Analysis of C-reactive protein/albumin ratio as a predictor of mortality in sepsis patients

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Original Article

ABSTRACT

Background: Sepsis is a leading cause of death among critically ill patients with infections. Abnormal levels of C-reactive protein (CRP) and albumin in sepsis patients have been shown to predict mortality. Combining the two markers can increase the predictive value of mortality.

Objective: The aim of this retrospective cohort study was to determine the cut-off value for the CRP/albumin ratio that could be used to predict mortality in patients with sepsis.

Methods: Secondary data from 63 medical records of sepsis patients treated in the ICU of RSUP dr. Wahidin Sudirohusodo Makassar from January 2018 to December 2020 was used. Statistical analysis was performed using the Kolmogorov-Smirnov and Mann-Whitney tests. The prognostic value of the CRP/albumin ratio was analyzed using the ROC curve to obtain a cut-off value. A p-value < 0.05 was considered significant.

Results: The sample included 43 deceased and 20 living patients with sepsis. The CRP/albumin ratio was significantly higher in the deceased patients (15.4) than in the living patients (2.4) (p<0.001). The ROC curve analysis revealed a CRP/albumin cut-off value of 4.3 with a sensitivity of 81.4%, specificity of 75.0%, positive predictive value (PPV) of 87.5%, negative predictive value (NPV) of 65.2%, and an accuracy of 79.4%.

Conclusion: The study suggests a significant relationship between the CRP/albumin ratio and mortality in patients with sepsis. A CRP/albumin ratio of 4.3 can be used as a predictor of mortality in sepsis patients.

Latar Belakang: Sepsis merupakan penyebab utama kematian akibat infeksi pada penderita kritis di rumah sakit. Kadar C-reactive protein (CRP) dan albumin yang abnormal pada sepsis secara bersama-sama dapat memprediksi mortalitas sehingga kombinasi keduanya lebih meningkatkan nilai prediktor mortalitas.

Tujuan: Tujuan penelitian ini untuk menentukan rasio cut-off CRP/albumin untuk digunakan sebagai prediktor mortalitas pada pasien dengan sepsis

Metode: Penelitian kohort retrospektif menggunakan data sekunder dari 63 rekam medis penderita yang dirawat di ICU RSUP dr. Wahidin Sudirohusodo Makassar sejak Januari 2018 hingga Desember 2020. Uji Statistik dilakukan dengan uji Kolmogorov-Smirnov dan uji Mann-Whitney. Nilai prognostik CRP/albumin dianalisis dengan ROC untuk mendapatkan cut-off. Hasil uji signifikan jika p<0,05.

Hasil: Sampel terdiri dari 43 penderita sepsis yang meninggal dan 20 yang hidup. Rasio CRP/albumin ditemukan signifikan lebih tinggi pada subyek yang meninggal yaitu 15,4 dibandingkan yang hidup yaitu 2,4 (p<0,001). Kurva ROC menunjukkan nilai cut-off CRP/albumin yaitu 4,3 dengan sensitivitas 81,4%, spesifisitas 75,0%, positive predictive value (PPV) 87,5%, negative predictive value (NPV) 65,2%, dan nilai akurasi 79,4%.

Kesimpulan: Terdapat hubungan signifikan antara rasio CRP/albumin dengan mortalitas penderita sepsis. Rasio CRP/albumin 4,3 dapat digunakan sebagai prediktor mortalitas pada penderita sepsis.

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INTRODUCTION

Sepsis is still the leading cause of death from infection in critically ill hospitalized patients, especially if it is not immediately recognized and treated. Therefore, the recognition of sepsis requires urgent attention. Sepsis is a life-threatening state of organ dysfunction in which the body's response to infection is dysregulated. Septic shock is defined as an advanced condition of sepsis in which the cellular and circulatory metabolic abnormalities accompanying the patient are severe enough to increase mortality. Sepsis can be caused by infection with various microorganisms, including gram-negative and gram-positive bacteria, viruses, fungi, and parasites. The most common cause of sepsis is gram-negative bacteria (60-70%), although there is an increase in gram-positive bacteria (20-40%) due to opportunistic infections and fungi (5%).[1-3]

Based on the International Classification of Disease, the incidence of sepsis varies from 132 to 300 per 100,000 population worldwide per year. In the United States in 2017, an estimated 750,000 cases of sepsis occurred, resulting in 200,000 deaths each year. The mortality rate for sepsis is quite high, with a rate of 50% for generalized sepsis, 25-50% for severe sepsis, and 40-70% for septic shock. The available data on the prevalence of sepsis in Indonesia is limited. In 2020, RSUP dr. Wahidin Sudirohusodo Makassar recorded 494 cases of sepsis, and the intensive care unit (ICU) in the same hospital reported 139 cases. Unfortunately, the mortality rate among sepsis patients in the ICU is alarmingly high, with 88% of cases resulting in death.[2,4,5]

In recent years several assessment models have been developed to describe the severity of disease in patients admitted to the intensive care unit or to predict the outcome of intensive care. The Sequential Organ Failure Assessment (SOFA) score can be used to predict mortality in septic patients. In addition to the SOFA score, other biomarkers can be used to predict the prognosis and evaluate mortality in patients with sepsis or septic shock. These biomarkers must be able to reflect the concept or inflammatory process that plays a role in the pathophysiology of sepsis and can be short-term and long-term markers for prognosis. Because the infection is one of the strongest stimuli of the inflammatory response, a biomarker that could be used to predict prognosis and evaluate mortality in patients with sepsis or septic shock is the use of the C-reactive protein (CRP)/albumin ratio.[6-12]

C-reactive protein (CRP) is an acute-phase protein released by liver cells after being stimulated by inflammatory mediators such as interleukin (IL)-6. Smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes also synthesize this protein. CRP binds to polysaccharides and peptidopolysaccharides found in bacteria, fungi, and parasites in the presence of calcium. In addition, CRP can also bind to core components of apoptotic or necrotic host cells, such as ribonucleoproteins, thereby contributing to tissue clearance. Serum CRP concentrations in the normal adult population mean 0.8 mg/L (range 0.3–1.7 mg/L) and are <10 mg/L in 99% of normal samples. The increase in concentration begins 4-6 hours after the stimulus, doubles every 8 hours, and peaks at 36-50 hours. With a very intense stimulus, CRP concentrations can reach 500 mg/L or more than 1000 times the reference value. After the stimulus is removed, CRP decreases rapidly due to its half-life of 19 hours. CRP's sensitivity as a sepsis biomarker ranges from 68% to 92%, with a specificity of 40% to 67%. The specificity of CRP is low because it is also increased in non-infectious inflammatory conditions such as post-surgery, burns, myocardial infarction, malignant tumours, and rheumatic diseases. This limitation causes CRP to have a low diagnostic role. CRP is more useful for evaluating and being a prognostic sepsis marker.[9,10,13-15]

Albumin is a protein that decreases in concentration in response to inflammation, making it a negative acute-phase protein. Its levels are therefore used to indicate the severity of inflammation. In sepsis, microcirculation dysfunction occurs due to endothelial damage that causes plasma leakage and hypoalbuminemia. This damage is caused by the immune system's activation with antigens, which release inflammatory mediators. These mediators produce cytokines that stimulate blood clotting, leading to thrombosis in the microcirculation. This process causes blood flow to be redirected from areas of dysfunctional microcirculation to areas of good microcirculation, creating a PO_2 gap between the arterial and venous microcirculation. This results in insufficient oxygen delivery to the

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lungs, kidneys, and brain, leading to decreased function of these organs in septic patients cared for in the ICU. Several studies have shown that albumin can serve as an additional parameter to assess mortality and prognosis in sepsis. One such study by Min Ho Seo found that the initial albumin value upon admission was associated with 28-day mortality in patients with severe sepsis, making it a strong prognostic indicator.[16-18]

Abnormal levels of CRP and serum albumin can provide a prognostic index that is positively correlated with infection in severe sepsis and septic shock. Each of these parameters can predict mortality, and combining them increases the predictor value of mortality even further. A study by Ranzani found that patients with a CRP/albumin ratio greater than 2 had poor prognoses and high mortality rates. Abdi concluded that the CRP/albumin ratio is a useful predictor of mortality in septic patients. Another study by Min Hyung Kim established a CRP/albumin ratio cut-off value of 5.09 for predicting mortality in patients with severe sepsis or septic shock. These findings suggest that the CRP/albumin ratio can serve as a reliable predictor of mortality in sepsis.[9,10,19,20]

While there have been several reports on the CRP/albumin ratio in sepsis patients, to the author's knowledge, few studies still consider it a predictor of mortality in sepsis patients in Indonesia, particularly in Makassar.

METHODS

This retrospective cohort study analyzed secondary data from medical records of patients treated for sepsis at the intensive care unit (ICU) of RSUP dr. Wahidin Sudirohusodo Makassar. The study included patients aged 18-65 with a clinical diagnosis of sepsis who were treated at the hospital between January 2018 and December 2020 and had their CRP and albumin levels examined. Patients who received albumin transfusions or had malnutrition were excluded.

Sepsis diagnosis was based on an increase in SOFA score 2 and quick SOFA 2, as determined by clinicians. CRP and albumin levels were obtained from clinical pathology laboratory examinations of sepsis patients and recorded in their medical records. Samples were taken upon patient admission to the emergency room and at the same time. The CRP/albumin ratio was calculated by dividing the CRP value by albumin based on the laboratory test results. Patients were then grouped based on their outcomes, which were recorded in their medical records as either survival or death.

Data analysis was carried out using the statistical package for the social sciences (SPSS) version 25. The statistical analysis methods used were descriptive statistical calculations and frequency distribution, the Kolmogorov-Smirnov test statistical test to assess the normality of the data, the Mann-Whitney test, and the receiver operating curve characteristics (ROC) to assess the area under curve (AUC) and determine the cut-off value of the CRP/albumin ratio as a predictor of mortality in patients with sepsis. The test results are significant if $p<0.05$.

Research permission was obtained from the Health Research Ethics Committee of the Hasanuddin University State Higher Education Hospital – RSUP dr. Wahidin Sudirohusodo Makassar with the number: 592/UN4.6.4.5.31/PP36/2021.

RESULTS

The study was conducted in September 2021 at RSUP dr. Wahidin Sudirohusodo Makassar. Secondary data were collected from inpatients diagnosed with sepsis between January 1, 2018, and December 31, 2020. The total number of patients with sepsis who met the inclusion and exclusion criteria was 63.

Table 1 demonstrated that the majority of the subjects were male (66.7%) and >55 years old (33.3%). Among the patients with sepsis, 43 (68.3%) died, while 20 (31.7%) survived. The CRP levels ranged from 0.1 mg/L to 434.9 mg/L, with a mean of 61.6 mg/L. The albumin levels ranged from 1.0 g/dL to 4.7 g/dL, with a mean of 2.7 g/dL, while the CRP/albumin ratio ranged from 0.04 to 254.1, with a mean of 29.4.

Table 2 indicates a significant relationship between CRP levels and mortality in sepsis patients, as CRP levels were significantly higher in subjects who died (80.4) compared to those who survived (21.2) with $p<0.001$. However, there was no significant difference in albumin levels between patients who died and those who survived with $p>0.790$. The CRP/albumin ratio was significantly higher in subjects who died (36.6) compared to those who survived (13.8),

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with a p-value of <0.001, indicating a significant relationship between the CRP/albumin ratio and mortality in sepsis patients. This relationship is also illustrated in Figure 1.

The cut-off value of the CRP/albumin ratio is determined using ROC curve analysis to determine whether the CRP/albumin ratio can be used as a predictor of mortality in patients with sepsis. Based on the area under curve (AUC) value, the CRP/albumin ratio was 0.819 (81.9%) and significant (p<0.001). This result indicates that the CRP/albumin ratio can be used as a predictor of mortality in sepsis.

Table 1. Characteristics of research sample (n=63)

Variable		n	%	Median (min-max)	Mean±SD
Gender	Male	42	66.7		
	Female	21	33.3		
Age	16-25 years old	14	22.2	17(16-24)	17.3±2.1
	26-35 years old	7	11.1	32(28-33)	31.7±1.8
	36-45 years old	9	14.3	39(36-44)	39.8±3.5
	46-55 years old	12	19.0	50(46-55)	49.8±2.8
	>55 years old	21	33.3	61(56-63)	59.9±2.6
Outside	Die	43	68.3		
	Life	20	31.7		
CRP		63		19.6(0.1-434.9)	61.6±82.9
Albumin		63		2.6(1.0-4.7)	2.7±0.7
CRP/albumin ratio		63		7.6(0.04-254.1)	29.4±50.2

Table 2. CRP value, albumin, and CRP/albumin ratio by the outcome

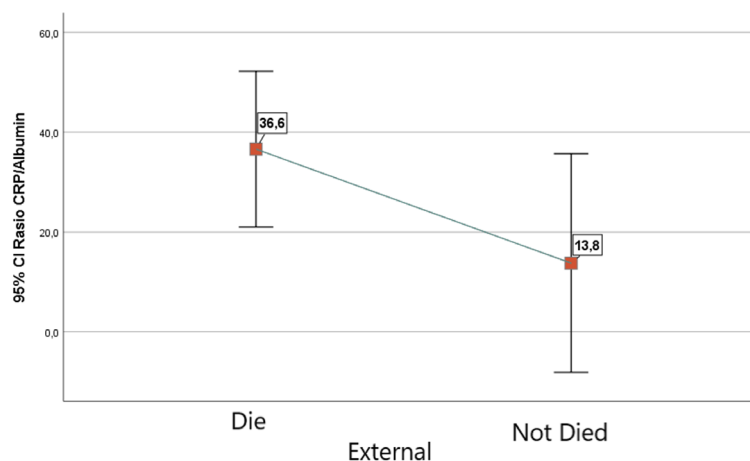| Variable	Statistics	Outside		p-value*
		Die (n=43)	Life (n=20)	
CRP	Mean	80.4	21.2	<0.001
	Std. deviation	87.2	55.6	
Albumin	Mean	2.7	2.6	
	Std. deviation	1.0	1.2	0.790
Rasio CRP/albumin	Mean	36.6	13.8	
	Std. deviation	50,7	46,8	<0.001

*Mann-Whitney test

Figure 1. Comparison of CRP/albumin ratio by output

In order to evaluate the predictive value of the CRP/albumin ratio for mortality in sepsis patients, the ROC curve analysis was utilized to determine the optimal cut-off value. The resulting AUC value of 0.819 (81.9%), with a significant p-value <0.001, indicates that the CRP/albumin ratio is a useful predictor of mortality in sepsis patients. Based on the ROC curve, the optimal cut-off point for the CRP/albumin ratio is 4.3, which provides a sensitivity of 81.4%, specificity of 75.0%, positive predictive value (PPV) of 87.5%, negative predictive value (NPV) of 65.2%, and accuracy of 79.4%.

DISCUSSION

The study sample consisted of patients aged 16-63 years, with the majority being male (66.7%) and the largest age group being over 55 years (33.3%), as shown in Table 1. This sample is consistent with a previous study by Kim et al., which found that males were more prone to sepsis than females, with 352 male patients (52.54%) and the highest incidence in patients over 65. The higher incidence of sepsis in older age groups is thought to be due to dysregulation of the innate and adaptive immune systems during ageing. Male sex hormones have been found to suppress the immune response, while female sex hormones have a protective effect on women.[20-22]

Based on the outcome, it was found that more patients with sepsis died than those who survived. Specifically, 43 subjects (68.3%) died, which is consistent with the findings of Vivianni et al, who reported that 62.5% of patients with sepsis died compared to 42.86% who survived. The incidence of sepsis accompanied by an inflammatory process can cause both local and systemic changes in the body. This often leads to extensive cellular damage and may serve as a precursor to organ dysfunction. If not identified and treated promptly, septic shock and mortality can result. Despite advancements in medical care, sepsis remains a global health challenge due to its difficulty in treatment and the high associated cost, which contributes to the high mortality rate.[23,24]

This study demonstrated that CRP levels ranged from 0.1 mg/L to 434.9 mg/L, with a mean level of 61.6 mg/L. Albumin levels ranged from 1.0 g/dl to 4.7 g/dl, with a mean level of 2.7 g/dl. These findings are consistent with a study by Abdi which reported CRP levels on the first day of ICU admission ranging from 23.37 mg/L to 285.12 mg/L and albumin levels ranging from 1.3 mg/L to 3.8 mg/L.[19] Kim et al. also reported that the average CRP level on the first day of ICU admission was 15.22 mg/L, and the average albumin level was 3.1 mg/L. The CRP/albumin ratio ranged from 0.04 to 254.1, with a mean ratio of 29.4 observed in this study. This finding is consistent with a study by Abdi et al., which found that the CRP/albumin ratio on the first day of ICU admission was highly variable, ranging from 7.79 to 153.85.[19] Kim et al. reported that the mean CRP/albumin ratio on the first day of ICU admission was 5.28. CRP is an acute-phase protein released by liver cells when stimulated
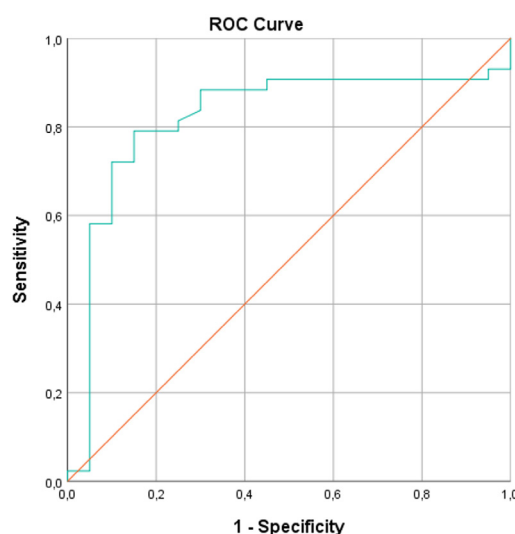

Figure 2. ROC curve CRP/albumin ratio

by inflammatory mediators, such as IL-6. Its level increases during inflammation and the intensity of the stimulus and rate of synthesis affect the level. The level also depends on the pathological state. On the other hand, albumin is a negative acute phase protein that decreases in response to inflammation, making it a useful marker for assessing the severity of inflammation.[16,19]

This study found that the mean CRP was significantly higher in patients who died than in those still alive. A greater mortality likelihood is observed in the higher CRP levels in sepsis patients. Sepsis triggers a broad natural immune response that coordinates a defence response involving both humoral and cellular components. Mononuclear cells release pro-inflammatory cytokines, such as IL-1, IL-6, IL-12, IL-15, IL-18, and tumour necrosis factor (TNF)-α, which cause liver cells to release acute-phase protein, CRP. This result is consistent with previous studies indicating a positive relationship between higher CRP levels and increased mortality in sepsis. Sepsis causes circulatory, cellular, and metabolic changes that are severe enough to increase mortality compared to non-septic conditions.[19,20]

In contrast, this study revealed that the mean albumin levels did not differ significantly between dead and living patients. However, this finding differs from a study by Min Ho Seo et al. which reported that the initial albumin value upon admission was associated with 28-day mortality in patients with severe sepsis. The absence of a relationship in this study may be due to other factors that could affect sepsis and septic shock mortality. Several factors can affect the course of sepsis and predict mortality. These factors include clinical factors such as age, gender, and the site of infection. Other laboratory tests like platelet count, bilirubin, and creatinine levels, as well as hemodynamic conditions such as blood pressure and heart rate, respiratory parameters like respiratory rate and oxygen levels (PaO_2/FiO_2), and comorbid conditions such as hypertension, diabetes, chronic renal failure, and malignancy, can also influence the course of sepsis and predict mortality.[16]

This study demonstrated a significant relationship between the mean CRP/albumin ratio and mortality in patients with sepsis. A positive correlation was found between higher ratios and mortality rates. This finding supports Kim et al.

study, which reported that the CRP/albumin ratio upon admission could be used as an independent predictor of 180-day mortality in patients with severe sepsis or septic shock.[20]

During an infection, the liver releases CRP in response to cytokines like IL-6, IL-1, and TNF-α. CRP synthesis happens quickly, and its serum concentration peaks around 24-48 hours after a slight stimulation. Simultaneously, there is an albumin leakage, resulting in hypoalbuminemia related to the intensity of the inflammatory response caused by the infection. Combining these two markers provides a more comprehensive assessment of inflammation, indicating a higher inflammatory status that could predict mortality in patients with sepsis.[19]

The results of this study demonstrated that the CRP/albumin ratio could be a reliable predictor of mortality in sepsis patients. The analysis of the ROC curve yielded an AUC value of 0.819 (p<0.001) for CRP/albumin ratio. The ROC curve coordinates suggest a cut-off value of 4.3, which provides a sensitivity of 81.4% and specificity of 75.0%. This finding is in accordance with Kim et al. study, which suggested a CRP/albumin ratio cut-off of 5.09 with 61% sensitivity and specificity for predicting mortality in severe sepsis or septic shock patients. Similarly, Ranzani et al. demonstrated a CRP/albumin ratio greater than 2 in sepsis patients with high mortality and poor prognoses.[10,19]

One limitation of this study is that the CRP and albumin tests were not always performed simultaneously, which could potentially affect the accuracy of the results. Additionally, factors such as patient comorbidities and individual patient conditions may impact both CRP and albumin levels, as well as the CRP/albumin ratio. In order to address this limitation, the study only included patients who had both CRP and albumin tests performed, which led to a reduction in the sample size.

CONCLUSION

Our study shows a significant correlation between the CRP/albumin ratio and mortality in patients with sepsis. As the ratio increases, the likelihood of mortality also increases. The CRP/albumin ratio of 4.3 can serve as a reliable predictor of mortality in patients with sepsis and may aid in their management. Our cohort-prospective study utilized the CRP/albumin ratio

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and its association with the SOFA score to predict mortality in sepsis patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence. 2014;5(1):36–44.

2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Medicine. 2017;43(3):304–77.

3. Khilnani P. Severe sepsis and septic shock. ICU Protocols: A Step-wise Approach. 2012;703–7.

4. Hospital DWS. Medical record RS dr. Wahidin Sudirohusodo. Makassar; 2020.

5. Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K. Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. BJA: British Journal of Anaesthesia. 2017;119(4):626–36.

6. Vincent J-L, De Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Critical Care Medicine. 2014;26(11):1793–800.

7. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Vol. 43, Intensive Care Medicine. Springer Berlin Heidelberg; 2017. 304–377 p.

8. Haq A, Patil S, Parcells AL, Chamberlain RS. The simplified acute physiology score III is superior to the simplified acute physiology score II and acute physiology and chronic health evaluation II in predicting surgical and ICU mortality in the "oldest old." Current Gerontology and Geriatrics Research. 2014;2014:10–3.

9. Kim CH, Kim SJ, Lee MJ, Kwon YE, Kim YL, Park KS, et al. An increase in mean platelet volume from baseline is associated with mortality in patients with severe sepsis or septic shock. PLoS One. 2015;10(3).

10. Ranzani OT, Zampieri FG, Forte DN, Azevedo LCP, Park M. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One. 2013;8(3).

11. Ho KM, Lee KY, Dobb GJ, Webb SAR. C-reactive protein concentration as a predictor of in-hospital mortality after ICU discharge: A prospective cohort study. Intensive Care Medicine. 2008;34(3):481–7.

12. Baig MA, Sheikh S, Hussain E, Bakhtawar S, Khan MS, Mujtaba S, et al. Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic shock patients in the emergency department of a low middle income country. Turkish Journal of Emergency Medicine. 2018;18(4):148–51.

13. Purwanto DS, Astrawinata DAW. Pemeriksaan laboratorium sebagai indikator sepsis dan syok septik. Jurnal Biomedik JBM. 2019;11(1):1–9.

14. Oh J, Kim SH, Park KN, Oh SH, Kim YM, Kim HJ, et al. High-sensitivity C-reactive protein/albumin ratio as a predictor of in-hospital mortality in older adults admitted to the emergency department. Clinical and Experimental Emergency Medicine. 2017;4(1):19–24.

15. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Frontiers in Immunology. 2018;9:754.

16. Rahajeng EP. Analisis laktat, albumin dan rasio laktat albumin sebagai prediktor luaran pada pasien sepsis dan syok septik di RSUP dr. Wahidin Sudirohusodo Makassar. Jurnal Kesehatan Andalas. 2020;9(1):26–32.

17. Soltani F, Pipelzadeh M, Akhondzadeh R, Rashidi M, Ekrami A. Evaluation of C - reactive protein, albumin and the C - reactive protein/albumin ratio as prognostic markers in trauma patients admitted to intensive care unit. British Journal of Medicine and Medical Research. 2016;12(10):1–7.

18. Apelgren KN, Rombeau JL, Twomey PL, Miller RA. Comparison of nutritional indices and outcome in critically ill patients. Critical Care Medicine. 2013;10(5):305–7.

19. Abdi T. Rasio C reactive protein/albumin sebagai prediktor mortalitas pada pasien sepsis di ICU RSUP. H. Adam Malik Medan dan dihubungkan dengan skor SOFA. 2018.

20. Kim MH, Ahn JY, Song JE, Choi H, Ann HW, Kim JK, et al. The C-reactive protein/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock treated with early goal-directed therapy. PLoS One. 2015;10(7):e0132109.

21. Starr ME, Saito H. Sepsis in old age: Review of human and animal studies. Aging and disease. 2014;5(2):126–36.

22. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological aspects. Virulence. 2014;5(1):12–9.

23. Vivianni A, Nugroho HS K, Bakhtiar Y. Faktor–faktor prediktor mortalitas sepsis dan syok sepsis di ICU RSUP Dr Kariadi. Diponegoro University; 2016.

24. Hatman FA. Analisis faktor risiko terhadap lama perawatan pasien sepsis yang meninggal di ruang perawatan intensif RSUD Dr Soetomo Surabaya. Universitas Airlangga; 2020.