Risk Factors and Scoring Systems for Patients with Candidemia at a Tertiary Hospital in Jakarta, Indonesia

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ABSTRAK

Tujuan: *untuk mengidentifikasi faktor risiko kandidemia dan mengembangkan sistem skoring kandidemia yang dapat digunakan di Rumah Sakit Cipto Mangunkusumo (RSCM), Jakarta, Indonesia.* ***Metode:*** *studi retrospektif dengan kasus kontrol dilakukan dengan menggunakan rekam medik pasien tahun 2011-2014. Semua pasien sepsis yang dirawat di RSCM dengan hasil kultur darah positif Candida dimasukkan sebagai kelompok kasus. Kelompok kontrol yaitu semua pasien sepsis tanpa kandidemia. Perbandingan kelompok kasus dengan kontrol adalah sama (1:1).* ***Hasil:*** *dari 234 pasien yang dianalisis, faktor risiko yang bermakna pada penelitian ini yaitu lama perawatan 8-14 hari (OR 3,464; 95% CI 1,458-7,800), lama perawatan lebih dari 14 hari (OR 6,844; CI 3,0-15,330), sepsis berat (OR 16,407; 95% CI 1,458-7,800) dan pembedahan (OR 3,03; 95% CI 1,492-6,152). Prediktor kandidemia di RSCM yaitu lama perawatan 8-14 hari (nilai 1), lama perawatan lebih dari 14 hari (nilai 2), sepsis berat (nilai 3) dan pembedahan (nilai 1) dengan nilai cut off 3,5.* ***Kesimpulan:*** *hasil studi ini mengindikasikan bahwa sistem skoring sebagai panduan terapi empirik kandidemia dapat dikembangkan dengan menggunakan faktor risiko kandidemia dari pasien yang diidentifikasi sebagai pasien berisiko di RSCM.*

Kata kunci: *kandidemia, faktor risiko, sistem skoring.*

ABSTRACT

Aim: *to identify the risk factors of candidemia and to develop a scoring system that could be implemented in Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia.* ***Methods:*** *this study was a retrospective study with case control design using the medical records of patients since 2011 to 2014. All sepsis patients hospitalized in the RSCM with a positive blood culture for Candida were included in this study as a case group. The control group was all of the sepsis patients without candidemia. The ratio for case and control groups was equal (1:1).* ***Results:*** *from 234 patients who were analyzed, the risk factors that influenced the study were length of stay of 8-14 days (OR 3.464; 95% CI 1.458-7.800), length of stay of more than 14 days (OR 6.844; 95% CI 3.0-15.330), severe sepsis (OR 16.407; 95% CI 1.458-7.800), and surgery (OR 3.03; 95% CI 1.492-6.152). The predictors for candidemia in RSCM were length of stay in hospital for 8-14 days (score 1), a length of stay ≥14 days (score 2), severe sepsis (score 3), and surgery (score 1), with a cut off score of 3.5.* ***Conclusion:*** *the results of this study have indicated that a scoring system in order to guide an empirical treatment for candidemia can be developed by using the risk factors for candidemia from patients who have been identified as patients with risk at Cipto Mangunkusumo Hospital.*

Keywords: *candidemia, risk factor, scoring system.*

INTRODUCTION

Candida species have become an important cause of nosocomial infections due to their potential cause of mortality and a prolonged hospitalization time.[1] Candida is the fourth most common cause of nosocomial blood stream infections in the United States with a mortality rate of more than 40%, even though adequate antifungal therapy was given. The incidence of invasive candidiasis is various in countries and it ranges between 3.4% to 5.79%.[2,3] There is a shifting of the causative agents for invasive candidiasis infections from Candida albicans to a non-albicans Candida species.[3,4]

An early identification of sepsis patients who have high risk for fungal infection is challenging, because of the complexity of a patient's condition, a low rate of success, and a long period of time in order to obtain the results for fungal culture.[5] It is important to develop a tool to predict high risk patients who might develop candidemia and need an empirical antifungal therapy. A prediction system of candidemia that was based on patient's clinical status was developed by Paphitou[6] and Ostrosky Zeichner.[7] In addition, a scoring system that is now called a "Candida Score" was also developed and was based upon some parameters.[8] A limitation of the lack clinical prediction is the possibility of a massive antifungal therapy problem that can change a local epidemiological pattern in a hospital, as well as increasing the resistance to antifungals.[6,9] This study aimed at identifying the risk factors of candidemia in RSCM hospital in Jakarta, Indonesia. It was conducted in order to develop a scoring system that is based upon the risk factors that have been identified for candidemia which can be implemented to predict the occurrence of candidemia.

METHODS

A retrospective case control study was conducted using the medical records of sepsis patients during the period of 2011 to 2014. All sepsis patients hospitalized in RSCM with a positive blood culture for Candida were included in the case study group. The control group were sepsis patients with a negative candidemia (a sterile culture or a bacterial growth). The ratio for case and control group was equal (1:1). For the control group, we matched the same age groups and the wards of the patients.

Quantitative data analyzes were presented as mean and standard deviations (SD) or as median with a maximum and minimum value. Frequency was used to describe the categorical data. To obtain the risk factors for candidemia, we performed bivariate analysis. The variables with significant risk factors ($p<0.25$) were included in multivariate and logistic regression models.

The accuracy of the scores was determined by a Receiver Operating Curve (ROC). The data was analyzed by using SPSS 11.5 software. An ethical clearance was obtained from the Ethical Committee at the Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia (No. 742/UN2.FI/ETIK/2O14).

RESULTS

A total of 234 sepsis patient's data was obtained for this study. From that number, 117 were sepsis patients with candidemia and the same amount was included as a control group. The patient's data and bivariate analysis are presented in **Table 1**.

The results obtained have shown that the major age group of patients was 16 to 60 years (43.6%), of which 70% of them had severe sepsis and 77% had chronic diseases. The majority of the patients had neutrophils of more than 500 (85%) and 52.1% of the patients had a normal monocyte count (2%-8%). From patients who were hospitalized in ICU and HCU (60.7%), the hospital length of stay was more than 14 days (43.2%) and the length of stay in ICU ranged between 1-7 days (68.3%). Most of patients had urinary catheter (86.3%), central venous catheter (53%) and had antimicrobial therapy administered for more than five days (77.8%). Most of the patients were treated with two antimicrobial regimens.

The bivariate analysis of the risk factors for candidemia showed that the variables associated with an increased risk of candidemia with $p<0.25$ were severe sepsis, neutrophil count <500, hospital length of stay of more than 7 days, length of stay in ICU of more than 7 days,

urinary catheter, mechanical ventilator, central venous catheter, surgery, abdominal surgery, antimicrobial therapy >5 days, and a number of antimicrobials of 2 to more than 3.

The multivariate analysis for candidemia risk factors are shown in **Table 2**. It is shown that a length of stay of 8-14 days, a length of stay of more than 14 days, severe sepsis, and surgery, were associated with the development of candidemia.

To develop the scoring system, we used a logistic regression model, in order to predict the relationship between the independent variables that were obtained from the multivariate analysis, with a dependent binary variable (without candidemia or with candidemia). The results are shown in **Table 3**.

In the logistic regression analysis, the results showed that the probability of a patient having candidemia would be one time, if the length of

Table 1. Variables associated with Candidemia

Risk Factor	Total (N=234) n (%)	Sepsis with Candidemia n (%)	Sepsis Without Candidemia n (%)
Age			
- <1 year	27 (11.5)	13 (11.0)	14 (12.0)
- 1-16 years	57 (24.4)	29 (25.0)	28 (24.0)
- 16 to <60 year	102 (43.6)	51 (44.0)	51 (44.0)
- ≥60 years	48 (20.5)	24 (21.0)	24 (21.0)
Severe Sepsis	162 (69.2)	106 (91.0)	56 (48.0)
Candida Colonization	56 (24.0)	29 (25.0)	27 (23.0)
Chronic Disease	156 (77.0)	77 (66.0)	79 (68.0)
Neutrophil Count			
- ≥500	199 (85.0)	94 (47.2)	105 (52.8.0)
- <500	35 (15.0)	23 (20.0)	12 (10.0)
Monocyte Count 2-8%	122 (52.1)	61 (52.0)	61 (52.0)
- >8	63 (26.5)	27 (23.0)	36 (31.0)
- <2	49 (20.9)	29 (25.0)	20 (17.0)
Hospital Length of Stay			
- 1-7 days	71 (30.3)	17 (15.0)	54 (47.0)
- 8-14 days	61 (26.1)	31 (27.0)	30 (26.0)
- >14 days	101 (43.2)	69 (59.0)	32 (27.0)
Length of Stay in the ICU			
- 1-7 days	97 (68.3)	41 (73.0)	56 (87.0)
- 8-14 days	29 (20.4)	18 (25.0)	11 (16.0)
- >14 days	16 (11.3)	12 (17.0)	4 (6.0)
Urinary Catheter	202 (86.3)	109 (93.0)	93 (80.0)
Immunosuppression Drugs	20 (12)	14 (12.0)	6 (5.0)
Mechanical Ventilator	96 (41)	56 (48.0)	40 (34.0)
Central Venous Catheter	124 (53)	73 (62.0)	51 (44.0)
Surgery	110 (47)	67 (57.0)	43 (37.0)
Abdominal Surgery	65 (27.8)	46 (39.0)	19 (16.0)
Total Parenteral Nutrition	49 (21)	23 (20.0)	26 (22.0)
Antimicrobial >5 days	182 (77.8)	102 (87.0)	80 (68.0)
Number of Antimicrobials			
- 1	69 (29.5)	23 (27.0)	46 (34.0)
- 2	72 (30.8)	32 (28.0)	40 (34.0)
- 3	47 (20.1)	29 (25.0)	18 (15.0)
- >3	43 (18.4)	32 (27.0)	11 (9.0)

Table 2. Multivariate analysis of the variables associated with Candidemia

Risk Factor	p value	OR (95% CI)
Hospital Length of Stay		
- 1-7 days		Ref
- 8-14 days	0.004	3.464 (1.458-7.800)
- >14 days	0.000	6.844 (3.00-15.330)
Length of Stay in the ICU		
- 1-7 days		Ref
- 8-14 days	0.516	0.687 (0.222-2.133)
- >14 days	0.416	1.938 (0.394-9.545)
Urinary Catheter	0.104	2.954 (0.802-10.890)
Abdominal Surgery	0.095	2.641 (0.846-8.245)
Mechanical Ventilator	0.384	1.444 (0.631-3.302)
Central Venous Catheter	0.795	1.114 (0.492-2.525)
Immunosuppression Drugs	0.294	1.981 (0.553-7.102)
Antimicrobial >5 days	0.738	1.185 (0.439-3.200)
Number of Antimicrobials		
- 1		Ref
- 2	0.580	1.289 (0.524-3.171)
- 3	0.859	0.910 (0.322-2.571)
- >3	0.499	1.562 (0.429-5.694)
Severe Sepsis	0.000	16.407 (1.458-7.800)
Surgery	0.002	3.030 (1.492-6.152)
Neutrophils <500	0.066	2.729 (0.935-7.967)

stay was between 8-14 days (score 1). It would be twice when the length of stay was more than 14 days (score 2). The score is added one time if they had surgery (score 1), and added 3 times if they had severe sepsis (score 3). The implementation of this scoring is, as follows: when patients were hospitalized for 16 days with severe sepsis and had surgery, they would have a score of 2 for a hospitalization of more than 14 days, a plus score of 3 for severe sepsis, a plus score of 1 for the surgery, a total score of 6.

The accuracy of the testing depends on how well the test distinguished the groups being tested, into those with and without the disease in question. The accuracy was measured by the area under the Receiver Operating Characteristic (ROC) curve. The ROC results are shown in Figure 1 and **Table 4**.

With the cut off value obtained was 3.5 with 81% sensitivity and 72% specificity, the AUC was 0.838; 95% CI 0.79-0.89. This result meant that the accuracy of this scoring as diagnostic test was good. This also meant that these three variables (the length of the stay in the hospital, severe sepsis and surgery) were good mediators to differentiate the patients with candidemia or without candidemia.

To validate the candidemia scoring with a cut off value 3.5, the scoring was then tested with the study group and the control group. The results are shown in **Table 5**.

The results of the implementation of the scoring showed that the sensitivity was 95/117=80%, the specificity was 84/117=70%, the Positive Predictive Value (PPV) was 95/128=74% and the Negative Predictive Value (NPV) was 84/106=79%.

DISCUSSION

Candidemia is an uncommon case and it remains a significant concern for hospitalized patients, especially for those in the Intensive Care Units.[10] Candidemia is mainly developed in critically ill patients with terminal disease and with co-existing multiple organ failures.[11]

Table 3. The calculation of the scores: variables that were selected by the logistic regression model for Candidemia in the hospital

Variables	Coefficient (β)	Standard Error	Wald X2	P value
Length of Stay 8-14 days	1.263	0.431	8.598	0.003
Length of Stay>14 days	1.932	0.412	21.951	0.000
Surgery	0.790	0.362	9.161	0.002
Severe Sepsis	2.819	0.431	42.880	0.000
Constant	-3.726	0.533	48.886	0.000

Table 4. Cut-off value for the ROC curve for the Candidemia scoring system in the hospital

Cut-off value	Sensitivity	False positive
-1.0	1.0	1.0
0.5	1.0	0.880
1.5	0.991	0.675
2.5	0.974	0.581
3.5	0.812	0.282
4.5	0.624	0.145
5.5	0.333	0.042
7.0	0.000	0.000

Table 5. The scoring system with a cut-off of 3.5 when tested with the study group and the control group

Score	Sepsis with Candidemia n (%)	Sepsis without Candidemia n (%)	Total
>3.5	95 (80.0)	33 (30.0)	128
<3.5	22 (20.0)	84 (70.0)	106
Total	117	117	234

The age range of the patients in this study had the same results as Wu et al.[12] in which the patients ages were 1-88 years with a median of 40 years. In this study, 77% of the patients had chronic diseases. The presence of a chronic disease was important as a risk factor and in the management of the patients. This was because the drug interactions for antifungal should be considered in those patients with diabetes mellitus or tuberculosis, who have had therapy for their concomitant diseases.[13]

In the multivariate analysis, the hospital length of stay, severe sepsis and surgery, were associated with candidemia. Several other risk factors that have been associated with candidemia in other studies were not associated with candidemia in the present study. In this study, candidemia was associated with a longer hospital stay, which is similar to the study of Zaoutis et al.[14] Surgery, especially abdominal surgery, caused an interruption in the integrity of the gastrointestinal tract mucous that caused a port of entry for the Candida to pass from the lumen to the bloodstream.[15]

Furthermore, this study has the same results as the study of Leon et al.[8] who developed the Candida Score. In fact, the score system that we have developed offers several advantages over the Candida Score. Two variables of the Candida Score (severe sepsis and surgery) are used at our hospital. For an addition, one new variable, which was the hospital length of stay, was identified. This new scoring system is easy to remember, since it is only has a few variables, including severe sepsis and surgery. This type of scoring does not need to include a laboratory examination (i.e., a culture to confirm Candida colonization). This has not been routinely conducted in our hospital, because it is costly and labor extensive.[16] The sensitivity and the specificity of this new scoring are proposed to

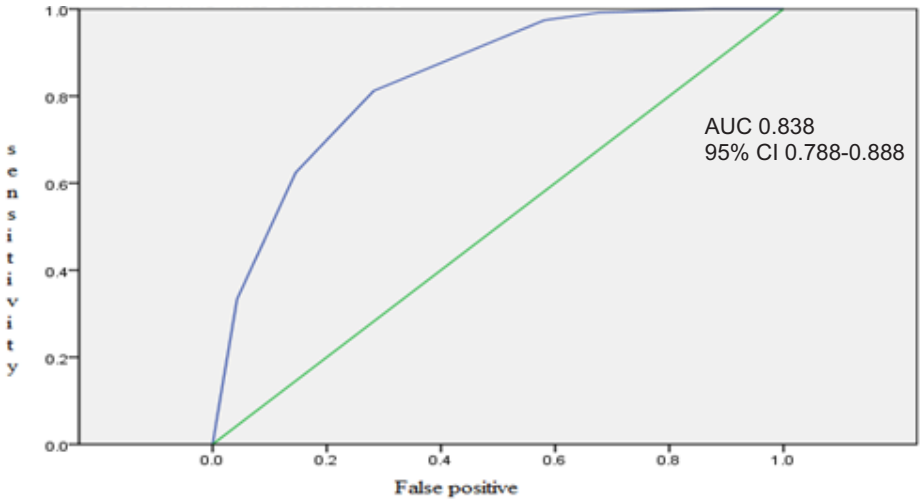

Figure 1. Receiver operating characteristic (ROC) curve and the area under the curve (AUC) power to assess the scores

be used for screening the patients who need antifungal therapy and can minimize any unnecessary treatment.

The scoring system obtained in this study might be implemented in RSCM, rather than Candida score, but it requires further validation. The validation should be performed in a prospective study, with a selected ward, or in two different hospitals, as in the Michalopoulos study.[17]

The limitation of this study is sample size. The sample size was quite small because candidemia is rare and the culture does not always available. Since the data were from one center, it needs careful, interpretation if the results were to be implemented in other centers. The calculations for the scoring were from secondary data, so the scores that were obtained were not as accurate as the patient's condition at the time. The strength of the study was the case control study design that could analyze important variables in a Candida infection.

It is necessary to record data and evaluate the health care-associated infection, especially Candidemia, in all of the wards at a hospital, so that prevention can be instigated. The implementation of a scoring system is important for the reasons to start an empiric antifungal therapy.

CONCLUSION

The significant risk factors associated with candidemia in this study were the hospital length of stay, severe sepsis and surgery. The new scoring system that has been developed can be implemented in order to predict those patients that might result in a possible candidemia condition, by following these criteria: a hospital stay of 8-14 days (score 1), a hospital stay of more than 14 days (score 2), severe sepsis (score 3) and surgery (score 1), with a cutoff value of 3.5.

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