Clinical Research

Procalcitonin prognostic value in predicting mortality among adult patients with sepsis due to Gram-negative bacteria

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ABSTRACT

BACKGROUND Sepsis is a leading cause of mortality and morbidity globally. Gram-negative bacteremia was reported to have a high risk of septic shock and poor prognosis. This study aimed to evaluate the role of procalcitonin in predicting mortality in patients with sepsis due to Gram-negative bacteria.

METHODS This was a retrospective cohort study performed based on medical records and sepsis registry of Tropical and Infectious Disease Division, Department of Internal Medicine, Cipto Mangunkusumo Hospital. The inclusion criteria were patients aged ≥18 years diagnosed with sepsis due to Gram-negative bacteria based on blood culture on admission and hospitalized between March 2017 and October 2020. Data taken from medical records included subjects' characteristics, laboratory parameters, and 28-day mortality outcomes during hospitalization. Receiver operating characteristic was used to determine the area under the curve (AUC) of procalcitonin and its accuracy.

RESULTS A total of 128 patients were eligible. The cumulative survival of patients with Gram-negative bacteremia was 48.4% (standard error 0.96%). The AUC of procalcitonin to predict mortality was 0.45 (95% confidence interval 0.36–0.54). *Escherichia coli* was the predominant microorganism in blood culture (n = 38, 29.7%).

CONCLUSIONS Procalcitonin has a poor performance in predicting mortality of patients with sepsis due to Gram-negative bacteria.

KEYWORDS bacteremia, mortality, procalcitonin, sepsis

Sepsis is a life-threatening organ dysfunction due to dysregulation of the host's systemic response toward infection.[1] According to the Centers for Disease Control and Prevention, 450,000 sepsis cases with >100,000 mortality cases were reported.[2] In 2009, a study of 16 Asian countries, including Indonesia, found 10.9% of cases with severe sepsis and septic shock among all patients hospitalized in the intensive care unit (ICU), with a 44.5% mortality rate. Data from a study conducted in a tertiary hospital in Jakarta, Indonesia reported 49% of mortality due to sepsis in 2009 and increased to 55% in 2011.[3] A study of 247 patients with Gram-negative bacteremia found a higher procalcitonin level in older patients.[4]

The American College of Chest Physicians/Society of Critical Care Medicine stated that accurate diagnosis methods are important to diagnose and treat sepsis. Sepsis occurs due to multifactorial causes and various pathogens.[5] Lung is the most susceptible organ, followed by the abdomen and urinary tract. The mortality rate was also higher in bacteremia.[6] There were 20–40% of patients with sepsis who had negative blood culture results.[7,8] Moreover, blood culture needs 5 days for incubation and 7 days to receive an antimicrobial resistance test. Furthermore, only 20–30% of patients had positive blood culture results. Patients with Gram-negative bacteremia had a higher mortality rate, reaching 29%.[9]

Besides using blood culture as a gold standard, procalcitonin can also be used to diagnose sepsis. Procalcitonin tends to increase as a response to bacterial infection. It may rise within 3–4 hours after bacterial infection with a half-time of 22 hours.[10] Previous studies reported that procalcitonin could be used to predict Gram-negative bacterial infection.[11] Moreover, procalcitonin re-examination could predict the 28-day mortality in patients with sepsis or septic shock admitted to the ICU. It also showed good sensitivity to predict bacterial or viral infection.[12] Furthermore, it could be used to predict infectious agents and mortality in patients with sepsis or septic shock admitted to the ICU.[13,14] Gram-negative bacteria cause more severe clinical presentation. Gram-negative bacteremia together with septic shock increase mortality.[6,9] This study aimed to identify the predictive value of procalcitonin for mortality in patients with sepsis due to Gram-negative bacteria and the proportion of the microorganisms.

METHODS

Study population

This was a retrospective cohort study performed in Cipto Mangunkusumo Hospital, Jakarta, Indonesia. This study analyzed medical records and sepsis registry of Tropical and Infectious Disease Division, Department of Internal Medicine, Cipto Mangunkusumo Hospital. The inclusion criteria were adult patients (≥18 years old) diagnosed with Gram-negative bacteremia and hospitalized in Cipto Mangunkusumo Hospital including the emergency unit, standard ward, and ICU between March 2017 and October 2020. Subjects were excluded if there were missing data, trauma patients, and pregnant women. The sample size was calculated following the receiver operating characteristic (ROC) formula, which resulted in 128 subjects. All patients diagnosed with sepsis based on the ICD-10 (A41.9) were consecutively included. Presumptive sepsis was defined at least 2 points of sequential organ failure assessment (SOFA) score when sepsis was suspected. This score was developed by European Society of Intensive Care Medicine for patients admitted to the ICU based on six organs evaluation including respiratory system (PaO_2/FiO_2), coagulation (thrombocyte), liver function (bilirubin), cardiovascular system (mean arterial pressure), central nervous system (Glasgow coma scale), and renal system (creatinine).[15] This study

was approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia (No: 0883/UN2.F1/ETIK/2018).

Data collection

Data taken from medical records were age, sex, type of infection (community/nosocomial), comorbidities, hemodynamic status, laboratory results (hemoglobin, leukocyte, thrombocyte, neutrophil-to-lymphocyte ratio, aspartate aminotransferase, alanine aminotransferase, ureum, creatinine, albumin, and procalcitonin), length of hospitalization, and microorganisms results from aerobic blood culture drawn from one site. The hospital course of the patients was followed from admission to 28 days of hospitalization. All data were extracted at the time of diagnosing sepsis and pooled in a questionnaire for each subject.

Data analysis

Data were analyzed using SPSS software version 20.0 (IBM Corp., USA). Each variable was analyzed to determine the distribution and percentage. Categorical data (sex, type of infection, and comorbidities) were presented in a table and numerical data in mean (standard deviation) or median (interquartile range [IQR]), depending on the data distribution. Survival analysis of Gram-negative bacteremia was reported in Kaplan–Meier curve. Procalcitonin was analyzed using ROC to determine the area under the curve (AUC), and the accuracy was also analyzed.

RESULTS

Of 150 subjects during the study period, 22 were excluded due to trauma cases (n = 5) and missing medical records (n = 17). The subjects' characteristics are shown in Table 1. The incidence of mortality was 51.6% (95% confidence interval [CI] 42.9–60.3), cumulative survival of 48.4% (standard error [SE] 0.96%), mean survival of 18.93 days (95% CI 17.05–20.82), and median survival of 22 days (Figure 1). The most common microorganisms from blood culture were *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* (Table 2). Procalcitonin had a poor predictive value to predict mortality within 28 days of hospitalization in adult patients with sepsis due to Gram-negative bacterial infection (Figure 2).

Table 1. Subjects' characteristics of septic patients with Gram-negative bacteria

Characteristics	N = 128
Sex, n (%)	
Female	63 (49.2)
Male	65 (50.8)
Age (years), median (IQR)	51.0 (37.0–61.0)
Length of stay (days), median (IQR)	15 (8–24.75)
Type of infection, n (%)	
Community	97 (75.8)
Nosocomial	14 (10.9)
Mixed	17 (13.3)
Comorbidities, n (%)	
Malignancy	45 (35.2)
Diabetes	36 (28.1)
Chronic kidney disease	26 (20.3)
Heart failure	19 (14.8)
Renal dialysis	15 (11.7)
Stroke	10 (7.8)
Cirrhosis	7 (5.5)
No comorbidities	38 (29.7)
Source of infection, n (%)	
Respiratory tract	87 (68.0)
Intraabdominal	47 (36.7)
Catheter-related	37 (28.9)
Skin and soft tissue	25 (19.5)
Urinary tract	22 (17.2)
Intracranial	10 (7.8)
Physical examination, median (IQR)	
Systolic blood pressure (mmHg)	102 (90, 120)
Diastolic blood pressure (mmHg)	68 (60, 78)
MAP (mmHg)	80 (33, 133)
Heart rate (times/min)	108 (88, 118)
Respiratory rate (times/min)	24 (20, 28)
PaO_2/FiO_2	243.95 (49.89, 888.75)
Laboratory examination, median(IQR)	
Hemoglobin (g/dl)	9.06 (8.0–10.5)
Hematocrit (vol%)	26.4 (22.73–30.08)
Leukocyte (/µl)	17,515 (11,667–25,760)
Platelet (/µl)	148,000 (66,250–306,250)
Neutrophil (%)	90.0 (86.1–93.9)
Lymphocyte (%)	4.80 (2.85–8.70)
NLR	19.33 (10.45–32.03)
AST (u/l)	51.50 (25.0–124.75)

Table 1. (continued)

Characteristics	N = 128
ALT (u/l)	42.5 (20.85–75.67)
Bilirubin (mg/dl)	7.87 (0.18–46.19)
Ureum (mg/dl)	75.0 (41.05–127.20)
Creatinine (mg/dl)	1.50 (0.72–3.43)
Albumin (g/dl)	2.40 (2.05–2.69)
Procalcitonin (ng/ml)	50.49 (11.20–112.19)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; IQR=interquartile range MAP=mean arterial pressure; NLR=neutrophil-to-lymphocyte ratio; PaO_2/FiO_2=ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2)
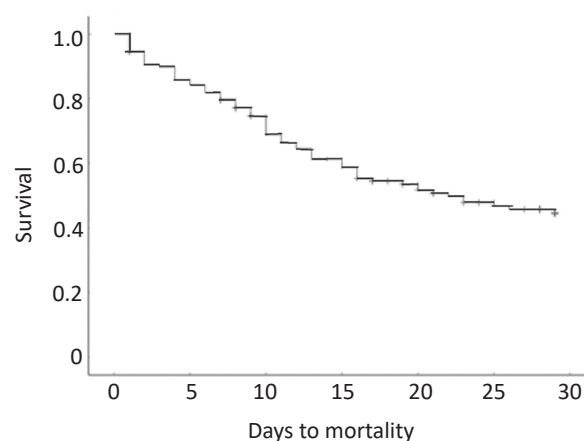
Figure 1. Survival analysis within 28 days in patients with Gram-negative bacteremia using Kaplan–Meier curve

Table 2. Microorganisms isolated from blood cultures in patients with Gram-negative bacteremia

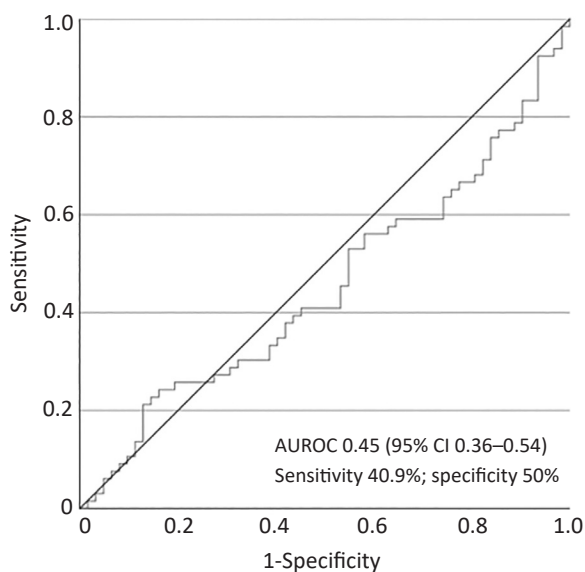| Microorganisms	n (%)
Escherichia coli	38 (29.7)
Klebsiella pneumoniae	36 (28.1)
Acinetobacter	17 (13.3)
Pseudomonas aeruginosa	14 (11.0)
Enterobacter	8 (6.3)
Klebsiella oxytoca	5 (3.9)
Burkholderia cepacia	2 (1.6)
Elizabethkingia meningoseptica	2 (1.6)
Proteus mirabilis	2 (1.6)
Citrobacter freundii	1 (0.8)
Proteus vulgaris	1 (0.8)
Salmonella sp.	1 (0.8)
Serratia marcescens	1 (0.8)

Figure 2. ROC curve of procalcitonin as the predictor of mortality within 28 days. AUROC=area under the ROC curve; CI=confidence interval; ROC=receiver operating characteristic

DISCUSSION

Procalcitonin is known as a marker of infection and indicator for the severity of infection. In this study, procalcitonin showed a poor result in predicting 28-day mortality of Gram-negative bacteremia. Several factors might influence this result, including various comorbidities and infection sources. Malignancy, diabetes, and chronic kidney disease (CKD) were the three most common comorbidities reported in this study.

Studies reported that most patients had comorbidity, which might influence the procalcitonin level, such as diabetes mellitus, malignancy, and kidney failure. Patients with diabetes have a higher risk of respiratory tract infection, urinary tract infection, and bacteriuria.[16] Procalcitonin increases in other conditions, such as malignancy, autoimmune, trauma, cardiac arrest, post-surgery, burn injury, kidney failure, and pancreatitis.[17]

Matzaraki et al[18] showed a solid tumor with metastasis, yet no source of infection represented an increased level of procalcitonin. In addition, procalcitoni n was used as an early indicator of neoplasm progressivity. However, Giovanella et al[19] reported that procalcitonin was not influenced by the presence of solid carcinoma. Nevertheless, several factors should be concerned in diagnosing infection in malignancy, including clinical manifestation as well as increased procalcitonin, C-reactive protein, and

leukocyte. A previous study had observed solid tumors with or without metastasis. In the metastasis group, 36 patients presented with sepsis showed a median procalcitonin of 3.48 (0.66–189.4) ng/ml, while the median procalcitonin of the non-metastasis group was 2.92 (1.1–921.4) ng/ml. The cut-off point of procalcitonin in malignant patients was higher compared with the non-malignant group by 1.14 ng/ml (sensitivity 86% and specificity 88% [AUC 0.956 (95% CI 0.916–0.996)]). Interpretation of increased procalcitonin in malignancy should be observed with clinical manifestation to differentiate the bacteremia condition or others.[20,21]

CKD is a condition that also influences the procalcitonin level. Procalcitonin level tends to increase as the estimated glomerular filtration rate is reduced. Increased procalcitonin might be found in CKD with or without dialysis. A retrospective study was conducted in CKD patients, including 168 CKD stage 1–4 and 373 CKD stage 5 (303 with dialysis and 70 without dialysis) patients. Of 373 CKD stage 5 patients, 26 showed a median procalcitonin of 6.29 (IQR 1.745–32.65). There was a significant difference in procalcitonin level between the non-infection, local infection, and sepsis groups ($p<0.001$). The study also showed that reduced kidney function influenced the increased level of pro-inflammation and stimulated immune system which might cause increased procalcitonin secretion.[22]

In this study, respiratory tract infection was the highest infection source. In line with a study conducted in one of the referral hospitals in Jakarta, Indonesia, the mortality rate of sepsis was 59%, with the most common source of infection leading to mortality was respiratory tract infection (81.2%), followed by gastrointestinal tract (46.1%); a similar result was also found in Gatot Soebroto hospital.[23,24] Furthermore, based on a study in 2015 by Katu et al[25] in Indonesia, respiratory tract infection was the most common source of infection (52.7%) in patients with sepsis.

Various Gram-negative bacteremias were reported in several sepsis studies. This study reported that *E. coli* was the most common microorganism isolated from blood cultures, followed by *K. pneumoniae*, *Acinetobacter*, and *Pseudomonas aeruginosa.* This result was quite different from a previous study in Cipto Mangunkusumo Hospital that compared sepsis cases between patients aged <60 years and ≥60 years. Of 247 cases, the microorganisms reported were: *K. pneumoniae* (67 cases), *Acinetobacter baumannii* (61

cases), *E. coli* (45 cases), *P. aeruginosa* (22 cases), and *Enterobacter* species (15 cases).[4] This result was similar to a study in Army Central Hospital Gatot Soebroto, Jakarta, Indonesia that showed *K. pneumoniae* as the most common Gram-negative bacteria found in sepsis patients.[24] It was in line with other findings such as Li et al[26] who showed a similar result. Gram-negative bacteria have lipopolysaccharide and capsular polysaccharide, which play an important role in the virulence of the pathogen.[24]

Our study result was in line with another regional hospital in Indonesia that the three most Gram-negative bacteria isolates from sepsis patients were *E. coli* (13.21%), *A. baumannii* (11.32%), and *K. pneumoniae* (11.32%).[27] Meanwhile, a study in an ICU of tertiary referral hospital of eastern Indonesia reported microbial profile of blood culture. The Gram-negative bacteria group showed *A. baumannii* as the most common cause of sepsis.[28]

Studies in the USA reported sepsis as the most common cause of death in critically ill patients with various types of organisms in culture-positive infected patients, with Gram-negative bacteria (62.2%) as the most causative types of causal organisms. Most microorganisms isolated from blood cultures in patients with Gram-negative bacteremia were *Pseudomonas* species (19.9%), *E. coli* (16%), *Klebsiella* species (12.7%), *Acinetobacter* species (8.8%), and *Enterobacter* (7.0%).[29]

Based on a meta-analysis of 21 studies, procalcitonin also has a limitation as a single tool for predicting the prognosis of septic patients due to its moderate accuracy.[30] Procalcitonin might be used as a component of the predictor prognosis tool if combined with other clinical indexes. A previous study reported a combination of SOFA score and procalcitonin changes in 24 and 48 hours as the prognostic factor of sepsis and septic shock cases.[17] Another study evaluated the role of procalcitonin as the predictor of mortality, yet combining it with Acute Physiology And Chronic Health Evaluation II score, sputum culture interpretation, and blood culture interpretation.[28]

Procalcitonin and lactate levels could be used as an evaluation tool for patients with sepsis. Procalcitonin was used to evaluate clinical conditions within 28/30 days of evaluation, yet still has limitations in predicting mortality. A previous study reported that the cut-off point of procalcitonin changes within 28 days of monitoring was 0.76 (95% CI 0.67–9.85).[31] A multivariate study reported that procalcitonin might be the predictor of mortality in patients with sepsis although not significant (*p* = 0.066).[32] Other studies also mentioned that procalcitonin had a poor value in predicting mortality of septic patients, especially with malignancy as the comorbidity (AUC 0.584, 95% CI 0.473–0.690).[33]

Durrance et al[34] also mentioned that the high level of procalcitonin especially >30 ng/ml was not related to the severity of sepsis and predictor of mortality. Furthermore, further study on the cut-off point of procalcitonin for predicting mortality is still needed. The high procalcitonin level might indicate sepsis, yet it should be confirmed with positive culture.

The incidence mortality of subjects with Gram-negative bacterial infection was 51.6% (95% CI 42.9–60.3) with a cumulative survival of 48.4% (SE 0.96), mean survival of 18.89 days (95% CI 17.00–20.77), and median survival of 22 days. This study showed higher incidence mortality and lower survival rates compared with previous studies. Perman et al[35] showed that the mortality of patients with sepsis was 19% within 28 days of follow-up. Another review of 14 studies found that patients with sepsis had a median length of hospital stay of 9 days (IQR 5–15 days).[36]

This study had some limitations. This was a retrospective study; by means, all parameters were evaluated based on medical records. Information bias, especially all data regarding organ function before sepsis, was unrecognizable. Patients who did not know about their comorbidities might influence the accuracy of sepsis diagnosis. Hence, this study was a single-center study that used a national referral hospital. Furthermore, varied comorbidities and the possibility of multidrug resistance and type of microorganisms might be the confounding factors. In general, most of the admitted patients were in severe infection.

In conclusion, the procalcitonin level showed a poor prognostic mortality predictor in patients with Gram-negative bacteremia. However, procalcitonin examination still could be considered for sepsis management in clinical practice.

REFERENCES

1. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063–143.

2. Epstein L, Dantes R, Magill S, Fiore A. Varying estimates of sepsis mortality using death certificates and administrative codes–United States, 1999-2014. MMWR Morb Mortal Wkly Rep. 2016;65(13):342–5.

3. Decree of the Minister of Health of the Republic of Indonesia No HK.01.07/MENKES/342/2017 - National regulation of sepsis management. 2017;1–82. Indonesian.

4. Suwarto S. Procalcitonin levels in elderly compare with non elderly patients with Gram negative bacteremia. eJKI. 2018;6(2):76–80.

5. Fujishima S. Organ dysfunction as a new standard for defining sepsis. Inflamm Regen. 2016;36(24).

6. Abe R, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Tateishi Y, et al. Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia. Crit Care. 2010;14(2):R27.

7. Fan SL, Miller NS, Lee J, Remick DG. Diagnosing sepsis - The role of laboratory medicine. Clin Chim Acta. 2016;460:203–10.

8. Mellhammar L, Kahn F, Whitlow C, Kander T, Christensson B, Linder A. Bacteremic sepsis leads to higher mortality when adjusting for confounders with propensity score matching. Sci Rep. 2021;11(6972).

9. Morgan MP, Szakmany T, Power SG, Olaniyi P, Hall JE, Rowan K, et al. Sepsis patients with first and second-hit infections show different outcomes depending on the causative organism. Front Microbiol. 2016;7:207.

10. Yap CYF, Aw TC. The use of procalcitonin in clinical practice. Proc Singapore Healthc. 2014;23(1):33–7.

11. Guo SY, Zhou Y, Hu QF, Yao J, Wang H. Procalcitonin is a marker of gram-negative bacteremia in patients with sepsis. Am J Med Sci. 2015;349(6):499–504.

12. Vijayan AL, Vanimaya, Ravindran S, Saikant R, Lakshmi S, Kartik R, et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care. 2017;5:51.

13. Gregoriano C, Heilmann E, Molitor A, Schuetz P. Role of procalcitonin use in the management of sepsis. J Thorac Dis. 2020;12(Suppl 1): S5-S15.

14. Jain S, Sinha S, Sharma SK, Samantaray JC, Aggrawal P, Vikram NK, et al. Procalcitonin as a prognostic marker for sepsis: a prospective observational study. BMC Res Notes. 2014;7:458.

15. Singer AJ, Ng J, Thode HC Jr, Spiegel R, Weingart S. Quick SOFA scores predict mortality in adult emergency department patients with and without suspected infection. Ann Emerg Med. 2017;69(4):475–9.

16. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis. 2005;41(3):281–8.

17. Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. PLoS One. 2018;13(11):e0206527.

18. Matzaraki V, Alexandraki KI, Venetsanou K, Piperi C, Myrianthefs P, Malamos N, et al. Evaluation of serum procalcitonin and interleukin-6 levels as markers of liver metastasis. Clin Biochem. 2007;40(5–6):336–42.

19. Giovanella L, Suriano S, Ricci R, Ravani P, Ceriani L. Circulating procalcitonin in aseptic carcinoma patients: a specificity study with (18)F-fluorodeoxyglucose positron-emission tomography/computed tomography as benchmark. Clin Chem Lab Med. 2010;48(8):1163–5.

20. Durnaś B, Wątek M, Wollny T, Niemirowicz K, Marzec M, Bucki R, et al. Utility of blood procalcitonin concentration in the management of cancer patients with infections. Onco Targets Ther. 2016;9:469–75.

21. Aziz SA, Nelwan EJ, Sukrisman L, Suhendro S. Higher cut-off serum procalcitonin level for sepsis diagnosis in metastatic solid tumor patients. BMC Res Notes. 2018;11:84.

22. Sun Y, Jiang L, Shao X. Predictive value of procalcitonin for diagnosis of infections in patients with chronic kidney disease: a comparison with traditional inflammatory markers C-reactive protein, white blood cell count, and neutrophil percentage. Int Urol Nephrol. 2017;49(12):2205–16.

23. Dharmawan A, Istia MJ, Tan HT, Suparto, Anastasia MC, Layanto N. The outcome of patients with sepsis at Tarakan Hospital Central Jakarta in 2018. Muhammadiyah Medical Journal. 2021;2(2):49–54.

24. Handayani N, Lardo S, Nugrohowati N. Difference of procalcitonin levels in Gram-positive and Gram-negative bacterial sepsis patients of Indonesia Army Central Hospital Gatot Soebroto in 2016. JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Univeristas Airlangga. 2022;13(1):38–41.

25. Katu S, Suwarto S, Pohan H, Abdullah M. [Factors influencing the success of empiric antibiotic therapy in patients with severe sepsis and septic shock in the inpatient ward in Cipto Mangunkusumo Hospital]. J Penyakit Dalam Indones. 2015;2(2):96–106. Indonesian.

26. Li S, Rong H, Guo Q, Chen Y, Zhang G, Yang J. Serum procalcitonin levels distinguish Gram-negative bacterial sepsis from Gram-positive bacterial and fungal sepsis. J Res Med Sci. 2016;21:39.

27. Mahendra AD, Tirtodiharjo K, Kusuma ITD. The pattern of bacteria and its resistance on adult sepsis patient at Dr. Moewardi General Hospital, Indonesia. Arch Clin Microbiol. 2016;7(5):28.

28. Octora M, Mertaniasih NM, Semedi BP, Koendhori EB. Predictive score model of clinical outcomes sepsis in intensive care unit tertier referral hospital of eastern Indonesia. Open Access Maced J Med Sci. 2021;9(B):1710–6.

29. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):4–11.

30. Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: a systematic review and meta-analysis. PLoS ONE. 2015;10(6):e0129450.

31. Poddar B, Gurjar M, Singh S, Aggarwal A, Singh R, Azim A, et al. Procalcitonin kinetics as a prognostic marker in severe sepsis/septic shock. Indian J Crit Care Med. 2015;19(3):140–6.

32. Viallon A, Guyomarc'h S, Marjollet O, Berger C, Carricajo A, Robert F, et al. Can emergency physicians identify a high mortality subgroup of patients with sepsis: role of procalcitonin. Eur J Emerg Med. 2008;15(1):26–33.

33. Jones E, Benowitz J, Swensen A, Schmidt M, Feinstein D. Procalcitonin and lactic acid: a review of predictive value in septic patients. EC Emerg Med Crit Care. 2019;6:362–73.

34. Durrance RJ, Ullah T, Patel H, Martinez G, Cervellione K, Zafonte VB, et al. Marked elevation in serum procalcitonin levels do not correlate with severity of disease or mortality in hospitalized patients: a retrospective study. Biomark Insights. 2020;15:1177271920917941.

35. Perman SM, Mikkelsen ME, Goyal M, Ginde A, Bhardwaj A, Drumheller B, et al. The sensitivity of qSOFA calculated at triage and during emergency department treatment to rapidly identify sepsis patients. Sci Rep. 2020;10(1):20395.

36. Lo RSL, Leung LY, Brabrand M, Yeung CY, Chan SY, Lam CCY, et al. qSOFA is a poor predictor of short-term mortality in all patients: a systematic review of 410,000 patients. J Clin Med. 2019;8(1):61.