt scores and prognoses were recorded from medical files and infection control committee records.

Results: One hundred fifteen patients were enrolled. Agents identified were *Candida albicans* in 41.7% of cases and Candida non-albicans in 58.3%. The crude mortality rate in the patients enrolled in the study was 65.2%. CCI, SOFA and Pitt scores were significantly high in the non-surviving patients. Multivariate analysis of the risk factors affecting mortality showed that a 1-unit increase in a patient's CCI, SOFA and Pitt scores increased mortality 1.6, 1.3 and 2.0 fold, respectively, and that failure to start appropriate antifungal therapy in the first 3 days increased mortality 4.6-fold.

Conclusion: The use of CCI, SOFA and Pitt scoring systems during evaluation in patients with risk factors and prompt initiation of antifungal therapy in patients with scores above cut-off values can be life-saving.

Keywords: Candidemia; Pitt Score; SOFA; Charlson Comorbidity Score

Introduction

Candidemias are becoming a growing problem for reasons such as the increasing need for both broad spectrum antibiotic use and total parenteral nutrition and the prolongation of life spans of patients with malignancies [1]. The fact that, despite all the technological advances that have been made, *Candida spp*. are seen in 50% of blood cultures shows that the problem is more serious than previously expected. These rates vary depending on the Candida species and culture technique employed [2,3]. The low sensitivity of culture systems, regarded as the gold standard in diagnosis, has necessitated the development of new methods. However, these new methods are insufficient in diagnosis because they are not specific for Candida, and their sensitivity and specificity vary [3]. Mortality rates are high, in parallel with the increased prevalence of Candidemia and delays in effective diagnosis. Mortality rates in patients with Candidemia rise significantly with delays in starting treatment [4]. The sensitivity of culture and non-culture diagnostic techniques being below desired levels obliges clinicians to develop new strategies. The most widely used of these are Candida colonization and Candida scores. However, there is no consensus regarding the effectiveness of these methods. Studies have shown that these techniques have low positive predictive values (PPV) but high negative predictive values (NPV). Another significant disadvantage of these scoring systems is that they require the collection of consecutive multiple cultures from the same patient. This in turn causes a disproportionate increase in patient costs [5-7]. The lack of a method with high sensitivity in diagnosing Candidemia, particularly in at-risk patient groups, results in diagnostic difficulties and delays in the commencement of effective treatment, and thus to marked increases in mortality and patient costs. For all these reasons, rather than patients' symptoms, findings and laboratory results being evaluated individually, scoring systems are required that are capable of assessing all these together.

The Charlson Comorbidity Index (CCI) is a scoring system showing general mortality in the light of comorbid conditions. The Sepsis-Related Organ Failure Assessment Score (SOFA) and the simplified version of this capable of use in emergency departments, quick SOFA (qSOFA), scoring systems predict sepsis-related mortality rather than diagnosing sepsis. In addition to these scoring systems, the Pitt score is used to assess short-term mortality in predominantly bacteraemic patients. The Pitt score has been reported to have high PPV and specificity in

determining patients with bacteraemia, and to be particularly correlated with APACHE 2 scores in predicting mortality [8,9].

The purpose of our study was to determine the place of the Pitt score, SOFA, and CCI in identifying patients with Candidemia and to establish whether the use of these systems alone or in combination might contribute to the initiation of effective treatment through diagnosis in the early period.

Materials and Methods

Study design:

Our study was performed retrospectively in a tertiary teaching hospital with an 860-bed capacity. One hundred fifteen patients aged over 18 hospitalized in the intensive care unit between January 2009, and December 2014, and with *Candida spp*. growth in blood and/or IV central catheter culture were enrolled. Data for the first Candidemia episode were included in cases of patients with more than one attack. Patients' clinical and demographic data, laboratory results, time of commencement of appropriate treatment, and CCI, SOFA and Pitt scores were obtained from subjects' medical records and infection control committee records. CCI, SOFA and Pitt scores were calculated based on clinical and laboratory values at the time of determination of Candidemia. Pitt scores were calculated on the basis of body temperature ≤ 35°C or ≥ 40°C receiving 2 points, 35.1°C-36°C or 39.0°C-39.9°C 1 point and 36.1°C-38.9°C 0 point; presence of hypotension (a decrease of >30 mmHg in systolic blood pressure and a decrease of >20 mmHg in diastolic blood pressure or intravenous vasopressors requirement or systolic blood pressure <90 mmHg) receiving 2 points; application of mechanical ventilation 2 points; presence of cardiac arrest 2 points; mental status-alert 0 point, disoriented 1 point, stupor 2 points and coma 4 points. CCI and SOFA scores were calculated as described in the literature [10,11]. Identification and antimicrobial sensitivity testing of the causative micro-organisms obtained from blood cultures (Bactec 9240, Becton Dickinson) was performed using the automated Phoenix system (Becton Dickinson, USA), and classical methods.

Statistical analysis:

Data recorded on Microsoft Excel were transferred to SPSS software. Values obtained by measurement were expressed as mean ± standard deviation or median values. Data obtained by counting as numbers (%) were analysed using the chi square test. Normal distribution of data obtained by measurement was analysed using the Kolmogorov-Smirnov test. Normally distributed data were analysed using Student's t test and non-normally distributed data using the Mann Whitney U test. Receiver Operating Characteristic (ROC) curve analysis was used to determine cut-off points for statistically significant parameters, area under curve (AUC), sensitivity, specificity, PPV and NPV. In addition, multivariate analyses were performed using logistic regression. The results of the analysis were presented as P values, Odds Ratio (OR), and 95% confidence interval (95% CI). P<0.05 was regarded as statistically significant.

Results

The mean age of the 115 patients in the study was 53.4 ± 22.2, and 60 (52.2%) were male. Median Candidemia development time was 15 (8-28) days, and patients were hospitalized for monitoring for 33 (23-46) days. Agents identified were *Candida albicans* in 41.7%, *Candida guillermondi* in 20%, *Candida parapsilosis* in 17.4%, *Candida tropicalis* in 7%, and other non-albicans Candida species in 13.9%. The crude mortality rate was 65.2%. CCI, SOFA and Pitt scores were significantly higher in the fatal cases. Long-term hospitalization, antibiotic use, presence of central venous catheter, total parenteral nutrition and admission to the intensive care unit were the most common risk factors (**Table 1**). Ten of the non-surviving patients had not been started on antifungal therapy. Thirty-two of the non-surviving and eight of the surviving patients were started on effective antifungal therapy after three days (p=0.026).

Table 1: Patients' epidemiological characteristics, risk factors and mean scoring values.

	Ex (n=75)	Surviving (n=40)	p
Age	58.2 ± 21.5	44.6 ± 20.9	0.002
Charlson comorbidity index	4.7 ± 2.1	3.2 ± 1.9	0.001
SOFA	9.4 ± 3.3	3.6 ± 2.4	<0.001
Pitt	6.3 ± 2.8	2.0 ± 1.6	<0.001
Sex (Male/ Female)	40/35 (53.3/46.7%)	20/20 (50/50%)	0.733
History of surgery	22 (29.3%)	22 (55%)	0.007
TPN	67 (89.3%)	23 (57.5%)	0.000
Admission to ICU	55 (73.3%)	19 (47.5%)	0.006
DM	21 (28%)	7 (17.5%)	0.307
Kidney failure	23 (30.7%)	8 (20%)	0.313
Immunosuppressive	31 (41.3%)	11 (27.5%)	0.142
Malignity	24 (32%)	13 (32.5%)	0.956
Trauma	15 (20%)	11 (27.5%)	0.360
Antibiotic use	75 (100%)	40 (100%)	-
Central venous catheter	71 (94.7%)	34 (85%)	0.093
Appropriate treatment being initiated in the first 3 days	32 (42.7%)	8 (20%)	0.026

When the factors affecting mortality were subjected to multivariate analysis, a one-unit rise in CCI score increased mortality 1.6-fold, while a one-unit increase in SOFA score increased it 1.3-fold, a one-unit increase in Pitt score increased it 2.0-fold and appropriate antifungal therapy not being started within three days increased it 4.6-fold (**Table 2**). In patients with

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Candidemia, CCI scores above 4, SOFA scores above 7 and Pitt scores above 3 predicted mortality with high sensitivity and specificity, while PPV reached 97.6% when SOFA and Pitt scores were assessed together (**Table 3**).

Table 2: Mean Pitt, SOFA and CCI values for all patients.

	p	OR	95%
CCI	0.009	1.64	1.13-2.37
SOFA	0.033	1.34	1.02-1.76
Pitt	0.002	2.04	1.30-3.19
Not commencing effective antifungal therapy within the first 3 days	0.048	4.56	1.01-20.53

Table 3: Scoring systems' power to indicate mortality in patients with Candidemia.

	Cut off	p	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Charlson Comorbidity Index	>4	0.001	0.686	46.7	80.0	44.4	81.4
SOFA score	>7	<0.001	0.918	73.3	95.0	65.5	96.5
Pitt score	>3	<0.001	0.910	84.0	82.5	73.3	90.0
SOFA+Pitt score		<0.001	0.761	54.7	97.5	53.4	97.6

Discussion

The sensitivity of blood cultures, the gold standard in the diagnosis of Candidemia, varies depending on the culture technique employed and the Candida species involved. Sensitivity results in the literature range between approximately 21% and 71% [2,3]. Patient-related factors such as neutropenia also affect sensitivity results [12]. Similar problems apply to non-culture diagnostic methods. The sensitivity and specificity of antigen-antibody tests, such as ß-glucan and mannan range between 65% and 95%, depending on the Candida species. There are also methods with sensitivity and specificity above 90%, such as the T2 Candida panel, but the most important handicap involving these is that they have not been validated. In addition, false positives can also be encountered with these serological tests [3,13]. Negativity on these tests cannot therefore exclude a diagnosis of fungal infection.

Despite the increased use of more broad spectrum antibiotics and invasive equipment and the application of more sophisticated methods of treatment, mortality rates in fungal infections are still high, with cited mortality rates of approximately 47% [4,14]. An increase in the prevalence of Candidemia also occurs together with this high mortality rate [15,16]. Another important factor that increases mortality in patients with Candidemia is delays in starting treatment. Mortality rates in studies increase in parallel to delays in starting antifungal therapy [17,18]. Factors such as the absence of diagnostic tests with high sensitivity and high mortality rates have obliged clinicians to turn to alternative methods, such as fever-based empirical treatment and prophylactic therapy. However, these methods also have their own inherent problems. Resistance problems associated with unnecessary antifungal use is encountered in prophylactic or fever-based therapeutic approaches [19]. In scoring systems such as the Candida score or Candida colonization index, large numbers of consecutive cultures need to be taken from the same patient. Leon et al. determined PPV of 16% and NPV of 98% for the Candida score [7]. The Candida score provides information more useful for excluding diagnosis, rather than supporting diagnosis. Unnecessary antifungal use can also not be prevented. This results in increased patient costs.

The purpose of our study was to assess the power to predict mortality in patients with Candidemia of the Pitt score, mostly used for patients with multiple organism bacteraemia, the CCI, which shows general mortality, and SOFA scores used for sepsis-related mortality by employing these together. The Pitt score is capable of predicting short-term mortality (30 days) in bacteraemic patients in previous studies and can be used in bacteraemias developing in association with both Gram-positive and Gram-negative pathogens, but is not pathogen-specific [20]. Different studies have shown that mortality increases in line with Pitt score [21-23]. In a study of intensive care patients, Rhee et al. reported that Pitt scores were particularly correlated with APACHE 2 scores in terms of predicting mortality and could be used as a tool for determining mortality [9]. Feldman et al. reported better PPV and specificity for the Pitt score compared to PSI, CURB-65 and CRP-65 in patients with bacteraemic pneumococcal pneumonia [8].

In our study, mortality increased independently of the day when treatment started when a cut-off value of 3 was adopted for the Pitt score. Additionally, Pitt score sensitivity and specificity exceeded 80% and PPV was 90%. Two newly published studies showed that the Pitt score can also be used in patients with fungaemia [24,25]. The absence of a decrease in Pitt score must therefore suggest fungal infections in patients

with identified bacterial pathogens and receiving appropriate antibacterial therapy.

The CCI, a scoring system based on patients' comorbid conditions, is capable of showing mortality in all subjects generally, not solely in a specific group of patients [25]. In our study, CCI exhibited lower PPV and NPV than SOFA and the Pitt score. The SOFA score predicts patients' sepsis-related risk of mortality, rather than diagnosing sepsis [26-28]. PPV of 96.5% for mortality was determined when a cut-off threshold of 7 was adopted for the SOFA score.

A history of hospitalization in the intensive care unit, use of broad spectrum antibiotics, receipt of total parenteral nutrition and history of surgery significantly increase the risk of Candidemia [4]. In agreement with the literature, in our study, a history of admission to the intensive care unit, receipt of total parenteral nutrition and having undergone surgery significantly raised the risk of Candidemia. Not starting appropriate antifungal therapy within the first three days increased the risk of mortality approximately 4.5-fold. Significant variation was present in CCI, SOFA and Pitt scores between our surviving and non-surviving patients. Every one-unit increase in CCI increased the risk of mortality 1.6-fold, compared to 1.3-fold for SOFA and 2.05-fold for the Pitt score. SOFA and Pitt score AUCs were particularly close to one another, with PPVs of 96.5% and 90% respectively. Pitt and SOFA scores in patients receiving appropriate antifungal therapy remaining high or previously decreased scores rising again may suggest a diagnosis of fungal infection in these subjects. The combined use of Pitt and SOFA scores will result in effective antifungal therapy directed toward the most probable Candida species being initiated without loss of time in patients with high scores and an approximately 3-fold increase in survival.

Conclusion

In conclusion, our findings show PPV of 90% and 96.5%, respectively, at cut-off thresholds of 3 for Pitt score and 7 for SOFA, and a PPV of 97.6% when the two scores are used together. In addition, we determined a 3-fold increase in survival with the start of appropriate antifungal therapy without loss of time due to the higher mortality among patients with high scores. The Pitt score can be calculated easily using clinical parameters at the bedside. For all these reasons, we conclude that the Pitt and SOFA scores can be particularly effectively used in at-risk patient groups.

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