World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Mortality predictors in emergency department adult patients with sepsis: A systematic review

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World Journal of Biology Pharmacy and Health Sciences, 2024, 19(03), 562–570

Publication history: Received on 11 August 2024; revised on 24 September 2024; accepted on 26 September 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.3.0680

Abstract

Background: Sepsis was regarded as a major global public health concern; it continues to be associated with a high death rate despite advancements in contemporary treatment. This research aims to evaluate the predictive effect of clinical scoring systems and biomarkers for sepsis patients in ED.

Method: In accordance with PRISMA principles, we carried out this systematic review. We used the internet databases MEDLINE, Google Scholar, and EMBASE to conduct a thorough search of the literature. Articles written in English and released between 2015 and 2023 were involved in the search. Using predictors and ED, we first conducted a comprehensive search that included sepsis and infectious illnesses.

Result: A total of 3029 patients from 7 publications—3 cohort, 2 observational, and 2 case control studies—were included in this study. The study by Song et al. in 2019 had the highest fatality rate (46.6%), while the study by Duplessis et al. in 2018 had the lowest mortality rate (6.4%). SIRS criteria, qSOFA score, International Sepsis Conference 2001, and American College of Chest Physicians Guidelines are the diagnostic criteria that are employed. AUC varied from 33.7 (MMP9) to 0.89 (IL-6).

Conclusion: AUC was increased significantly when CSSs were combined with IgE, presepsin, IL-6 and PCT.

Keywords: Sepsis; Emergency Department; Predictors; Mortality

1. Introduction

One of the main causes of in-hospital mortality is sepsis, a potentially fatal illness (1). Sepsis must be identified early in order to begin the right treatment on time (2). When a patient has a suspected infection, early-stage sepsis is frequently misdiagnosed, which delays treatment and raises mortality (3). Early sepsis identification in its early stages can occur at the ED, which is frequently the first setting to be attended by patients. Nonetheless, choices regarding patient disposition and treatment must be made within a specific time window in the ED. It's critical to identify ED patients who have a high risk of death in order to determine whether to admit them or not and to begin antibiotic treatment as soon as possible.

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There is a significant chance of death when a pathogenic microorganism infection causes the SIRS crtiteria (4). It is well established that the primary pathophysiological process leading to sepsis development is immune system malfunction. According to the most recent version of the Sepsis-3 definition, sepsis is defined as "a potentially fatal organ dysfunction that results from a dysregulated host response to an infection" (5). In patients in the intensive care unit (ICU), this is indicated by a shift in sequential organ failure assessment (SOFA) scale of more than two points (6).

Vital parameters are the foundation of clinical scoring systems (CSSs), which are frequently used to identify sepsis. For CSS to be effective in the ED and quickly determine the severity of a patient's condition, they should only require a minimal number of clinical criteria. A variety of CSS, such as MEDS (8) score and the Quick SOFA (7) score, have been approved for use in ED. This research aims to evaluate the biomarkers predictive value and CSSs for sepsis patients in the emergency department.

2. Method

The PRISMA criteria were followed in the conduct and reporting of this review. We used the internet databases MEDLINE, Google Scholar, and EMBASE to conduct a thorough literature search. Articles written in English and released between 2015 and 2023 were included in our search. Using predictors and ED, we first conducted a comprehensive search that included sepsis and infectious illnesses.

In this review, we did not employ a certain definition of sepsis. The definition for sepsis has evolved over the years, and we wanted to be sure that our search strategy included any potentially helpful articles. Following the first search, reviewers went through the studies one by one, screening them based on their titles and abstracts. The outcomes were contrasted, and disagreements were settled through conversation. The whole text was used to screen the remaining papers based on criteria of inclusion.

Articles that assessed at least one predictor or CSS in any infectious disease were included after abstract and abstract and title screening. Articles that examined at least one predictor in combination with another predictor or CSS and reported the prognostic value on in hospital mortality by AUC in sepsis patients were included during screening of full text. If the authors reported them, further measures of the examined prediction models were noted. We excluded studies on children or for which there was no English full text available.

The study aim, design, predictors, AUC, population characteristics, CSS utilized, biomarkers, sepsis diagnostic criteria, mortality rate, key findings, and conclusion were all contained in the data that was extracted into specified Google sheets and Google forms.

3. Result

Seven publications totaling 3029 patients—three cohort, two observational, and two case control studies—were included in this review investigation (fig 1). The study by Song et al. in 2019 had the greatest 28-day mortality rate (46.6%), whereas the study by Duplessis et al. in 2018 had the lowest mortality rate (6.4%). SIRS criteria, qSOFA score, International Sepsis Conference 2001 (9) and Guidelines of the American College of Chest Physicians (Table 1) are among the diagnostic criteria that are employed. The following predictors were examined: presepsin, PCT, immunoglobulin E (IgE), Pentraxin 3 (PTX3), (Matrix Metalloproteinases 2) MMP2, TIMP1, TIMP2, MMP9, nucleosomes, and cell-free DNA (cfDNA). AUC varied from 0.89 (IL-6) to 33.7 (MMP9) (Table 1).

In the same way as the CSSs APACHE II and MEDS, Presepsin facilitated outcome prediction at admission. The AUC rose to 0.878 when presepsin and MEDS score assessments were combined (10). When incorporated into a diagnostic prediction model that included APACHE II and PCT, both nucleosome and cfDNA concentrations showed a moderate ability to distinguish sepsis survivors and non-survivors and provided additive diagnostic predictive value in differentiating SIRS from sepsis (11). TIMP1 is a promising predictor in the setting of sepsis, according to a 2017 study by Nino et al (12). A rapid screening tool for the early detection of sepsis may be created by adding the ordinal scale of PCT value to the qSOFA score, which would significantly enhance the quick SOFA sensitivity (13). For septic shock (SS) and sepsis, IL-6 had better prognostic and diagnostic value than PCT and PTX3 (14). Higher IgE levels in sepsis patients were associated with a higher risk of death, and the prediction accuracy of severe sepsis and mortality was greatly improved when IgE levels and grading methods were combined (15) (Table 2).

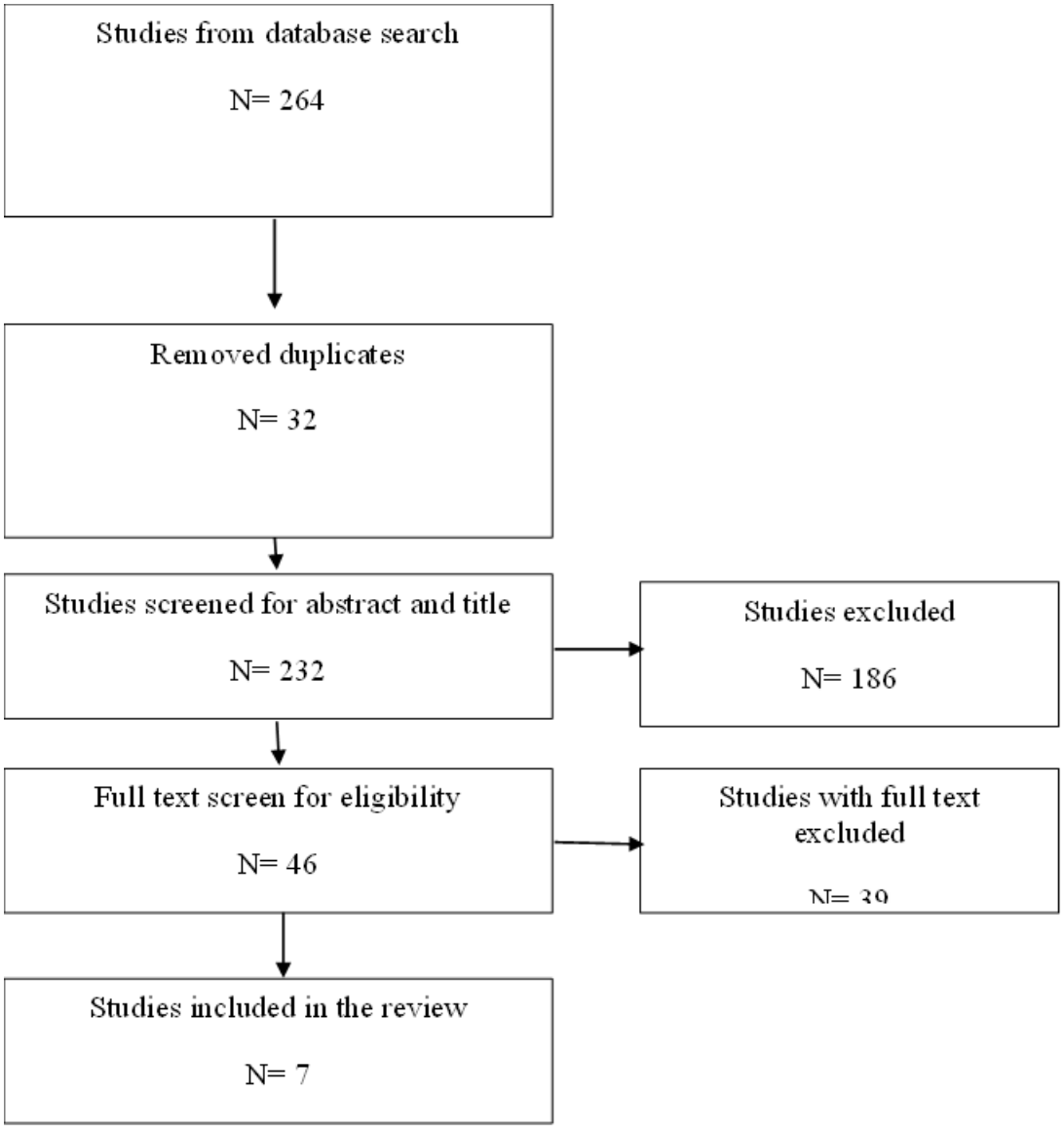

Figure 1 PRISMA consort chart of study selection

Table 2 Characteristics of included studies

Citation	Objective	Method	Population	Predictors	Sepsis diagnostic criteria	AUC	28 days in hospital mortality `	Percentage of mortality (%)
Henning et al., 2019	To ascertain if physicians' predictions of in-hospital mortality among ED patients exhibiting sepsis indications could be enhanced by the addition of indicators of endothelial activation and inflammation to unstructured physician judgment.	Prospective, observational study	Adult patients hospitalized to the ED who met two criteria of the SIRS, had organ dysfunction, a systolic blood pressure of less than 90 mm Hg, or had lactate levels greater than or equal to 4.0 mmol/L.	angiopoietin-2 and IL-6	SIRS criteria	angiopoietin-2 and IL-6 0.78	31/314	9.8
Yu et al., 2019	In order to determine whether improving the quick SOFA score's capacity to predict hospital mortality would involve adding either procalcitonin (PCT) or C reactive protein (CRP).	Retrospective cohort study	Adult patients who presented with symptoms suggestive of a systemic infection; within 24 hours of admission, PCT and blood culture tests were done.	SIRS criteria and qSOFA	qSOFA score and SIRS criteria	SIRS Criteria 0.56 qSOFA score 0.67 qSOFA_PCT 0.73	178/1318	13.5
Zhang et al., 2016	In order to compare with traditional clinical risk factors of sepsis severity, investigate the significance of plasma IgE levels upon admission in the assessment of the prognosis and severity of septic patients in the ED.	Prospective cohort study	Individuals who have been diagnosed with sepsis, SS, SIRS, or severe sepsis based on the guidelines of the 2001 International Conference Sepsis Definitions.	IgE	SIRS criteria	IgE= 0.83	183/480	38.1
Song et al., 2019	Using the Sepsis-3 criteria, examine the prognostic and diagnostic values of PCT, IL-6, and PTX3 in ED sepsis patients.	prospective controlled study	Adult ED patients suffering from SS or sepsis	IL-6, PTX3 and PCT	2 point or greater increase in SOFA score	IL-6= 0.89, PTX3= 0.84 PCT= 0.80	13/28	46.6

Nino et al., 2017	To clarify the biological function and importance of inflammatory biomarkers and how they relate to sepsis patients' severity and mortality.	prospective cohort study	Septic patients in the ICU or ED who were at least eighteen years old.	TEMP2, TEMP1, and MMP9	International Sepsis Conference 2001 (9)	TEMP2 61.9 TEMP1 68.8 MMP9 33.7	68/563	12
Duplessis et al., 2018	To ascertain if apoptotic biomarkers provided independent categorization usefulness, the authors added PCT and APACHE II score to predict sepsis mortality in the ED.	Case control study	Individuals believed to have contracted an infection as a result of community-acquired sepsis in ED were prospectively included.	cfDNA 0.61 nucleosomes 0.75 APACHEII 0.81	≥ 2 SIRS		13/203	6.4
carpio et al., 2015	Authors examined the prognostic and diagnostic validity of Presepsin in patients suspicious of sepsis on admission in the ED	Prospective observational study	Patients were classified as having sepsis if they met at least two SIRS criteria, had a confirmed infection, or had strong suspicions based on obvious clinical symptoms.	Presepsin	Guidelines of the American Chest Physicians College (16)	Presepsin 0.74 Presepsin in combination with MEDS score 0.87	24/123	19.5

Table 2 Main findings of the included studies

Citation	Main finding	Conclusion
Henning et al., 2019	Mortality rate in 28 days was 9.9%. Physician judgment and the best predictors model, which included IL-6 and angiopoietin-2, both performed mediocrely in mortality prediction. Performance was enhanced by combining biomarker models with physician judgment, which result in AUC change of 0.06 when compared to using physician opinion alone.	By combining ED physician judgment with indicators of inflammation and endothelial activity, it may be possible to improve the prediction of mortality among sepsis patients with critical illness.
Yu et al., 2019	Thirty-day death rate was 13.5%. Serum PCT levels and 30-day inpatient mortality had a strong connection with the quick SOFA score. The AUC for quick SOFA with PCT was 0.73, for quick SOFA score in 30-day mortality prediction it was 0.67, and for SIRS criterion it was 0.56. A net reclassification improvement of 35% indicated the improvement in risk prediction. The sensitivity of the quick SOFA model increased to 86.5% by adding PCT. quick SOFA with PCT significantly increased the sensitivity to 90.9% in the validation cohort.	The ordinal scale of PCT value might be added to the quick SOFA score as a straightforward change that would significantly enhance the unsatisfactory sensitivity issue and potentially act as a rapid screening tool for early sepsis detection.
Zhang et al., 2016	Higher IgE levels and higher scoring systems indicated that non-survivors were in a more severe critical state. IgE level was found to be an independent predictor of both severe sepsis mortality. IgE was a relevant criterion in the prognosis of severe sepsis and mortality, according to the AUC analysis. Crucially, out of all the parameters in this population, the AUC of IgE combination with MEDS performed for the most significant predictive capacity.	Higher IgE levels in septic patients were associated with a higher risk of death, and the prediction accuracy of sepsis and mortality was greatly improved when IgE levels were combined with scoring systems.
Song et al., 2019	Serum IL-6 levels were able to differentiate between sepsis and SS when compared to controls. Compared to the group with low IL-6, the group with high IL-6 had a significantly greater mortality. Among all patients, IL-6 was an independent risk factor for 28-day death. Initial and follow-up PTX3 levels in patients with SS were consistently considerably greater in patients who died than in those who recovered.	For sepsis and SS, IL-6 had better prognostic and diagnostic value than PCT and PTX3.
Nino et al., 2017	More than twelve percent of research participants died in the ICU during the first 30 days of hospitalization. Survivors had a higher level of MMP9, the mean values for MMP2, TIMP1, and survivors had a loer level of TIMP2. Serum MMP9 was a confounding factor for the TIMP1 variable but was not statistically linked with mortality, according to multivariate logistic regression, which also revealed that SOFA, age, Charlson scores, and TIMP1 value were statistically connected with mortality.	TIMP1 plasma levels represent a viable predictive biomarker. This study refutes TIMP1 and MMP9's predictive usefulness.
Duplessis et al., 2018	The AUC values of mortality prediction models utilizing cfDNA, APACHEII were 0.61 and 0.81, respectively. The AUC increased to 0.84 when a model that included nucleosomes and the APACHE II score was included. The AUC values of the diagnostic models that used PCT, nucleosomes (T0), or cfDNA (T0) to differentiate the sepsis from SIRS were 0.64,0.63, and 0.65, respectively. The AUC for the three-parameter model was 0.74.	When incorporated into a diagnostic model that included APACHE II and PCT, both nucleosome and cfDNA concentrations showed a moderate ability to diagnose and predict sepsis.
carpio et al., 2015	The sick group's and control group's mean presepsin concentrations significantly differ. Presepsin	Predicting the sepsis mortality at admission was made possible by

	demonstrated a substantial correlation with mortality, ranging from 10.3% in the first to 32.1% in the fourth quartile, and varied between sepsis, SIRS, severe sepsis, and SS. The AUC rose to 0.878 when presepsin and MEDS score assessments were combined, indicating a strong correlation with the outcome.	presepsin to the same extent as clinical ratings APACHE II and MEDS. Predictive power for sepsis mortality was increased when presepsin and MEDS score were combined.

4. Discussion

In the ED, biomarkers and CSSs aid in the early sepsis identification by doctors. In order to predict sepsis mortality ED, we looked into the combinations of predictors and CSSs in this review. We located seven distinct papers that examined seven different combinations of clinical grading system and biomarkers.

AUC varied from 33.7 (MMP9) to 0.89 (IL-6). Serum PTX3 and IL-6 levels effectively detect sepsis severity with ideal cut-off values, according to Song et al.'s 2019 study (14). When compared to PCT, CRP and PTX3, IL-6 had greater prognostic and diagnostic value. Regarding the diagnostic use of biomarkers including PTX3, IL-6, PCT, CRP and presepsin, a number of earlier investigations have produced contradictory findings (17–19). In comparison to presepsin, CRP and PCT, another investigation found that serum IL-6 levels had the best diagnostic value for SS (20). These findings concur with the 2019 study by Song et al. (14), which found that IL-6 had a better diagnostic value for sepsis than CRP, PTX3, and PCT.

As per the findings of the Carpio et al. (2015) study (10), presepsin facilitated the early prediction of mortality and unfavorable outcome at the time of admission, as demonstrated by ROC analysis. Moreover, presepsin values varied between non-survivors and survivors over the course of the disease, indicating that presepsin might be useful for tracking treatment interventions.

Nucleosomes and cfDNA, two byproducts of the apoptotic cascade with biological functions, approved to be helpful indicators of sepsis (21). These biomarkers tilt the delicate balance within numerous pathways and their counterregulatory cascades, modulate endothelium homeostasis, and are intricately related within the interdependent innate and adaptive immunity (22). The predictive accuracy of cfDNA to predict sepsis-mediated death was moderate in the Duplessis et al., 2018 study (11), but it is similar to that described in the literature for participants who were not admitted to the ICU (23, 24).

In order to use a novel pairing of biomarkers and CSSs in practice, the predictors needs to be made available as a basic laboratory test in the laboratory. Furthermore, given the brief duration of patients' stays in the ED, the CSS ought to only require a small number of factors. Only a few papers in our analysis fulfilled those requirements. Yu et al.'s (13) investigation of the quick SOFA and PCT combination demonstrated that the quick SOFA score performed better when PCT was added. With just three essential characteristics, the quick SOFA score is proven to be effective in identifying poor outcomes in sepsis patients early on. It becomes feasible to use this combination in the ED when added to with PCT, a biomarker that is already available as a regular measurement in many EDs.

Three studies (11, 13, 14) that used PCT in conjunction with a different biomarker or CCSs were located. In infectious disorders, PCT has been investigated as a predictor for sepsis severity. PCT is naturally synthesized by thyroid cells and is the precursor of calcitonin. It is frequently described as the biomarker that has the greatest ability to take the place of or substitute CRP (25).

In the research by Duplessis et al., nucleosome and cfDNA are examined as indicators of sepsis severity since they represent cellular death (11). The authors of this study demonstrate how improving the APACHE-2 score with nucleosomes increased the AUC for mortality prediction. The APACHE-2 did not improve with the addition of cfDNA. These findings highlight the potential utility of biomarkers derived from distinct pathways in sepsis as indicators of the illness severity.

Abbreviations

- ED; emergency department
- SIRS; systemic inflammatory response syndrome
- MEDS; Mortality in Emergency Department Sepsis
- AUC; area under the curve

5. Conclusion

The papers included in this review were too varied to draw a firm conclusion about which combination of factors should be employed in the ED to predict sepsis patients' mortality. AUC was increased significantly when IgE, presepsin, IL-6 and PCT were combined with CSSs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Vincent JL, Jones G, David S, Olariu E, Cadwell KK. Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis. Crit Care. 2019 May 31;23(1):196. doi: 10.1186/s13054-019-2478-6. PMID: 31151462; PMCID: PMC6545004.

[2] De Backer D, Dorman T. Surviving Sepsis guidelines: a continuous move toward better Care of Patients with Sepsis. JAMA. 2017;317(8):807–8. https:// doi.org/10.1001/jama.2017.0059.

[3] Husabo G, Nilsen RM, Flaatten H, Solligard E, Frich JC, Bondevik GT, et al. Early diagnosis of sepsis in emergency departments, time to treatment, and association with mortality: an observational study. PLoS One. 2020;15(1): e0227652. https://doi.org/10.1.

[4] Moore JX, Donnelly JP, Griffin R, Howard G, Safford MM, Wang HE. Defining Sepsis Mortality Clusters in the United States. Crit Care Med. 2016 Jul;44(7):1380-7. doi: 10.1097/CCM.0000000000001665. PMID: 27105174; PMCID: PMC4911271.

[5] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801–10.

[6] Freund Y, Lemachatti N, Krastinova E, et al. Prognostic accuracy of sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. JAMA 2017;317:301–8.

[7] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10. https://doi.org/10.1001/jama.201 6.0287.

[8] Sankoff JD, Goyal M, Gaieski DF, Deitch K, Davis CB, Sabel AL, Haukoos JS. Validation of the Mortality in Emergency Department Sepsis (MEDS) score in patients with the systemic inflammatory response syndrome (SIRS). Crit Care Med. 2008 Feb;36(2):421-6. doi: 10.1097/01.CCM.0B013E3181611F6A0. PMID: 18091538.

[9] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D et al. 2001 SCCM/ESICM/ACCP/ATS/ SIS International Sepsis Definitions Conference. Crit Care Med. 2003; 31:1250–6.

[10] Carpio R, Zapata J, Spanuth E, Hess G. Utility of presepsin (sCD14-ST) as a prognostic and diagnostic marker of sepsis in the emergency department. Clin Chim Acta. 2015;450:169–75. https://doi.org/10.1016/j.cca.2015.08.013.

[11] Duplessis C, Gregory M, Frey K, Bell M, Truong L, Schully K et al. Evaluating the discriminating capacity of cell death (apoptotic) biomarkers in sepsis. J Intensive Care. 2018;6(1):72.

[12] Nino ME, Serrano SE, Nino DC, McCosham DM, Cardenas ME, Villareal VP, et al. TIMP1 and MMP9 are predictors of mortality in septic patients in the emergency department and intensive care unit unlike MMP9/TIMP1 ratio: multivariate model. PLoS One. 2017;12(2):e0171191 DOI:10.1371/journal.pone.0171191

[13] Yu H, Nie L, Liu A, Wu K, Hsein YC, Yen DW et al. Combining procalcitonin with the quick SOFA and sepsis mortality prediction. Medicine (Baltimore). 2019; 98(23):e15981.

[14] Song J, Park DW, Moon S, Cho HJ, Park JH, Seok H, Choi WS. Prognostic and diagnostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions. BMC Infect Dis. 2019 Nov 12;19(1):968. doi: 10.1186/s12879-019-4618-7. PMID: 31718563; PMCID: PMC6852730.

[15] Zhang Q, Dong G, Zhao X LC. High immunoglobulin E values at admission predict mortality in ED patients with sepsis. Am J Emerg Med. 2016;34(8):1589–94.

[16] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-874.

[17] Ma L, Zhang H, Yin YL, Guo WZ, Ma YQ, Wang YB, et al. Role of interleukin-6 to differentiate sepsis from non-infectious systemic inflammatory response syndrome. Cytokine. 2016;88:126–35.

[18] Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med. 2001; 164(3):396–402.

[19] Takahashi W, Nakada TA, Yazaki M, Oda S. Interleukin-6 levels act as a diagnostic marker for infection and a prognostic marker in patients with organ dysfunction in intensive care units. Shock. 2016;46(3):254–60.

[20] Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, et al. Prognostic and diagnostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. Crit Care. 2014;18(5):50.

[21] Levy MM, et al. 2001 SCCM/ ESICM/ ACCP/ ATS/ SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530–8.

[22] Schneck E, Samara O, Koch C, Hecker A, Padberg W, Lichtenstern C, Weigand MA, Uhle F. Plasma DNA and RNA differentially impact coagulation during abdominal sepsis-an explorative study. J Surg Res. 2017; 210:231–43.

[23] Dwivedi DJ, Toltl LJ, Swystun LL, Pogue J, Liaw KL, Weitz JI, et al. Prognostic utility and characterization of cell-free DNA in patients with severe sepsis. Crit Care. 2012;16(4):R151. https://doi.org/10.1186/cc11466 Epub 2012/08/13 PubMed PMID: 22889177.

[24] Saukkonen K, Lakkisto P, Pettilä V, Varpula M, Karlsson S, Ruokonen E, et al. Cell-free plasma DNA as a predictor of outcome in severe sepsis and septic shock. Clin Chem. 2008;54(6):1000–7. Epub 2008/04/17. doi: https://doi.org/ 10.1373/clinchem.2007.1010.

[25] 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.