UNIVERSA MEDICINA

pISSN: 1907-3062 / eISSN: 2407-2230

Univ Med 2025;44:3-15

DOI: https://doi.org/10.18051/UnivMed.2025.v44.3-15

ORIGINAL ARTICLE

In-hospital mortality and its determinant factors among patients with sepsis

Fadrian Fadrian[1,2]*, Eva Decroli[3,4], Armen Ahmad[1,2], Alexander Kam[3,4], Disa Hijratul Muharramah[5], Genta Pradana[6], and Vidola Yasena Putri[7]

[1]Department of Internal Medicine, Division of Tropical and Infectious Disease, Dr. M. Djamil Central General Hospital, Padang, Indonesia
[2]Department of Internal Medicine, Division of Tropical and Infectious Disease, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[3]Department of Internal Medicine, Division of Endocrinology and Metabolic, Dr. M. Djamil Central General Hospital, Padang, Indonesia
[4]Department of Internal Medicine, Division of Endocrinology and Metabolic, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[5]Department of Epidemiology, Faculty of Public Health, Sriwijaya University, Palembang, Indonesia
[6]Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia
[7]Faculty of Medicine, Universitas Andalas, Padang, Indonesia

*** Correspondence Author:**
fadrian@med.unand.ac.id

Date of first submission, November 20, 2024
Date of final revised submission, January 30, 2025
Date of acceptance, February 17, 2025

Cite this article as: Fadrian F, Decroli E, Ahmad A, Kam A, Muharramah DH, Pradana G, Putri VY. In-hospital mortality and its determinant factors among patients with sepsis. Univ Med 2025;44:3-15

ABSTRACT

BACKGROUND

Sepsis is a heterogeneous syndrome characterized by a variety of clinical features. Multiple studies have identified sepsis as the leading cause of death in hospitalized patients. A comprehensive report on the incidence, clinical characteristics, and predictors of sepsis is important. This study aimed to determine the relative importance of predictors of in-hospital mortality in sepsis.

METHODS

A retrospective cohort study at Dr. M. Djamil Central General Hospital focused on sepsis patients. A total of 200 participants, aged 18 and older, were included based on specific criteria and recruited through consecutive sampling. Data was gathered from medical records and laboratory results to identify factors influencing mortality in sepsis patients. These factors were classified into sociodemographic, intrinsic, and extrinsic categories. Statistical analysis utilized simple and multiple logistic regression. A p-value of less than 0.05 indicated statistical significance for predicting in-hospital mortality in sepsis.

RESULTS

The sepsis patient mortality rate was 69.50%. Hospital-acquired pneumonia (HAP) emerged as the most common infectious diagnosis, impacting 47.50% of the patients. Type 2 diabetes mellitus (Type 2 DM) was identified as the most frequent comorbidity, present in 36.50% of cases. Multivariate analysis indicated that HAP (adjusted odds ratio [aOR] 2.32; 95% confidence interval [CI] 1.19–4.49; p=0.013) and hyperlactatemia (aOR 2.11; 95% CI 1.06–4.18; p=0.032) significantly increased the risk of mortality in sepsis patients.

CONCLUSION
Hospital-acquired pneumonia was the primary predictor of mortality in sepsis patients. Timely prediction and evaluation of sepsis outcomes are essential for developing strategies to reduce mortality rates.

Keywords: Mortality, risk factors, sepsis, management

INTRODUCTION

According to international guidelines from the Surviving Sepsis Campaign, sepsis is an acute condition with organ dysfunction caused by the body's response to an infection and can be life-threatening.[1] The 2020 Institute for Health Metrics and Evaluation (IHME) Global Burden of Sepsis study reported approximately 48.9 million sepsis incidents worldwide in 2017, equivalent to 677.5 cases per 100,000 age-standardized population.[2] In the Asia Pacific region, sepsis rates vary from 120 to 1600 per 100,000 people.[3] Data on sepsis prevalence in Indonesia is limited; however, a recent retrospective observational study of 14,076 hospitalized patients with sepsis in four Indonesian centers found that 61.8% of patients survived.[4]

Sepsis is a major global public health concern and a common complication during hospitalization, with 23.6% of cases being hospital-acquired (HA). In intensive care units (ICUs), 24.4% of sepsis cases with organ dysfunction occurred during the ICU stay, while 48.7% had an origin within the hospital. HA sepsis, especially in ICUs, is associated with a higher mortality rate and should be a significant concern.[5] A 2022 study at Dr. M. Djamil Central General Hospital also indicated a notable increase in the sepsis patient mortality rate from 11.53% to 19.64% over the past six months.[6]

Sepsis presents a significant financial challenge for the healthcare system due to the high need for vital organ support.[7] A systematic review by van den Berg et al.[8] showed that the average hospital costs per patient varied widely between countries, ranging from €1101 to €91,951, with a median cost of €36,191. Sepsis costs vary widely between different countries but are consistently extremely high. Meanwhile in Indonesia, the average hospital cost for each surviving and deceased sepsis patient were reported to be US$1,011 and US$1,406, respectively.[4] Therefore, sepsis remains a widespread and economically impactful condition, leading to substantial financial costs and loss of lives in Indonesia and globally.

A systematic review and meta-analysis by Wu et al. [9] studied factors affecting mortality in ICU patients with severe sepsis. The research focused on several variables, including age, antibiotic use, comorbidities, organ dysfunction, and sites of infection. The findings revealed that older patients faced a significantly higher mortality rate, with an odds ratio (OR) of 2.28 (95% confidence interval [CI] 1.65-3.15). Additionally, patients with four or more organ failures exhibited a notably high risk of mortality (OR 0.19; 95% CI 0.11-0.30). Mortality rates also varied according to infection type: hospital-acquired infections had a mortality rate of 0.41 (95% CI 0.18-0.69), whereas for community- and ICU-acquired infections the mortality rate was 0.40 (95% CI 0.20-0.63) and 0.42 (95% CI 0.44-0.53), respectively.[9] A prior cross-sectional study conducted in Vietnam indicated that mechanical ventilation (OR 3.890; 95% CI 1.445–10.474) and renal replacement therapy (OR 2.816; 95% CI 1.318–6.016) are associated with increased mortality in patients with sepsis.[10] Existing studies have primarily concentrated on one or a few variables, leaving many other important factors unexplored. Therefore, additional research is needed to investigate other influences, especially laboratory markers, that could impact mortality in patients with sepsis.

Early prediction of sepsis patient outcomes through understanding the factors contributing to sepsis-related mortality is crucial for guiding treatment and reducing mortality.[11] Traditionally, outcome prediction in sepsis is based on clinical scores, such as sequential organ failure assessment (SOFA), acute physiology and chronic health evaluation (APACHE), or simplified acute physiology score (SAPS). Such mortality prediction scores for critically ill patients are used worldwide and have been extensively validated.[12] A study involving 547 medical records of patients with sepsis showed that the mortality rate among patients with sepsis was 46.2% and mainly attributable to respiratory infections.[13]

Sepsis is not a uniform disease, but a syndrome characterized by the striking variation of biological features.[14] More sophisticated

definitions of distinct molecular endotypes are based on leukocyte genome-wide expression profiles from samples collected on ICU admission.[15,16] However, the implementation of these complex prognostic and predictive strategies at the bedside of patients is limited.[17] Therefore, the present study aimed to assess the magnitude and associated factors of mortality among patients with sepsis admitted to the internal medicine ward of Dr. M. Djamil Central General Hospital.

METHODS

Study design

A hospital–based retrospective cohort study was conducted among patients diagnosed with sepsis and admitted to the internal medicine ward of Dr. M. Djamil Central General Hospital between February and December 2023.

Research subjects

A total of 200 subjects who met the inclusion criteria of being ≥18 years old, diagnosed with sepsis, and admitted to the internal medicine ward of Dr. M. Djamil Central General Hospital during the specified period were included in the study. Participants were required to provide written informed consent to take part in the study. Patients who refused to participate or had incomplete medical records were excluded.

Study variables

This study examines mortality among sepsis patients in the internal medicine ward at Dr. M. Djamil Central General Hospital. The independent variables include sociodemographic factors such as age and sex, intrinsic factors such as comorbidities and illness severity—measured by SOFA score, lactate levels, and other clinical markers—and extrinsic factors such as antibiotic use during hospitalization or in the previous 90 days, bacteriological culture results from infectious sites, and the use of medical devices (e.g., urinary catheter, nasogastric tube, endotracheal tube).

The intrinsic factors assessed include the SOFA score, which measures organ dysfunction across several domains: respiratory, cardiovascular, coagulation, liver, kidney, and consciousness. This score is calculated on the day sepsis is diagnosed, with a range from 2 to 24. Hyperlactatemia is defined as lactate levels exceeding 2 mmol/L. Critical illness-related corticosteroid insufficiency (CIRCI) indicates adrenal insufficiency, identified by cortisol levels under 10 µg/dL on the first day of treatment or decreasing levels afterward. Hypercortisolism is defined as cortisol levels ≥20 µg/dL, while hypocortisolism is indicated by levels under 10 µg/dL.

Sepsis-associated liver dysfunction (SALD) is diagnosed by acute liver failure signs. At least two criteria must be met: bilirubin levels over 2 mg/dL, serum glutamic pyruvic transaminase (SGPT)/serum glutamic-oxaloacetic transaminase (SGOT) more than double the normal value (above 112 U/L), and prothrombin time exceeding 1.5 times the control value or an international normalized ratio (INR) above 1.5. An INR above 1.22 indicates elevation. SGPT levels greater than 56 U/L also suggest liver dysfunction, while hypoalbuminemia is diagnosed by albumin below 3.5 g/dL.

Metabolic acidosis is identified with a pH under 7.35 and low bicarbonate (HCO_3^-) levels. Respiratory acidosis occurs with a pH below 7.35 and high arterial carbon dioxide (pCO_2). Hyponatremia is when sodium levels drop below 136 mmol/L; hypernatremia is when levels reach 146 mmol/L or higher. Anemia is recognized by hemoglobin levels below 13 g/dL for men and below 12 g/dL for women. In this research, mortality during treatment is the dependent variable.

Statistical analysis

The study examined risk factors for sepsis mortality using univariate, bivariate, and multivariate analyses, with a significance level of $p<0.05$. Both bivariable and multivariable logistic regression analyses were employed to identify associated factors. Variables significant at a p value <0.25 in the bivariable logistic regression analysis were entered into the multivariable logistic regression model to control for confounding effects. Adjusted odds ratios (aOR) with 95% CI were computed to evaluate the strength of association and variables with a p value less than 0.05 were declared statistically significant factors associated with the outcome variable.

Ethical approval

This study was approved by our Institutional Review Board of Dr. M. Djamil Central General Hospital, Padang (IRB no. LB.02.02/5.7/453/2023).

Clinical trials registration

The study has been registered in the Thai Clinical Trials Registry (TCTR ID: TCTR20240627004).https://www.thaiclinicaltrials.org/show/TCTR20240627004 under the WHO International Clinical Trials Registry Platform.

RESULTS

The characteristics influencing mortality risk of sepsis

The research involved 200 subjects, with 139 (69.50%) sepsis patients experiencing mortality. The main risk factors for sepsis mortality were age (≤ 65 years) in 66.00% of cases, and females accounting for 56.50%. Hospital-acquired pneumonia (HAP) was the most common infectious disease diagnosis (47.50%), followed by community-acquired pneumonia (CAP) at 45.00%. Comorbidities were present in 88.00% of sepsis patients, with type 2 diabetes mellitus (Type 2 DM) (36.50%), chronic kidney disease (CKD) (33.00%), and heart failure (32.50%) being the most prevalent conditions.

In the study, the majority of subjects experienced hyperlactatemia (71.50%), hypercortisolism (57.60%), and CIRCI (24.60%). Median values for various parameters such as SOFA score, Glasgow Coma Scale (GCS), PO_2/FiO_2 ratio, bilirubin level, creatinine level, mean arterial pressure (MAP), and platelet count were within specific ranges. Antibiotic use history was 53.00% and 38.00% showed multidrug-resistant organisms (MDRO) in culture results, with the most common medical device being the nasogastric tube (NGT) at 55.50%. The results of the analysis presented in Table 1 indicate that the variables satisfy the criteria for multivariate modeling, with a p value of less than 0.25.

Table 1. Characteristics and bivariate logistic regression analysis of sepsis mortality risk factors (n=200)

Risk factors	Survivors (n=139)	Non Survivors (n=61)	p-value
Demographic risk factors			
Age (years)			
>65	47 (69.10)	21 (30.90)	1.000
≤65	92 (69.70)	40 (30.30)	
Sex			
Male	57 (65.50)	30 (34.50)	0.353
Female	82 (72.60)	31 (27.40)	
Intrinsic risk factors			
Infectious disease			
Hospital-acquired pneumonia	73 (76.80)	22 (23.20)	0.046*
Community-Acquired pneumonia	59 (65.60)	31 (34.40)	0.346
Skin and soft tissue infections	24 (64.90)	13 (35.10)	0.631
Urinary tract infection	20 (57.10)	15 (42.90)	0.122*
Surgical wound infection	5 (71.40)	2 (28.60)	1.000
Intra-abdominal infection	6 (85.70)	1 (14.30)	0.678
Central nervous system infection	1 (25.00)	3 (75.00)	0.085
Other infections	0 (0.00)	2 (100.00)	N/A
Comorbid diseases			
Presence of comorbidities	125 (71.00)	51 (29.00)	0.303
Diabetes mellitus type 2	47 (64.40)	26 (35.60)	0.302
Chronic kidney disease	48 (72.70)	18 (27.30)	0.594
Heart failure	45 (69.20)	20 (30.80)	1.000
Stroke	26 (65.00)	14 (35.00)	0.618
Malignancy	27 (84.40)	5 (15.60)	0.074*
Chronic lung disease	9 (52.90)	8 (47.10)	0.202*
Chronic liver disease	12 (75.00)	4 (25.00)	0.780
Neutropenia	6 (100.00)	0 (0.00)	N/A
Systemic lupus erythematosus	5 (100.00)	0 (0.00)	N/A
Hypertension	30 (65.20)	16 (34.80)	0.592
Human immunodeficiency virus	1 (100.00)	0 (0.00)	N/A

Table 1. Continued

Hyperlactatemia	107 (74.80)	36 (25.20)	0.015*
CIRCI	23 (79.30)	6 (20.70)	0.793
Hypercortisolism	54 (74.00)	19 (26.00)	0.602
Hypocortisolism	9 (75.00)	3 (25.00)	1.000
SALD	16 (76.20)	5 (23.80)	0.650
Elevated INR	53 (79.10)	14 (20.90)	0.053*
Elevated SGPT Levels	36 (75.00)	12 (25.00)	0.442
H**y**poalbuminemia	100 (68.50)	46 (31.50)	0.737
Metabolic acidosisf	32 (84.20)	6 (15.80)	0.046*
Respiratory acidosis	6 (75.00)	2 (25.00)	1.000
Hypernatremia	24 (82.80)	5 (17.20)	0.145*
Hyponatremia	45 (70.30)	19 (29.70)	1.000
Anemia	101 (69.70)	44 (30.30)	1.000
SOFA score, Median (Min-Max)	8 (1-17)	6 (2-17)	0.007*
Glasgow Coma Scale, Median (Min-Max)	1.90 (0.20-31.12)	12 (5-15)	0.010*
PO_2/FiO_2 **r**atio, Median (Min-Max)	201.81 (47.20-809.39)	218.78 (43.11-161311.00)	0.362
Bilirubin levels (mg/dL), Median (Min-Max)	0.80 (0.10-31.50)	0.70 (0.20-25.00)	0.444
Creatinine levels (mg/dL), Median (Min-Max)	1.80 (0.30-18.00)	1.25 (0.10-11.70)	0.615
Platelet count (/mm^3), Mean ± SD	223683.45 ±144611.58	232475.41±26733.26	0.682
Mean arterial pressure Median (mmHg), (Min-Max)	80 (35-170)	80 (50-140)	0.483
Extrinsic risk factors			
History of antibiotic use	77 (72.60)	29 (27.40)	0.384
Infection source culture			
Multidrug–Resistant Organisms	54 (71.10)	22 (28.90)	0.396
Medical device			
Nasogastric tube	76 (68.50)	35 (31.50)	0.842
Urinary catheter	69 (67.60)	33 (32.40)	0.669
Mechanical ventilator	17 (94.40)	1 (5.60)	0.032*

*****Data presented as n (%); variables with p<0.25 included in multivariate logistic regression analysis; CIRCI : Critical illness-related corticosteroid insufficiency; SALD : Sepsis-associated liver dysfunction; SOFA : Sequential organ failure assessment.

Factors affecting mortality risk in sepsis

The study conducted both bivariate and multivariate analyses to identify the risk factors associated with mortality in patients with sepsis. Table 2 presents the findings from the multivariate logistic regression analysis, which examined the risk factors linked to death in these patients. For this analysis, we included all variables with a p-value of less than 0.25 from the previous bivariate analysis. The results indicated that intrinsic risk factors, particularly HAP, were significantly associated with mortality in sepsis patients. The crude OR was 1.96 (95% CI 1.05–3.64), while the adjusted OR was 2.16 (95% CI 1.06–4.37). In contrast, factors such as urinary tract infections, central nervous system infections, comorbidities such as malignancy and chronic lung disease, as well as metrics including hyperlactatemia, elevated INR values, metabolic acidosis, hypernatremia, SOFA scores, and GCS scores did not show significant associations after adjustment.

In the initial analysis of extrinsic risk factors, a high risk was associated with the use of mechanical ventilators (OR 8.36; 95% CI 1.08–64.32). However, this association lost significance after adjustment (aOR 4.75; 95% CI 0.57–39.49). Ultimately, HAP emerged as a significant risk factor in the comprehensive model, while other factors did not show a substantial link to mortality in patients with sepsis after adjustment.

Using logistic regression analysis with the backward elimination method, a final model was developed that highlighted the variables significantly linked to mortality in sepsis patients, as shown in Table 3. The analysis identified HAP (aOR 2.32; 95% CI 1.19–4.49; p=0.013) and hyperlactatemia (aOR 2.11; 95% CI 1.06–4.18; p=0.032) as significant predictors of death. Other variables, such as elevated INR (aOR 1.95; 95% CI 0.94–4.01; p=0.071), metabolic acidosis (aOR 2.60; 95% CI 0.97–6.96; p=0.057), and mechanical ventilator use (aOR 6.91; 95% CI 0.86–55.20; p=0.068), did not reach statistical significance, even though they had high odds ratios.

Table 2. Crude OR-and adjusted OR on sepsis mortality risk factors after all variables with p<0.25 were included into the multivariate logistic regression

Variable	OR Crude (95%CI)	OR Adjusted (95%CI)
Intrinsic risk factors		
Infectious disease		
Hospital-acquired pneumonia	1.96 (1.05-3.64)	2.16 (1.06-4.37)
Urinary tract infection	0.50 (0.24-1.09)	0.57 (0.25-1.31)
Central nervous system infection	0.14 (0.01-1.37)	0.32 (0.03-3.48)
Comorbid diseases		
Malignancy	2.7 (0.98-7.34)	1.75 (0.59-5.19)
Chronic lung disease	0.46 (0.17-1.25)	0.41 (0.14-1.24)
Hyperlactatemia	2.30 (1.22-4.43)	1.96 (0.97-3.99)
Elevated INR	2.06 (1.40-4.10)	1.63 (0.75-3.52)
Metabolic Acidosis	2.74 (1.08-6.95)	2.41 (0.859-6.88)
Hypernatremia	2.34 (0.85-6.45)	1.76 (0.57-5.45)
SOFA Score	1.13 (1.02-1.25)	1.04 (0.85-1.08)
Glasgow Coma Scale	0.88 (0.79-0.98)	1.06 (0.93-1.21)
Extrinsic risk factors		
Mechanical ventilator	8.36 (1.08-64.32)	4.75 (0.57-39.49)

*OR : Odds Ratio; CI : Confidence Interval

Table 3. Multivariate logistic regression analysis for risk factors of sepsis

Variable	OR Adjusted	95% CI		p value
		Lower	Upper	
Hospital-acquired pneumonia	2.32	1.19	4.49	0.013*
Hyperlactatemia	2.11	1.06	4.18	0.032*
Elevated INR	1.95	0.94	4.01	0.071
Metabolic acidosis	2.60	0.97	6.96	0.057
Mechanical ventilator	6.91	0.86	55.20	0.068

*p-value<0.05 means that the variable is statistically significant; OR : Odds Ratio; CI : Confidence Interval

This model shows that hospital-acquired pneumonia (HAP) and hyperlactatemia are major risk factors for mortality in patients with sepsis, with HAP being the most significant predictor of in-hospital mortality among these patients. The other variables were retained in the logistic regression analysis despite not achieving statistical significance (p>0.05) because they may improve the overall fit of the model and account for confounding influences on the significant predictors. In the backward elimination method, the removal of variables is based not only on p-values but also on their contribution to the model's completeness and their interactions with other variables.

DISCUSSION

The study showed a high sepsis patient mortality rate of 69.50% at Dr. M. Djamil Central General Hospital in West Sumatra, Indonesia. The hospital being the main referral center resulted in a higher incidence of terminal conditions and organ dysfunction. Similar findings were reported in a prior study at RSU Dr. Saiful Anwar, where 72.94% of sepsis patients did not survive.[18] High mortality rates in sepsis patients are associated with organ dysfunction, as evidenced in the study of Pedersen et al.[19] who found that patients with new organ failures had significantly higher mortality rates compared to those without new organ failures.

According to the statistical analysis, most participants in this study were aged 65 years or younger, accounting for 66.00% of the subjects. Similar findings were reported in a study, where 66.67% of sepsis patients were under 65 years of age, while only 33.33% were aged 65 years or older.[20] In contrast, a study by Chen et al.[21] reported that 63.8% of 254 sepsis patients were 65 years of age or older. This disparity may be due to their study being limited to ICU patients and to its prospective design.

Regarding gender, the majority of subjects in our study were female at 56.50%, compared to 43.50% male subjects. Research on gender

differences in sepsis hospitalization similarly found that women experienced sepsis more frequently, with a prevalence of 53.7% in females versus 46.3% in males.[22] This contrasts with the study by Khwannimit and Bhurayanontachai,[23] which indicated a predominance of males (56.9%) in severe sepsis and septic shock cases. This difference may arise from their focus solely on patients with severe conditions and from their prospective research approach.

In the present study, HAP accounted for 47.50% of cases, followed by CAP at 45.00%. Previous research at Dr. M. Djamil Central General Hospital yielded similar findings, indicating that the lungs were the primary infection source in sepsis patients, representing 80% of cases.[24] The vulnerability of the lungs during sepsis is often triggered by lung infection, leading to increased suffering and a higher mortality risk for these patients.[25] Another study by He et al.[26] revealed that patients with pulmonary sepsis exhibited higher age, higher APACHE II scores, and increased ICU and one-year mortality rates compared to those with abdominal sepsis.

In our study, 88.00% of sepsis patients had comorbidities. A retrospective study showed that 97.4% of sepsis patients had previously been diagnosed with at least one comorbidity, indicating a significant history of comorbidity in this patient population.[27] The data is supported by the study of Stenberg et al.[28] showing that male sex, advanced age, lower education, and the presence of comorbid conditions are all positively correlated with sepsis. Consequently, comorbidities play a significant role in mortality, and the occurrence of death from sepsis without relevant comorbidities is rare.[29]

Our study found that type 2 DM was the most common comorbid condition in sepsis patients at 36.50%. In Indonesia, the prevalence of type 2 DM increased from 6.9% in 2013 to 8.5% in 2018. Another report revealed that 13,733 people in Padang City had type 2 DM.[30] Poor dietary habits, such as low intake of fruits and vegetables and high consumption of salt, of sweets, and of fatty foods, contribute to the rising prevalence of diabetes mellitus in Indonesia.[31]

In our study, over 70% of subjects showed hyperlactatemia, associated with tissue underperfusion and organ dysfunction. Sepsis patients with lactate levels exceeding 2 mmol/L indicate organ dysfunction, similar to findings in other studies on sepsis patients.[32] For instance, a study on 4861 sepsis patients revealed that 53% had hyperlactatemia.[,33] Additionally, a study by Sheikh et al.[34] found that 36.4% of intensive care patients with sepsis had hyperlactatemia, with a higher frequency in elderly patients compared to younger and middle-aged patients.

In the present study, hypercortisolism was found in 57.60% of participants, while hypocortisolism was present in 11.00%. These results suggest cortisol dysregulation in sepsis patients, affecting the body's inflammatory response. In comparison, in the study by Rivas et al.,[35] the proportion of patients with cortisol levels of ≥20 mcg/dL (42.6%) was lower than those with levels of <20 mcg/dL (57.4%). Our research also found a smaller percentage of patients (13.1%) with hypocortisolism (<10 mcg/dL), showing similarities with the study of Rivas et al.[35]

In our study, CIRCI was found in 24.60% of participants. In addition to its relationship with sepsis and septic shock, CIRCI is associated with conditions including acute respiratory distress syndrome (ARDS), major trauma, bacterial pneumonia, and non-septic shock scenarios such as those in cardiopulmonary bypass patients, cardiogenic shock, and burns. In cases of sepsis, CIRCI conditions ranged from 12% to 75%.[36] In a cross-sectional analysis, patients with adrenal insufficiency or CIRCI showed nearly identical outcomes, with 25.3% of sepsis patients being affected.[37]

In our study, 24.00% of participants had high SGPT levels, indicating liver dysfunction. High SGPT levels can be mild, moderate, or severe, corresponding to less than 5 times, 5–10 times, and 10–50 times the upper limit, respectively. In sepsis, liver dysfunction is part of multiple organ dysfunction syndrome (MODS) and has a poor prognosis (exact incidence unknown). Another study found a significant correlation between high SGPT levels and sepsis.[38-40]

The present study found that 10.50% of subjects had sepsis-associated liver dysfunction (SALD). Recent research indicates that liver dysfunction is more common at the onset of sepsis. Although rare, SALD in sepsis patients can lead to serious complications.[38] The presence of SALD in sepsis patients is associated with higher mortality and a poorer prognosis. A retrospective observational study found that the SALD group had a 24.7% ICU mortality rate compared to 9.0% for the control group, and hospital mortality rates

were 34.2% for the SALD group compared to 13.8% for the control group.[41]

Patients with liver failure and sepsis often develop coagulation disorders associated with SALD, which if progressing to acute liver failure can cause complications, including coagulopathy such as disseminated intravascular coagulation (DIC), typically measured through INR.[42] In our study, 33.50% of participants showed increased INR levels. The study by Wada et al.[43] reported a higher INR level (50.14%). Research indicated that sepsis patients with organ dysfunction had higher mortality rates due to elevated INR, often associated with an increase in DIC score.

In the present study, the median SOFA score was 7 (1-17), GCS 11 (3-15), PO_2/FiO_2 ratio 204.60 (43.11-809.39), bilirubin level 0.70 (0.10-31.50), creatinine level 1.75 (0.20-31.12), MAP 81 (35-170), and mean platelet count 226,36 ±139,14. The use of mean values in presenting results could potentially obscure the differences in median values for these two variables. Discrepancies in sample sizes and research methodologies may also contribute to these variations.

In our study, antibiotic use prevalence was 53.00%. At Dr. M. Djamil Central General Hospital, a referral center, patients may have previously received antibiotics elsewhere. The rise in antibiotic resistance is mainly due to increased use of broad-spectrum antibiotics. A similar study at the hospital found that 73.5% of patients had used antibiotics, consistent with our findings.[44]

The use of prior antibiotics is associated with mortality, and timely appropriate antibiotic treatment is crucial for patients with sepsis and septic shock. An observational study found that early inappropriate antibiotic therapy significantly increased the risk of mortality with an OR of 10.4.[45] This aligns with a systematic review, which showed that patients receiving appropriate antibiotics had significantly lower mortality rates compared to those receiving initial inappropriate antibiotics with an OR of 0.44 (95% CI 0.38–0.50).[46] In a prior hospital study, Fadrian et al.[47] evaluated antibiotic use using the Gyssens algorithm. The study found a 1.96 and 4.05 times increased risk of death with inappropriate use (Gyssens I-IV) and use without indications (Gyssens V), respectively.

In this study, culture results showed that 38.00% were MDRO, 24.00% were non-MDRO, and 38.00% showed no growth from the infection source. Factors such as insufficient nutrients, culture media toxicity, or interference by other bacteria may explain the lack of growth. Fadrian et al.[44] found a higher prevalence of MDRO (66.93%) compared to non-MDRO (33.06%) in sepsis patients. Conversely, at Cipto Mangunkusumo Central General Hospital, the prevalence of MDRO (40.6%) was lower than non-MDRO (59.4%) in CAP patients.[48] The increase in multidrug-resistant organisms has raised the occurrence of sepsis and related deaths, emphasizing the importance of early diagnosis and treatment.[49]

In a study on medical device usage, NGT was used in 55.50% of cases, urinary catheters in 51.00%, and mechanical ventilators in 9.00%. Increased NGT usage is often associated with addressing the nutritional needs of sepsis patients with reduced consciousness and individuals with chronic swallowing issues. Furthermore, 88% of the patients had comorbidities such as stroke, malignancies, and others, highlighting the necessity for adequate nutrition.[50]

In this study's multivariate analysis, increased INR levels were not found to be a significant risk factor for mortality among patients with sepsis. Coagulation issues frequently occur in sepsis and can raise mortality rates. Initially, patients with sepsis may experience a prothrombotic state. This is marked by the activation of the extrinsic pathway and heightened coagulation due to cytokines, alongside reduced anticoagulant activity and impaired fibrinolysis. As sepsis advances, DIC results in decreased coagulation overall.[51] The INR test is often recommended for patients suspected of having DIC due to sepsis. A different retrospective cohort study indicated that a higher INR is associated with increased hospital mortality among these patients. The odds ratio for hospital mortality was 1.86 (95% CI 1.37–2.52). Additionally, the hazard ratio for one-year mortality was 1.465 (95% CI 1.24–1.74).[52] While these studies share similarities in design, the differences in sample sizes may lead to variations in their findings.

The use of mechanical ventilators did not emerge as a risk factor for mortality in sepsis patients. Among 200 patients studied, 18 required intubation. This contrasts with findings from a retrospective cohort study by Liu et al.[53] which identified a significant link between intubation and increased mortality. Sepsis is responsible for approximately 70% of ARDS cases that involve organ failure, especially in the lungs. While intubation may be necessary for septic patients, it

also raises the risk of mechanical injury. A retrospective analysis revealed a 34% incidence of ARDS among sepsis patients, with a corresponding higher mortality rate. Additionally, the study indicated a notable association between pneumonia and the worsening of ARDS (OR 2.512; 95% CI 1.039-6.067).[54] Furthermore, variations in sample sizes and research methodologies used may also contribute to these differences.

Among our 200 sepsis patients studied, 38 were found to have metabolic acidosis. Our multivariate analysisindicated that metabolic acidosis was not a significant risk factor for mortality in these patients. Renal function, which influences acidosis, is a known predictor of mortality, regardless of whether patients have renal dysfunction. Interestingly, only 33% of participants had CKD, suggesting that CKD did not primarily cause metabolic acidosis. Instead, lactic acidosis due to hyperlactatemia was observed, affecting 71% of participants. This was further supported by the analysis, which showed that hyperlactatemia contributed to a 2.11-fold increased risk of mortality. In contrast, a retrospective cohort study at RS. Dr. Soetomo in Surabaya found a significant association between metabolic acidosis and mortality (OR 5.00; 95% CI 0.933-26.785).[55] Differences in sample sizes and research methodologies may explain the conflicting results.

In this study, we found that hyperlactatemia is a significant risk factor for mortality in sepsis patients. Lactate is a crucial marker for inadequate tissue oxygenation and perfusion. Sepsis patients with high lactate levels are at a 2.11 times higher risk of mortality (95% CI 1.06-4.18). Another study with 4983 sepsis patients also found a significant association between hyperlactatemia and mortality (HR 1.54; 95% CI 1.29-1.81).[56] Hyperlactatemia is characterized by elevated lactate levels exceeding 2 mmol/L. This condition may arise from escalated lactate production via aerobic or anaerobic pathways, coupled with reduced lactate clearance, consequently leading to acidosis. An increase in aerobic lactate production, either local or general, can be caused by an inflammatory process and hyperlactatemia is an indicator of a severe inflammatory state.[32] In the aforementioned study by Liu et al.[57] it was determined that lactate serves as an independent prognostic indicator for mortality in patients with sepsis. Additionally, a retrospective study revealed a correlation between lactate levels exceeding 2.3 mmol/L and mortality in septic patients with acidosis (OR 2.60; 95% CI 2.15-3.15).[58]

In both simple and multiple logistic regression analyses, HAP emerged as the most significant predictor of mortality in patients with sepsis. Out of 200 sepsis patients, 95 patients with HAP displayed a notable link between HAP and increased mortality (OR 2.32; 95% CI 1.19-4.49). The respiratory tract is the most common location for infections that cause sepsis and is more likely to cause death than any other focus of infection. Nosocomial infections, also known as hospital-acquired infections (HAIs), refer to infections that are not present or are in the incubation stage at the time of hospital admission. These types of infections are typically caused by multi-resistant organisms, which can lead to more severe clinical infections and limit the available options for antibiotic therapy.[59] In a study by Rose et al.[60] HAP was the most prevalent HAI in sepsis patients, with rates of 45.1% and 52.2% in sepsis and severe sepsis patients, respectively. Permpikul et al.[61] found that HAP significantly contributed to 62.2% of 28-day mortality and 53.8% of overall in-hospital mortality in sepsis patients. Another prospective cohort study showed a significant association between various sites of infection and in-hospital mortality. The study revealed a notable correlation between pneumonia and in-hospital mortality (OR 3.4; 95% CI 2.2-5.2).[62]

The present study has several limitations that must be acknowledged. Firstly, it was conducted using a retrospective design, which introduces potential biases, particularly in terms of information accuracy. Furthermore, the research was carried out at a single hospital in Padang, Indonesia, which limits the geographic scope. This confinement may affect the applicability of the findings to other healthcare settings and populations. Additionally, the study focuses only on a specific set of factors that influence mortality among sepsis patients. However, it is important to recognize that many other variables also contribute to sepsis-related mortality. Due to constraints related to subject availability and research funding, we were unable to investigate all of these factors.

Recognizing these limitations is crucial, as they highlight the need for broader research. Future studies should aim to include multiple hospitals or explore more diverse geographic areas. This expanded approach would provide a more thorough understanding of in-hospital sepsis

mortality and the various determinants involved, ultimately enhancing clinical practices and patient outcomes in treating sepsis.

CONCLUSIONS

Hospital-acquired pneumonia emerged as the strongest predictor of mortality in patients with sepsis. Identifying the risk factors that contribute to mortality in these patients is crucial for developing effective management strategies to lower death rates. Furthermore, additional multicenter studies are necessary. These should focus on gathering detailed data about patient characteristics, clinical outcomes, and relevant diagnostic tests to uncover more predictors of mortality in sepsis.

Conflict of Interest

The authors disclose no conflicts.

Funding

The study is supported by Dr. M. Djamil Central General Hospital Grant No. LB.01.02/XVI.1.3.2/1508/IX/2023.

Acknowledgment

The authors thank the Research and Development Department of Dr. M. Djamil Central General Hospital for supporting this study by providing input and consultation throughout the study. We would also like to thank the Medical Record Department of Dr. M. Djamil Central General Hospital and the laboratory of Dr. M. Djamil Central General Hospital for their support and assistance in providing data and information for the study.

Author Contributions

FF: conceptualization, methodology, investigation, validation, visualization, supervision, project administration, original draft writing, review & editing. ED: conceptualization, methodology, investigation, visualization, supervision, original draft writing, review & editing. AA and AK: conceptualization, investigation, supervision, original draft writing, review & editing. DHM: methodology, formal analysis, validation, software data. GP and VYP: data curation, investigation, software data, original draft writing, review & editing. All authors have read and approved the final manuscript.

Data Availability Statement

The supplementary dataset for this study will be made available by the corresponding author upon reasonable request.

Declaration the Use of AI in Scientific Writing

The authors affirm that artificial intelligence (AI) was not employed in the creation of this manuscript.

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