

FACTORS ASSOCIATED WITH MORTALITY IN SEPSIS PATIENTS

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ABSTRACT

Background: Sepsis is a life-threatening illness caused by the body's response to uncontrolled infection. Studies in low-resource settings showed that the majority patients with sepsis still have a high mortality rate. This study aimed to determine the factors associated with mortality in sepsis patients.

Subjects and Method: A retrospective cohort study conducted at Cipto Mangunkusumo Hospital, Jakarta, West Java from January 2016 to October 2022. The study population were sepsis patients. Retrospectively subjects were identified and followed up until death or patients recovered. The data were analyzed using multivariate logistic regression.

Results: The mortality prevalence in sepsis patients was 69%. The risk of mortality in sepsis patients increased with metabolic disease (aOR= 0.45; 95%CI= 0.25 to 0.79; p=0.006).

Conclusion: The risk of mortality in sepsis patients increases with metabolic disease.

Keywords: mortality, sepsis, patients

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BACKGROUND

Sepsis is defined as a life-threatening organ dysfunction caused by dysregulation of the host's response to infection. Sepsis is the most common cause of death in hospitals and is one of the diseases with high economic and social costs (Rudd et al., 2020; Angus et al., 2001). In fact, based on several epidemiological studies, the incidence of sepsis has increased rapidly in the last decade.

The overall sepsis mortality rate was 28.6%, and this increased in patients with comorbidity and organ failure (Angus et al., 2001). Data from large

studies in Europe, show that severe sepsis accounts for 29.6% of intensive care unit (ICU) admissions (Vincent et al., 2006) Sepsis is currently an important disease with high prevalence rates and high mortality.

An studies on factors related to sepsis mortality are still rare, especially in developing countries. In addition, risk factors can differ significantly between hospitals and between countries. Therefore, this study was conducted to determine mortality and mortality risk factors of patients treated for sepsis.

SUBJECTS AND METHOD

1. Study Design

This study used the retrospective cohort method. Samples were sepsis patients who were treated at the Cipto Mangunkusumo Regional General Hospital from January 2016 to October 2022.

2. Population and Sample

The subjects of the study were followed until mortality occurred during sepsis or recovery from sepsis. The study subjects were selected from medical records using the consecutive sampling method.

The inclusion criteria used in this study were 18-year-old patients diagnosed with sepsis according to the qSOFA criteria with a score of 2. qSOFA is a score developed through sofa simplification for faster diagnosis in non-ICU settings. The exclusion criterion is incomplete medical record data.

3. Study Variable

The independent variables studied were age, sex, hemoglobin levels, leukocyte count, neutrophil or lymphocyte count ratio, type of infected organ, solid cancer, hematological cancer, metabolic disease, autoimmune disease, chronic kidney disease, autoimmune therapy, liver function disorders, antiplatelet therapy, blood culture, time to start antibiotics, kidney failure, and heart failure. The dependent variable in this study was inpatient mortality.

4. Definition Operational of Variable

The gender of the patient is based on the data registered in the medical record. The age of the patient is the age of the patient diagnosed with sepsis with an age category of less than 60 years or 60 years and above. The infected

organs in the study were categorized into respiratory or non-respiratory organs. In this study, the solid cancers in question were all cancers excluding neoplasms, bone marrow, and lymph nodes. Hematological cancers include leukemia, multiple myeloma, and lymphoma.

Metabolic diseases recorded are diabetes mellitus (type I or II), dyslipidemia, and hypertension. In this study, liver dysfunction was defined as an increase in AST or ALT more than three times the normal level or history of known chronic liver comorbidities such as cirrhosis of the liver, chronic hepatitis, and fatty liver. Autoimmune diseases included in this study are systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, and vasculitis. The definition of heart failure in the study refers to Framingham's criteria, history of renal failure undergoing hemodialysis obtained from medical records, or eGFR below 30 mL/min/m². eGFR is calculated using the MDRD equation.

The definition of hematological parameters is as follows: anemia is defined as hemoglobin levels below 13 g/dL for men and below 12 g/dL for women, leukocytosis is defined as leukocyte levels above 10,000/mm³, and neutrophil/ leukocyte ratios above 9.0 are considered high.

5. Study Instrument

In this study did not use research instruments.

6. Study Analysis

Medical record data from 2016 to 2022 were processed descriptively to determine the incidence of mortality in sepsis patients. Numerical data with a

normal distribution are presented as mean and standard deviation. Numerical data with an abnormal distribution are presented as median values and minimum-maximum values. Categorical data are presented in the form of percentages.

Bivariate and multivariate analysis of logistic regression was performed to determine which independent variables contributed to mortality events and obtain an Odds Ratio (OR). The value of $p < 0.050$ is considered to indicate a significant difference. All statistical analysis was performed using SPSS software version 20 (SPSS Inc.,

Armonk, NY, USA).

RESULTS

A total of 248 sepsis patients were obtained from medical records after selection through inclusion and exclusion criteria. Sepsis patients with mortality totaled 171 patients (69%). The total number of patients who experienced KID was 50 patients (20.2%). The majority of sepsis patients had the male sex (51.2%) The mean age of sepsis patients in this study was 54.43 years. Characteristics of sepsis patients can be seen in table 1 and table 2.

Table 1. Sample characteristics continuous data (N= 248)

Variables	Mean	SD	Min.	Max.
Age	54.43	15.12	-	-
Hemoglobin	9.66	2.61	-	-
Hematokrit	28.10	7.52	-	-
Leukosit	15305	-	6.6	163340
Trombosit	220500	-	439	855000
Neutrofil/limfosit ratio	13.32	-	0.03	107.6
AST	40	-	6	6859
ALT	26.50	-	6	1632
Albumin	2.53	-	1.29	4.67
Ureum	69.35	-	7.2	298.2
Creatin	1.40	-	0.1	15
eGFR	49.65	-	3	261
D-dimer	3785	-	100	352000
Fibrinogen	416.35	-	38	1044
GFR	49.65	-	3	261

Table 2. Sample characteristics categorical data (N= 248)

Characteristics	Frequency	Percentage
Mortality	171	69%
Disseminated intravascular coagulation	50	20.2%
Male	127	51.2%
Pulmonary Infection	183	73.8%
Solid cancer	84	33.9%
Hematological cancer	24	9.7%
Metabolic disease	90	36.3%
Liver disease	48	19.4%
Antiplatelet therapy	12	4.8%
Autoimmune disease	15	6%
Heart failure	24	9.7%
Chronic Kidney Disease	139	56%

Characteristics	Frequency	Percentage
Hemodialysis	71	28.6%
Positive blood culture	55	22.2%
Antibiotic >1 hour	163	65.7%

The results of the bivariate analysis can be seen in table 3. Based on the results of bivariate analysis of logistic regression, it was found that the risk

factor that was significantly associated with mortality in sepsis patients was metabolic disease (OR= 0.48; 95%CI= 0.28 to 0.84; p= 0.010).

Table 3. Bivariate analysis of factors associated with mortality in sepsis patients

Independent Variables	OR	95% CI		p
		Lower limit	Upper limit	
KID	1.54	0.75	3.15	0.230
Non KID				
Male	0.95	0.55	1.64	0.876
Female				
Age>60 Years	1.12	0.64	1.94	0.689
Age<60 Years				
Lung infections	1.08	0.59	1.98	0.798
Non infections lung				
Solid cancer	1.30	0.72	2.32	0.372
Non solid cancer				
Hematological cancer	1.80	0.64	5.01	0.261
Non hematological cancer				
Metabolic diseases	0.48	0.28	0.84	0.010
Non metabolic diseases				
Liver disease	1.11	0.56	2.22	0.754
Non liver disease				
Autoimmune diseases	1.86	0.51	6.79	0.347
Non autoimmune diseases				
Heart failure	1.10	0.43	2.78	0.834
Non heart failure				
Albumin ≤2.5 g/dL	1.22	0.71	2.11	0.457
Albumin >2.5 g/dL				
eGFR <60 mL/min/1.73 m ²	1.48	0.86	2.54	0.155
eGFR >60 mL/min/1.73 m ²				
Antiplatelet therapy	0.89	0.26	3.06	0.861
No antiplatelet therapy				
Anemia	0.92	0.43	1.99	0.851
Non anemia				
Leukocytosis	1.10	0.58	2.09	0.760
Non leukocytosis				
High NLR Categories	1.46	0.84	2.53	0.178
Lower NLR Category				
Positive blood culture	1.41	0.72	2.79	0.311
Non-positive blood culture				
Antibiotic <1 hour	1.24	0.70	2.17	0.451
Antibiotic > 1 hour				

Meanwhile, in the multivariate analysis of logistic regression (Table 4), metabolic diseases were found to be related to mortality, where metabolic diseases are protective. Meanwhile,

kidney function <60 mL/min/ 1.73 m² was not associated with mortality. The total multivariate steps obtained amounted to 18 steps.

Table 4. Multivariate analysis of factors associated with mortality in sepsis patients

Independent Variables	OR	95% CI		P
		Lower limit	Upper limit	
Metabolic diseases	0.45	0.25	0.79	0.006
Non Metabolic diseases				
eGFR <60 mL/min/ 1.73 m ²	1.64	0.94	2.86	0.081
eGFR >60 mL/min/ 1.73 m ²				
Constant	2.31			<0.001

DISCUSSION

This study shows that metabolic disease does not constitute a mortality risk in sepsis patients. Patients with diabetes have a higher risk for infection and sepsis. In type 1 and 2 diabetes, there is an increase in blood glucose levels and changes in immune responses that depend on glucose levels that may affect the pathogenesis and output of sepsis (Vincent et al., 2006; Constantini et al., 2021). Diabetes, especially type 2, causes prolonged inflammation, suppression of the immune response, and significant morbidity due to infection. In diabetes, there is activation of inflammatory pathways through activation of receptors such as tolls such as TLR2 and TLR4 as well as indirect activation through TLR signaling (Frydrych et al., 2017).

It is necessary to know that from the literature that exists today, not all studies identify hyperglycemia as an independent predictor of mortality in patients with acute medical disorders. A meta-analysis study showed that diabetes is not a risk factor for mortality but that this meta-analysis has a

high heterogeneity (Nugent et al., 2016). Therefore, all studies investigating the relationship between hyperglycemia or metabolic disease in patients with sepsis need to take into account the characteristics of the patient and the comorbidity of the patient. In addition, the duration of diabetes and the quality of patient outpatient management (HbA1c levels) before sepsis may be important factors in patients that need to be studied. This may result in a variety of studies giving varying results regarding the relationship of glucose to mortality in sepsis.

In terms of mechanism, hyperglycemia often occurs in patients with sepsis and can actually have a positive effect on some patients because high levels can increase the diffusion gradient in the blood vessels. Nevertheless, hyperglycemia generally gives more negative effects, but, these negative effects depend on the level of glucose in the patient and the variability of glucose. Hyperglycemia is closely related to high lactate levels, and these lactate levels need to be considered in any analysis of the importance of hyperglycemia (Poston and Koyner,

2019).

In this study, metabolic diseases were found to be protective of sepsis mortality. The current speculation is because patients with DM are treated better than patients without DM because they directly use insulin when sepsis occurs. Data from the research of Vincent et al showed that patients with a history of diabetes treated with insulin, although they had more severe disease and had a higher risk of kidney failure, these patients did not experience an increase in mortality in the ICU or hospital (Vincent et al., 2006)

The study also found that poor kidney function had no role as a mortality risk factor in sepsis patients (OR= 1.64; 95%CI= 0.94 to 2.86; p= 0.081). However, the p-value results are close to 0.05 and at higher sample numbers may give significant results. Various literature suggests that poor kidney function can signal organ damage and decreased tissue perfusion resulting from sepsis, the degree of decrease in kidney function can indirectly correlate with the severity of sepsis (Poston and Koyner, 2019; Gómez and Kellum, 2016). In this study population, sepsis patients with metabolic disease had lower mortality compared to sepsis patients without metabolic disease. Prospective cohort research is required to confirm the results of this study.

AUTHOR CONTRIBUTIONS

The conceptualization was compiled by I khwan R inaldi and Mondastri Korib Sudaryo; methodology compiled by I khwan R inaldi and Mondastri Korib Sudaryo; validation was carried out by I khwan R inaldi, Mondastri Korib Sudaryo and Nurhayati Adnan

Prihartono ; formal analysis was performed by I khwan R inaldi; the investigation was conducted by Ikhwan R inaldi; data retrieval was carried out by Ikhwan R inaldi; manuscript writing done by I khwan R inaldi, Mondastri Korib Sudaryo and Nurhayati Adnan Prihartono; supervision was carried out by Mondastri Korib Sudaryo and Nurhayati Adnan Prihartono; research administration Ikhwan Rinaldi; acquisition of funding by Ikhwan Rinaldi and Mondastri Korib Sudaryo.

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CONFLICT OF INTEREST

No conflict of interest in the study

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