Identifying Predictors of Mortality in Sepsis Patients with Malignancy: A Retrospective Cohort Study

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ABSTRACT

Background: *Sepsis is a major problem that contributes to a high mortality rate. Its mortality is especially high in patients with malignancy. One study reported that sepsis patients with malignancy have a 2.32 times higher risk of mortality compared to patients without malignancy. For this reason, factors that influence mortality in sepsis patients with malignancy become especially important to provide effective and efficient therapy. This study aims to identify factors that influence mortality in sepsis patients with malignancy.* ***Methods:*** *This study is a retrospective cohort study using medical records of sepsis patients with malignancy who were treated at Cipto Mangunkusumo Hospital from 2020 to 2022. A bivariate analysis was carried out and followed by a logistic regression analysis on variables with p-value<0.25 on the bivariate analysis.* ***Results:*** *Among the 350 eligible sepsis subjects with malignancy, there was an 82% mortality rate (287 subjects). Bivariate and multivariate analyses revealed significant associations between mortality and both SOFA score (adjusted Odds Ratio of 5.833, 95%CI 3.214–10.587) and ECOG performance status (adjusted Odds Ratio of 3.490, 95%CI 1.690–7.208).* ***Conclusion:*** *SOFA score and ECOG performance status are significantly associated with sepsis patient mortality in malignancy cases.*

Keywords: *Sepsis, malignancy, mortality.*

INTRODUCTION

Sepsis is a life-threatening state of organ dysfunction caused by a dysregulation of the patient's body's response to infection. Sepsis can lead to shock, multiorgan failure, and death.[1-3] Globally, sepsis incidence reached 48.9 million cases in 2017, with an associated mortality rate of approximately 11 million cases (22.5%).[4] Unfortunately, specific data for the Indonesian population is currently unavailable. However, data collected from five central hospitals in Indonesia in 2018 reported 14,076 cases of sepsis, with an alarming mortality rate of 8,200 cases (58.3%).[5]

Sepsis patients with malignancy have a more complex pathophysiological process that involves interplay between sepsis and cancer. Furthermore, sepsis patient with malignancy was also reported to have a higher mortality rate compared to those without malignancy. Dager et al.[6] reported that patients with a history of malignancy had a significantly increased risk of mortality, with an odds ratio of 2.326. Similar findings were also observed in studies by Moore et al. and Hajjar et al.[7,8] This difference in complexity and prognosis causes the need for other factors in addition Sequential Organ Failure Assessment (SOFA) score to estimate the mortality of sepsis patients with malignancy.[9]

Several factors potentially contributed to sepsis-related mortality in individuals with malignancies, including age, body mass index, history of chemotherapy, history of radiotherapy, ECOG performance status, SOFA score, cancer stage, neutropenic status, and septic shock.[10-14] Given the multitude of suspected factors and the absence of specific data for the Indonesian population, we aimed to investigate these factors so that they could provide valuable insights for clinical applications.

METHODS

This study was conducted at Cipto Mangunkusumo Hospital, a tertiary care hospital and the national referral center for government hospitals. This study is a retrospective cohort study using sepsis and malignancy patients' medical records from January 2020 to December 2022.

Selection and Characteristics of Included Participants

Sepsis patients with malignancy were included in this study. Sepsis diagnosis was made according to sepsis-3. In patients with insufficient data for calculating the SOFA score, the mSOFA score was used. Meanwhile, malignancy diagnoses were established through the gold standard examination for each type of malignancy with histopathological evidence of malignancy before or during sepsis. The patient's performance status was assessed using Eastern Cooperative Oncology Groups (EGOG) during admission to the hospital ward.

Inclusion criteria in this study include: adult (≥18 years old) patients, sepsis diagnosis was done during admission or hospitalization, sepsis diagnosis was done using gold standard examination while patients with insufficient data were excluded from this study. Medical records of sepsis patients admitted to CiptoMangunkusumo Hospital from December 2020 to December 2022 were first screened for age (≥18 years old) and malignancy. Then, patients without gold standard examinations for malignancy were excluded from this study.

Statistical Analysis

The data obtained was analyzed using SPSS 20.0. Numerical variables were first tested for normality using the *Kolmogorov-Smirnov test*. A normal distribution was defined as a p-value≥0.05. Variables with normal distribution are presented descriptively as mean±SD and are presented as median (min-max) otherwise. Bivariate analysis was performed using either the chi-square test or Fisher's exact test. The variables analyzed were age (<60 years old vs. ≥60 years old), body mass index (<25 kg/m² vs. ≥25 kg/m²), chemotherapy within 28 days, radiotherapy within 28 days, malignancy (solid vs. hematologic), stage of solid tumor (metastasis vs. non-metastasis), SOFA score (≤6 vs. >6), neutropenia, ECOG performance status (0-1 vs. 2-4), and initial sepsis-related shock with mortality as an outcome. Independent variables that show a p-value < 0.25 in the bivariate analysis will proceed to multivariate analysis using logistic regression analysis.

RESULTS

Selection of Subjects

The screening was conducted on sepsis patients who were treated at Cipto Mangunkusumo Hospital between January 2020 and December 2022, using their medical records. Patients aged <18 years and those without cancer were excluded from the study. Additionally, patients lacking a gold standard examination for their respective malignancy diagnoses were also excluded. A total of 350 subjects were included in this study. (**Figure 1**)

Baseline Characteristics of Included Participants

The majority of subjects were women (54.29%) with a median age of 56 years and a body mass index (BMI) of 20.4 kg/m2. Most subjects were in stage IV (69.93%), with a median SOFA score of 7 and a median ECOG score was 3. Fifty-one subjects (14.5%) were treated in the high-care unit. Sepsis occurred after the initiation of treatment in 266 (76%) subjects. The mortality rate was 82%. (**Table 1**).

The lung was the most common source of infection, accounting for 229 cases (65.4%), followed by the urinary system in 42 subjects (12%). Biliary tract infection ranked third, with 41 cases (11.7%), followed by intraabdominal infection in 40 cases (11.4%). Other sources

Table 1. Demographic characteristics of subjects (n=350).

Variables	
Gender	
Male, n(%)	160 (45.71)
Female, n(%)	190 (54.29)
Age (years)*	56 (18-84)
Body Mass Index (kg/m^2)*	20.4 (9.2-37.78)
Stage of solid tumor, n (%)	
I	2 (0.70)
II	8 (2.80)
III	54 (18.88)
IV	200 (69.93)
No data	22 (7.69)
SOFA/mSOFA*	7 (3-17)
ECOG performance status*	3 (1-4)
Intensive or High Care Unit, n (%)	51 (14.5)
Sepsis Intrahospital, n (%)	266 (76)
Blood culture, n (%)	275 (78.6)
Positive Blood culture, n (%)	104 (29.7)
Type of Malignancy, n (%)	
Hepatobiliary dan Pancreas	81 (23.16)
Head and Neck	32 (9.16)
Kidney and urinary system	16 (4.47)
Gastrointestinal	32 (9.12)
Hematological	58 (16.59)
Bone	4 (1.16)
Lung and intrathoracic	12 (3.43)
Thyroid	3 (0.86)
Breast	31 (8.86)
Female Reproduction	59 (16.86)
Others	22(6.29)
Mortality, n (%)	287 (82)

* The data is presented as the mean ± standard deviation (SD) for variables with a normal distribution and as the median (min-max) for variables with a non-normal distribution

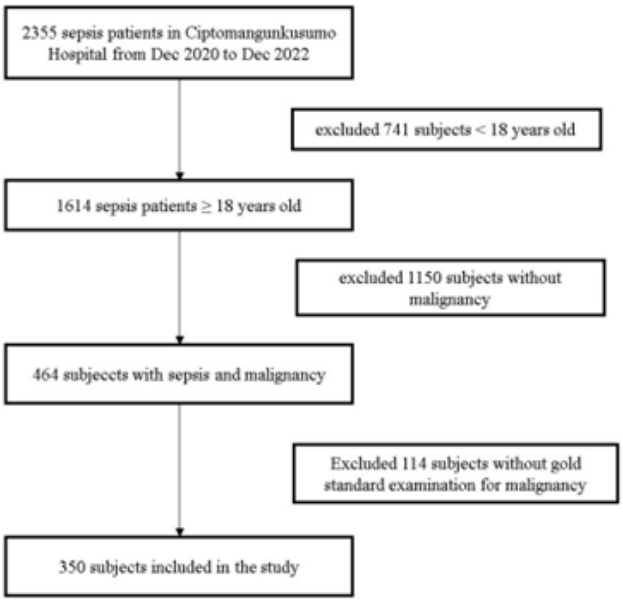

Figure 1. Flowchart of the study.

included skin and soft tissue, neutropenic febrile episodes, catheter-associated bloodstream infections, digestive system infections, ear, nose, and throat infections, and others. (**Table 2**)

Table 2. Infection site.

Infection Site	n (%)
Lung	229 (65.40)
Urinary System	42 (12)
Biliary System	41 (11.7)
Intraabdominal	40 (11.4)
Skin and Soft Tissue	26 (7.40)
Febrile Neutropenia	12 (3.4)
Catheter-Associated Blood Stream Infection	6 (1.7)
Gastroenterology System	6 (1.7)
Head and Neck	2 (0.5)
Others	2 (0.5)

Bivariate Analysis

The bivariate analysis demonstrated statistical significance for both ECOG performance status and SOFA score, with relative risks (RR) of 1.380 (95% CI: 1.096-1.737) for ECOG performance status and 1.492 (95% CI: 1.299-1.714) for SOFA score. (**Table 3**)

Multivariate Analysis

In the multivariate analysis, statistical significance was found for ECOG performance status and SOFA score, with RR values of 1.380 (95% CI: 1.096-1.737) and 1.492 (95% CI: 1.299-1.714), respectively. (**Table 4**)

Table 3. Bivariate analysis.

Variable	Total N (%)	Mortality n (%)	Relative Risk	95% CI	p-value
Age					
< 60 years old	223 (63.71)	176 (78.92)	1.107	1.007-1.217	0.059
≥ 60 years old	127 (36.29)	111 (87.40)			
Body Mass Index					
< 25 kg/m^2	290 (82.86)	235 (81.03)	1.053	0.917-1.210	0.667
≥ 25 kg/m^2	41 (11.71)	35 (85.37)			
Chemotherapy in 28 days					
No	296 (84.57)	248 (83.78)	0.862	0.725-1.025	0.053
Yes	54 (15.43)	39 (72.22)			
Radiotherapy in 28 days					
No	328 (93.71)	268 (81.71)	1.057	0.888-1.258	0.777
Yes	22 (6.29)	19 (86.36)			
Malignancy					
Solid	286 (81.71)	235 (82.17)	0.989	0.869-1.126	0.858
Hematologic	64 (18.29)	52 (81.25)			
Stage of solid tumor					
Non-metastasis	64 (24.24)	49 (76.56)	1.091	0.940-1.266	0.263
Metastasis	200 (75.76)	167 (83.5)			
SOFA Score					
≤ 6	89 (25.43)	53 (59.55)	1.492	1.299-1.714	< 0.001
> 6	261 (74.57)	234 (89.66)			
Neutropenia					
No	311 (88.86)	256 (82.31)	0.966	0.817-1.142	0.660
Yes	39 (11.14)	31 (79.49)			
Performance Status					
0-1	47 (13.43)	29 (61.70)	1.380	1.096-1.737	<0.001
2-4	303 (86.57)	258 (85.15)			
Shock at initial sepsis					
No	161 (46)	127 (78.88)	1.073	0.971-1.186	0.166
Yes	189 (54)	160 (84.66)			

Table 4. Multivariate analysis.

Variables	p-value	Adjusted Odds Ratio	Confidence Interval
Age	0.190	1.564	0.801 – 3.053
Chemotherapy in 28 days	0.470	0.741	0.329-1.671
Shock at initial sepsis	0.315	0.712	0.367 – 1.381
SOFA Score	<0.001	5.833	3.214 – 10.587
ECOG performance status	0.001	3.490	1.690 – 7.208

DISCUSSION

Sepsis patient with malignancy involves an interplay between the two conditions and several other factors (e.g. chemotherapy, invasive procedures, etc.) which causes a more complex process with higher severity.[15] This raised the question of whether the SOFA score can accurately predict mortality in sepsis patients with malignancy as it does not adequately capture the complex interplay of factors displayed in sepsis patients with malignancy. Furthermore, studies have shown that sepsis patients with malignancy have a significantly worse prognosis compared to sepsis patients without malignancy. A meta-analysis by Xiang et al reported a statistically significant increase in mortality in sepsis patients with malignancy compared to sepsis patients without malignancy (OR = 2.46, 95%CI: 1.42-4.25, I2 = 99%).[16]

While the SOFA score has been proven to have a good prognostic value in the general population, its simplistic nature still struggles to adjust to the complexity presented in patients with malignancy. A validation cohort by Greenberg et al. reported prognostic performance of SOFA score in sepsis patients with cancer. In this study, SOFA scores had an Area Under the Curve (AUC) of 0,68 (95%CI: 0.64-0.72) for predicting in-hospital mortality. This prognostic performance is lower compared to when the SOFA score is used in the general population with an AUC of 0.74. Thus, several factors in addition to SOFA score should be considered to more accurately estimate the prognosis of sepsis patients with malignancy. [17,18]

In our study, we evaluated age (<60 years old vs. ≥60 years old), body mass index (<25 kg/m² vs. ≥25 kg/m²), chemotherapy within 28 days, radiotherapy within 28 days, malignancy (solid vs. hematologic), stage of solid tumor (metastasis vs. non-metastasis), neutropenia, ECOG performance status (0-1 vs. 2-4), and initial sepsis-related shock as an additional factors aside from SOFA score (≤6 vs. >6) in patients with malignancy. In the bivariate analysis, we found that age, history of chemotherapy for the last 28 days, shock at the initial diagnosis of sepsis, SOFA score, and ECOG performance status had p-values <0.25. We then performed logistic regression analysis which shows that the SOFA score and ECOG performance status had a significant association with mortality.

We found that SOFA score > 6 is associated with increased mortality in both bivariate and multivariate analysis with p-value<0.001 and adjusted Odds Ratio of 5.833 (95% CI: 3.214 – 10.587). This is to be expected as similar findings have been reported in several previous studies.[19,20] In this study, however, for subjects whose SOFA score cannot be calculated, the SOFA score was replaced using the mSOFA score. This practice is justified by Grissom et al. It was found that the SOFA score and mSOFA score were equally good at predicting mortality.[21]

Patients with ECOG scores 2-4 also have higher mortality compared to patients with ECOG scores 0-1 in this study in both bivariate and multivariate analysis with a value of p = 0.001 and *adjusted Odds Ratio* of 3.490 (95% CI: 1.690 – 7.208). Similar findings were also reported by Torres et al and Rosolem et al in Brazil.[14] This can be attributed to the fact that individuals with poor ECOG performance status often have low organ functional capacity which increases the risk of mortality.[22] Additionally, ECOG performance status reflects overall health and physical condition which also measures how well the body can tolerate the physiological stress during sepsis.

Other variables such as age, stage of cancer, history of chemotherapy, and septic shock were initially suspected of influencing the mortality of sepsis patients with malignancy. However, none

of the variables have statistical significance to mortality. This could be because most patients in these studies have advanced-stage cancer. Only 3.5% were diagnosed with early stages I and II in our study. So, it is likely that the mortality tends to be the same between groups as most patients have poor prognosis to begin with. In the case of the history of chemotherapy, several studies have stated that the effect of chemotherapy on immunosuppression occurs in 7-10 days with a maximum effect observed at 14 days after chemotherapy.[23] This could explain why patients who have completed chemotherapy for more than 14 days may have improved their immunological status and show the same results as those without a history of chemotherapy.

We suggested several differences related to research findings compared with other studies. This may be due to most subjects having advanced malignancy stages and the place of treatment which is a tertiary care hospital and the national referral center for government hospitals. This study illustrated the situation in Indonesia, such as the proportion of cancer cases first diagnosed at the advanced stage (60%), the majority of cancer patients being women and the number of ICUs is low compared to the total population (2.7 per 100,000).[23] For this reason, this study is suitable for describing sepsis patients with malignancy in Indonesia.

Limitation of Study

The drawback of this research is that it uses secondary data. This research was also conducted at one health center only. In addition, several subjects could not be counted on SOFA scores and were replaced with mSOFA.

CONCLUSION

The SOFA score > 6 and ECOG performance status of 2-4 are associated with increased risk of mortality in sepsis patients with malignancy at Cipto Mangunkusumo Hospital.

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