



The Relationship Between Lactic Acid Levels and Mortality in Patients with Sepsis Pneumonia at H. Adam Malik Hospital Medan in 2023

Senna Oktora Nasution* , Syamsul Bihar, Ella Rhinsilva, Rina Amelia

Universitas Sumatera Utara, Indonesia

Email: sennanst0710@gmail.com* , syamsul.bihar@usu.ac.id, ellarhinsilva@gmail.com,
rina2@usu.ac.id

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ABSTRACT

Sepsis associated with pneumonia is a critical condition with a high risk of mortality due to systemic inflammation, tissue hypoperfusion, and progressive organ dysfunction. Serum lactate has been widely recognized as an important biomarker of tissue hypoperfusion and altered cellular metabolism, whereas procalcitonin is commonly used as a biomarker of bacterial infection and systemic inflammatory response. However, evidence regarding the prognostic value of these biomarkers in Indonesian tertiary hospitals remains limited. This study aimed to determine the relationship between serum lactate levels and mortality among patients with sepsis associated with pneumonia at H. Adam Malik Hospital in Medan in 2023 and to compare this relationship with that of procalcitonin levels. This analytical study employed a cross-sectional design using medical record data from patients diagnosed with sepsis associated with pneumonia between January and December 2023. A total of 93 patients who met the inclusion criteria were analyzed. The associations between biomarker levels and mortality were assessed using the chi-square test, with statistical significance set at $p < 0.05$. Patients with serum lactate levels >2 mmol/L had a higher mortality proportion (91.9%) than those with levels <2 mmol/L (77.4%). Statistical analysis demonstrated a significant association between serum lactate levels and mortality ($p = 0.043$). In contrast, procalcitonin levels were not significantly associated with mortality ($p = 0.600$). Elevated serum lactate levels were significantly associated with mortality among patients with sepsis associated with pneumonia and may have potential value as a prognostic marker. Procalcitonin should be interpreted in conjunction with other clinical parameters rather than as a standalone predictor of mortality. Further prospective studies incorporating serial biomarker measurements are recommended.

INTRODUCTION

Sepsis is a serious medical condition that requires rapid recognition and appropriate management. According to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (J. B. Singer, 2014). Rather than representing a specific disease, sepsis is a clinical syndrome that can be triggered by various infections, in which a dysregulated host response can result in tissue and organ injury. When sepsis is accompanied by profound circulatory, cellular, and metabolic abnormalities, it may progress to septic shock, a condition associated with a substantially higher risk of mortality than sepsis alone (J. B. Singer, 2014).

Globally, sepsis remains a major cause of mortality and critical illness. The World Health Organization (WHO) reported approximately 49 million cases of sepsis and 11 million sepsis-related deaths worldwide in 2017, representing a substantial proportion of global mortality, with 41.5% of cases occurring in children younger than five years (World Health Organization, 2020). The burden of sepsis is disproportionately high in low- and middle-income countries, where limited access to early diagnosis, laboratory services, and critical care resources may contribute to delayed recognition and higher case-fatality rates (World Health Organization, 2020; Xie et al., 2020). Among the numerous infectious causes of sepsis, gastroenteritis and lower respiratory tract infections, particularly pneumonia, have been identified as frequent underlying causes, together accounting for a substantial proportion of sepsis episodes and nearly 68% of cases in some reports (World Health Organization, 2020; Xie et al., 2020). Because pneumonia is common and can progress to systemic infection and organ dysfunction, it represents an important condition for the early identification of patients at risk of developing sepsis and septic shock (Cillóniz et al., 2019; Darkwah et al., 2024; Donaliazarti, 2022; M. Singer et al., 2016).

Pneumonia plays an important role in the epidemiology of sepsis because of its high incidence and potential to progress rapidly to systemic illness. When pneumonia-associated sepsis progresses to septic shock, mortality may reach 50%, while the overall mortality rate among patients with pneumonia-associated sepsis has been reported to be approximately 19% (Eshwara et al., 2020; Rees et al., 2023). The Surviving Sepsis Campaign guidelines emphasize that early recognition and timely management, including appropriate antimicrobial therapy, source control when indicated, and hemodynamic optimization, are essential for improving clinical outcomes (Rees et al., 2023). Bacteremia, although recognized as a factor associated with the progression and severity of infection, has been documented in only approximately 14% of pneumonia-associated sepsis cases. Therefore, blood culture positivity alone cannot reliably identify patients at the greatest risk of adverse outcomes, highlighting the need for additional markers of disease severity and physiological derangement to complement clinical assessment (Eshwara et al., 2020).

Because clinical judgment alone may be insufficient to identify patients with sepsis who are at increased risk of deterioration, several clinical scoring systems have been developed to standardize severity assessment. The quick Sequential Organ Failure Assessment (qSOFA) score provides a rapid bedside assessment to identify patients with suspected infection who may be at increased risk of poor outcomes outside the intensive care unit, whereas the Sequential Organ Failure Assessment (SOFA) score provides a more comprehensive assessment of organ dysfunction using clinical and laboratory parameters. These tools primarily assess clinical and physiological abnormalities and organ dysfunction, which has prompted interest in laboratory biomarkers that may complement clinical assessment and provide additional information regarding tissue perfusion and metabolic abnormalities (Donaliazarti, 2022; Fernando et al., 2020; Ranzani et al., 2019; Waxman & Moran, 2023).

Serum lactate has emerged as one of the most extensively studied biomarkers for this purpose. Elevated lactate levels may reflect impaired tissue oxygen utilization, tissue hypoperfusion, accelerated aerobic glycolysis, or impaired lactate clearance, all of which may occur during sepsis and septic shock (Park et al., 2023; J. B. Singer, 2014; Wright et al., 2022). Lactate measurement may help identify occult tissue hypoperfusion even in patients without

overt hemodynamic instability; however, its specificity is limited because hyperlactatemia can also result from mechanisms unrelated to tissue hypoxia, including impaired hepatic clearance and catecholamine-mediated accelerated glycolysis (J. B. Singer, 2014; Wright et al., 2022). Combining lactate measurements with clinical parameters such as hypotension, capillary refill time, and validated severity scores may provide more comprehensive prognostic information than relying on a single parameter alone. Several cohort studies have demonstrated an association between elevated lactate levels and adverse clinical outcomes, including mortality, intensive care unit (ICU) admission, and prolonged hospitalization, supporting the clinical importance of lactate measurement in patients with sepsis (Hespanhol & Bárbara, 2020; Wright et al., 2022).

Procalcitonin has also been proposed as a biomarker to support the assessment of bacterial infection and sepsis because its concentration generally increases in response to systemic bacterial infection compared with many viral or noninfectious inflammatory conditions (Chen & Li, 2015). Beyond its diagnostic role, procalcitonin has been investigated as a prognostic biomarker and as a tool for antimicrobial stewardship, with serial measurements potentially providing greater clinical value than a single measurement for assessing treatment response and supporting decisions regarding antibiotic discontinuation (Chen & Li, 2015; Demirel, 2018). Nevertheless, its performance as a standalone predictor of mortality in sepsis has been inconsistent across studies because procalcitonin kinetics may be influenced by factors such as the timing of infection, causative pathogen, severity of infection, and previous antimicrobial therapy. Furthermore, comparative evidence regarding lactate and procalcitonin measured within the same population of patients with sepsis associated with pneumonia remains limited.

In Indonesia, where pneumonia contributes substantially to severe respiratory infections requiring hospitalization, locally generated evidence regarding the comparative prognostic value of these biomarkers remains limited. Much of the available evidence regarding lactate levels and mortality in sepsis has been generated in healthcare settings outside Indonesia, and these findings may not be directly generalizable to Indonesian tertiary referral hospitals because differences in patient characteristics, disease severity at presentation, healthcare access, and resource availability may influence biomarker profiles and clinical outcomes. Establishing whether elevated serum lactate levels are associated with mortality in a local population of patients with sepsis associated with pneumonia, and comparing this association with that of procalcitonin, may provide additional evidence regarding the clinical utility of these biomarkers in mortality risk assessment.

Therefore, this study aimed to analyze the relationship between serum lactate levels and mortality among patients with sepsis associated with pneumonia treated at H. Adam Malik General Hospital in Medan and to compare this relationship with that of procalcitonin levels. The study was intended to provide evidence regarding the potential prognostic value of these biomarkers for mortality risk assessment in this patient population.

METHOD

Research Design

This analytical study employed a cross-sectional design to assess the relationship between serum lactate levels and mortality among patients with sepsis associated with pneumonia at H. Adam Malik Hospital in Medan.

Place and Time of Research

The research was carried out after passing the ethical feasibility of the research ethics commission in the field of health of the Faculty of Medicine, University of North Sumatra and the ethics and medical commission of the H. Adam Malik Hospital Medan. The research will be carried out by collecting data on sepsis pneumonia cases from medical records starting from January 2023 to December 2023

Population and Research Subjects

Research Population

Patients diagnosed with sepsis pneumonia at H. Adam Malik Hospital Medan from January 2023 to December 2023.

Research Subject

All patients diagnosed with sepsis pneumonia based on qSOFA scores and clinical diagnoses that met the inclusion criteria at H. Adam Malik Hospital Medan from January 2023 to December 2023.

Inclusion and Exclusion Criteria

Criteria Inclusion

1. Patients over 18 years old
2. Patients diagnosed with sepsis pneumonia based on diagnosis and qSOFA value at H. Adam Malik Hospital Medan

Exclusion Criteria

1. No lactic acid level test was carried out when diagnosed with sepsis pneumonia
2. Patients diagnosed with sepsis without underlying lung disease
3. Incomplete medical record data

Sample Size and Research Sampling Techniques

This study analyzes the relationship between variables, where the sample size is calculated using a formula sourced from secondary data in the form of results from patients' medical records. The formula is as follows:

$$n = \frac{N}{1 + N(e)^2}$$

Description :

n = sample size required N = population size (150)

E = Percentage of study relaxation (e = 0.1)

Therefore, it was found that the minimum number of patients in this study was 60 people.

Research Variables

In this study, free variables and bound variables such as

Independent variables : Asam lactate until

Bound variables : Mortality in patients with sepsis pneumonia

Operational Definition

Table 1. Operational Definitions

Variabel	Remarks	Methods and measuring tools	Measurement results	Skala Ukur
Sepsis pneumonia	Sepsis is a life-threatening organ dysfunction caused by dysregulation of the body's response to infection accompanied by infiltrate from the thoracic photo, clinically diagnosed and qSOFA scores.	View medical record data	-Sepsis pneumonia -Not sepsis pneumonia	Nominal
Asam lactate until	The lactic acid levels included in the study were lactic acid levels for the first time when the patient was diagnosed with sepsis pneumonia. Value <i>Cut-off</i> from the rate Lactate is 2 mmol/L.	View medical record data	-Lactate asam > 2mmol/L -Lactic acid < 2mmol/L	Ratio
qSOFA score	Scoring system used	View data Medical Records	- qSOFA <u>score</u> ≥ 2	Ratio

Research Framework

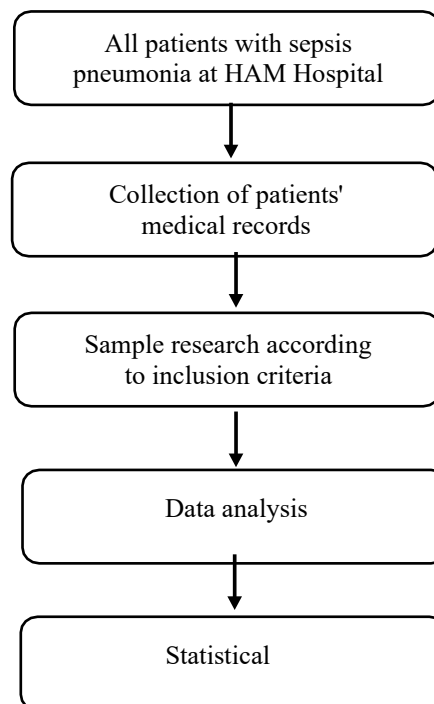


Figure 1. Research flow.

Data Collection Procedure

1. Doing permit management to H.Adam Malik Hospital Medan

The research was carried out after receiving approval from the ethics commission of FK USU, the ethics commission of H. Adam Malik Hospital Medan, and permission from the medical committee of H. Adam Malik Hospital Medan.

2. Data collection of research population

Conducting data collection of research samples, namely patients diagnosed with sepsis at H. Adam Malik Hospital Medan who met the inclusion and exclusion criteria in January 2023-December 2023.

3. Basic and clinical data logging

Basic data was recorded by researchers at H. Adam Malik Hospital Medan such as patient name, gender, patient age, laboratory results, and patient comorbid history (malignant disease, liver disease, cardiovascular disease, cerebrovascular disease, and kidney disease), qSOFA score.

4. External data

The lactic acid levels included in the analysis were the levels of lactic acid that were first taken when the patient was first diagnosed with pneumonia with sepsis.

Data Analysis

1. Once the data is collected, it is checked again to see for completeness. Then, the data is encoded to facilitate pentabulation. The tabulated data is entered into the master table using SPSS software.
2. Normally distributed numerical data will be displayed in the average value of $SD \pm$ (standard deviation) while non-normally distributed numerical data will be presented in the form of a median value (minimum-maximum value). Categorical data will be displayed in the form of a sum (percentage).
3. The normality test uses the Shapiro-wilk test (if the sample is less than 50) or the Kolmogorov-Smirnov test (if the sample is more than 50). The data is said to be distributed normally if the p value > 0.05 .
4. Hypothesis tests were used to see the relationship between qSOFA scores and lactic acid levels using the chi-square test if the data were normally distributed or the Mann-Whitney test if the data were not normally distributed.
5. A 95% confidence interval with a $p < 0.05$ value is considered statistically significant.

Research Ethics

Before collecting data on the research sample, the researcher first submitted an ethical clearance to the Health Research Ethics Committee, Faculty of Medicine, University of North Sumatra.

RESULT AND DISCUSSION

Overview of Research Locations

This research was carried out at H. Adam Malik Hospital Medan. The selection of the research location was based on the prevalence of sepsis pneumonia at H. Adam Malik Hospital Medan (Arnold et al., 2013; Florin et al., 2021; Katz, 2016; Krüger et al., 2008; Lemay et al., 2014).

Based on the results of the study, it was known that of the 62 patients who had lactic acid levels > 2 mmol/L, there were 57 patients (91.9%) who experienced mortality (died) and 5 patients (8.1%) who were outpatient (cured), and of the 31 patients who had lactic acid levels < 2 mmol/L, there were 24 patients (77.4%) who experienced mortality and 7 patients (22.6%) who were outpatient. Based on the results of the study using the chi-square statistical test, the result was $p < 0.05$ ($p = 0.043$). This means that there is a significant relationship between lactic acid levels and the incidence of mortality in patients at H. Adam Malik Hospital in 2023. The relationship between mortality and the incidence of sepsis pneumonia in patients at H. Adam Malik Hospital in 2023 can be seen in Table 2.

Table 2. Relationship between Lactic Acid Levels and Mortality Incidence at H. Adam Malik Hospital in 2023

Asam Until Lactate	Mortality Incidence						<i>p</i>	<i>RP (95%CI)</i>
	Died		Heal		Quantity			
	World							
	n	%	n	%	n	%		
								1,188 (0,68-1,456)
>2 mmol/L	57	91,9	5	8,1	62	66,7	0,043	
<2 mmol/L	24	77,4	7	22,6	31	33,3		

The Relationship between Procalcitonin Levels and Mortality Incidence

Based on the results of the study, it was known that of the 72 patients who had procalcitonin levels >2 ng/ml, there were 62 patients (86.1%) who experienced mortality and 10 patients (13.9%) who were outpatient, out of 21 patients who had procalcitonin levels <2 ng/ml, there were 19 patients (90.5%) who experienced mortality and 2 patients (9.5%) who were outpatient. Based on the results of the study using the chi-square statistical test, the result of $p > 0.05$ ($p = 0.600$) was obtained. This means that there is no significant relationship between procalcitonin levels and mortality incidence in patients at H. Adam Malik Hospital in 2023. The relationship between procalcitonin levels and mortality incidence in patients at H. Adam Malik Hospital in 2023 can be seen in Table 3.

Table 3. Relationship between Procalcitonin Levels and Mortality Incidence at H. Adam Malik Hospital in 2023

Mortality Incidence								
Up to Procalcitonin	Died		Heal		Quantity		<i>p</i>	<i>RP</i> (95%CI)
	World							
	n	%	n	%	n	%		
>2 ng/ml	62	86,1	10	13,9	72	77,4	0,600	0,653 (0,131-3,242)
<2 ng/ml	19	90,5	2	9,5	21	22,6		

Relationship of Lactic Acid Levels with Mortality Incidence in Sepsis Pneumonia Patients

Based on the results of the study, it was found that there was a relationship between lactic acid levels and mortality incidence in sepsis patients in hospitals. H. Adam Malik in 2023. The chi-square statistical test obtained a result of $p < 0.05$ ($p = 0.043$), but no risk estimate was found in the prevalence ratio.

In theory, increased lactic acid levels in sepsis are closely related to tissue hypoperfusion processes and cellular metabolic dysfunction due to systemic inflammatory responses. In sepsis, there is a microcirculation disorder, systemic vasodilation, and capillary leakage that causes the supply of oxygen to the tissues to be inadequate. This triggers the occurrence of anaerobic metabolism with the accumulation of pyruvate which is then converted to lactate. In addition, in the advanced phase of sepsis, there is also a disruption of mitochondrial function which further aggravates lactate accumulation in the circulation. Studies show that lactate

levels of ≥ 2 mmol/L are already associated with an increased risk of death, while a value of ≥ 4 mmol/L is often used as a diagnostic cut-off for septic shock with higher mortality. (Jansen, 2010) reported that patients who did not experience a lactate decrease of at least 10% in the first 6 hours had higher mortality than patients with adequate lactic clearance. Similarly, The research of (Hernández, 2019) confirms that the persistence of hyperlactatemia up to the first 24 hours is a strong predictor of mortality in sepsis patients.

This is contrary to the research conducted by Almira as a result of statistical calculation, a value of $r = 0.018$ ($p = 0.917$) was obtained for the relationship between lactic acid levels and mortality of sepsis patients, so it can be concluded that there is no relationship between lactic acid levels and mortality of sepsis patients.⁵⁶ This result is in line with research conducted by Wang, who stated that lactic acid levels have a fairly strong relationship with sepsis mortality ($r = 0.5315$, $p < .0001$).

The prognosis of sepsis can be measured through two aspects, namely morbidity and mortality. Almost all sepsis patients have high morbidity and last for a long time, namely for > 3 months. Morbidity in sepsis patients is directly related to sepsis complications such as polyneuropathy and chronic lung disease, and indirectly such as stress and impaired cognitive function. Mortality in sepsis patients varies and is highly determined by the presence of organ dysfunction. In a study in Europe in 2005, mortality in sepsis patients without organ dysfunction was 26%, while sepsis patients with organ dysfunction was 42%.⁵⁶ Patients with septic shock had the highest mortality rate at 61%. Sepsis shock that has already experienced respiratory failure and kidney function has the worst prognosis, with mortality reaching 70%. Thus, it can be concluded that the occurrence of septic shock and other morbidities is a sign of poor prognosis in sepsis patients.

In addition, there are many factors other than lactic acid that affect mortality in sepsis.⁵⁸ According to research conducted by Chen, there are several factors that affect sepsis mortality, including the occurrence of Disseminated Intravascular Coagulation (DIC) in sepsis which has an association strength of $OR = 4.211$ with sepsis mortality (IK 95%, 1.622 – 10.933; $p = 0.003$).⁵⁹ In the study, it was also stated that increased body temperature in sepsis also has association of $OR = 1.679$ with sepsis mortality (95% IK, 1.129 – 2.498; $p = 0.011$).⁶⁰ In a study conducted by Lemay, it was found that comorbid sepsis, including diabetes mellitus with complications, also had an association with mortality in sepsis ($HR = 1.08$; IK 95%, 0.87 – 1.35), while other comorbidities such as cancer metastases also had a strong association with mortality in sepsis ($HR = 2.00$; I 95%, 1.47 – 2.72).

The Relationship of Procalcitonin Levels with Mortality Incidence in Sepsis Pneumonia Patients

Procalcitonin is a molecule considered to be the primitive form of defense against bacterial infections that is released before a more effective immune system works. mHowever, it should be noted that circumstances such as trauma, surgery, cardiogenic shock, burns, acute respiratory distress syndrome (ARDS), necrosis after acute pancreatitis, and tissue rejection reactions to transplantation can also increase PCT levels. PCT levels continue to increase and do not decrease after Therapy administration indicates therapy failure.

Boussekey et al. in 2005 conducted a study on the prognostic value of PCT in CAP subjects and found that $PCT > 2$ ng/ml was associated with an increased incidence of bacteremia, sepsis shock, multiorgan failure, and mortality.⁶⁵ Kruger et al. examined the more

specific function of PCT as a predictor of the severity of community pneumonia. High PCT levels were more prevalent in patients who died during follow-up. Serum procalcitonin levels were very low in healthy individuals and levels increase in conditions of severe infection and bacterial infection.

A study by Jain, et al found that procalcitonin levels as a biomarker decreased as the disease progressed. The study measured procalcitonin levels in sepsis, severe sepsis, and sepsis shock patients on days 0, 7, and 28, and found significant decreases in the surviving patient group, while the decrease in the deceased patient group was not reported. In theory, PCT levels begin to increase within 6–12 hours after systemic bacterial infection occurs and peak within 24–48 hours. In patients with severe sepsis or septic shock, PCT levels remain high when the infection continues, but will decrease gradually if antibiotic therapy is effective. In the context of death from sepsis pneumonia, some studies have shown that PCT levels increase significantly about 2–3 days before death in non-ICU patients. This indicates that PCT serial examinations should be carried out from the beginning of diagnosis (day 0) and monitored every 24–48 hours, so that a pattern of increasing or decreasing PCT levels can be detected. One of the important limitations of this study is the lack of serial monitoring of procalcitonin (PCT) levels in patients with sepsis pneumonia.

The results found in this study are similar to the meta-analysis conducted by Liu et al in 2016. Liu et al conducted a meta-analysis of 21 studies with 6,007 patients. Liu et al looked at the prognostic value of procalcitonin levels in patients with pneumonia and sepsis. In this meta-analysis, increased procalcitonin levels were a risk factor for mortality in pneumonia, especially patients with low CURB-65 values.

A slightly different study was also conducted by (Darkwah et al., 2024; Monti et al., 2015; Schuetz, 2017). Schuetz et al examined measurements of serial procalcitonin levels from day one to day four in patients with sepsis. Of the 858 inpatients, 646 patients survived. The 28-day mortality from all-cause increased doubled when procalcitonin did not show a decrease of more than 80% with the first measurement. The conclusions drawn in this study differed from the conclusions of Schuetz et al's study due to differences in methods and related viewpoints procalcitonin with sepsis. In addition, the variable limitations of sepsis due to pneumonia may also need to be taken into account, although pathophysiologically the increase in procalcitonin due to sepsis does not differ between causes from one cause to another.

There was no association between procalcitonin levels and mortality of sepsis patients in this study likely because patients with higher procalcitonin levels received more immediate treatment, as organ damage in these patients was more massive.

CONCLUSION

Based on the findings among patients with sepsis associated with pneumonia at H. Adam Malik Hospital in Medan in 2023, serum lactate levels were significantly associated with mortality. Of the 62 patients with serum lactate levels >2 mmol/L, 91.9% died, and the statistical analysis demonstrated a significant association between serum lactate levels and mortality ($p = 0.043$). These findings suggest that elevated serum lactate levels may have potential value as a prognostic marker of mortality in patients with sepsis associated with pneumonia. In contrast, procalcitonin levels were not significantly associated with mortality. Of the 72 patients with procalcitonin levels >2 ng/mL, 86.1% died; however, the association

was not statistically significant ($p = 0.600$). Although procalcitonin is commonly used as a biomarker of bacterial infection and systemic inflammatory response, elevated procalcitonin levels were not significantly associated with mortality in this study. Therefore, serum lactate may provide useful prognostic information regarding mortality risk in patients with sepsis associated with pneumonia, whereas procalcitonin should be interpreted in conjunction with other clinical and laboratory parameters rather than as a standalone predictor of mortality.

Based on these findings, serum lactate measurement should be considered as part of the initial assessment and subsequent monitoring of patients with sepsis associated with pneumonia because elevated levels were significantly associated with mortality. Procalcitonin may continue to be used as a biomarker to support the assessment of bacterial infection but should be interpreted alongside other clinical and laboratory parameters when evaluating mortality risk. Accurate medical records and systematic monitoring of relevant laboratory biomarkers should also be maintained to support clinical assessment and risk stratification. Further prospective studies with larger sample sizes are recommended to evaluate the prognostic value of serum lactate and procalcitonin while accounting for potential confounding factors, including comorbidities, treatment received, disease severity, and timing of sepsis onset. Serial measurements of serum lactate and procalcitonin should also be investigated to determine whether changes in biomarker levels over time provide greater prognostic value than single measurements.

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