ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Assessment of the Diagnostic and Prognostic Value of the Serum Netrin-1 Level in Patients Presenting the Emergency Department with Sepsis

Acil Servise Sepsis Nedeniyle Başvuran Hastalarda Serum Netrin 1 Düzeyinin Tanı ve Prognoz Üzerine Etkisi

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ABSTRACT

Aim: *Sepsis affects approximately 50 million people across the world each year and causes 11 million deaths. Many biomarkers have been investigated for the early diagnosis of sepsis and patient responses to infection and treatment, as well as to help clinicians predict risk and plan treatment. Netrin-1 plays an important role by directing the migration of neutrophils, particularly monocytes, in inflamed tissue. This study aimed to determine whether Netrin-1 was an effective marker in the diagnosis, treatment follow-up, and prognosis evaluation of patients with sepsis and septic shock.*

Material and Method: *This observational and prospective study was conducted at the emergency department with 121 individuals over 18, including 71 patients diagnosed with sepsis and 50 healthy volunteers. The patients were further evaluated in two subgroups: sepsis and septic shock. Blood samples were taken from the patient and control groups at the time of presentation and on the third day. Netrin-1 levels were examined in both groups.*

Results: *The netrin-1 levels of the patients with sepsis and septic shock upon presentation to the hospital were significantly higher than the control group (p<0.0001). However, there was no significant difference between the netrin-1 levels measured at the time of presentation and on the third day in the sepsis and septic shock groups (p: 0.0522 and 0.0786, respectively). Neither the presentation nor the third-day netrin-1 level had a statistically significant correlation with mortality (p=0.075 and 0.254, respectively).*

Conclusion: *Our results showed that netrin-1 was an effective biomarker for diagnosing sepsis and septic shock. However, it was not a risk factor for mortality or clinical risk scores in patients with these conditions.*

Key words: *netrin-1; sepsis; emergency department*

ÖZET

Amaç: *Sepsis; dünya çapında yıllık yaklaşık 50 milyon kişiyi etkilemekte ve 11 milyon kişinin ölümüne neden olmaktadır. Sepsisin erken tanısı, hastanın enfeksiyona tepkisini, tedavinin yanıtını ve klinisyenin hasta riskini tahmin etmesine ve tedavinin planlanmasına yardımcı olmak için birçok biyobelirteç araştırılmıştır. Netrin-1, nötrofillerin ve özellikle de iltihaplı dokudaki monositlerin göçünü yönlendirerek önemli bir rol oynar. Bu çalışmada sepsis ve septik şoklu hastalarda Netrin –1'in tanıda, tedavi takibinde ve prognozu göstermede etkili bir belirteç olup olmadığını belirlemeyi amaçladık.*

Materyal ve Metod: *Bu gözlemsel ve prospektif çalışma, acil serviste 18 yaş üstü 71 sepsis tanısı konan hasta ve 50 gönüllü olmak üzere 121 hasta ile yapılmıştır. Hastalar sepsis ve septik çok olarak ikiye ayrıldı. Hasta ve kontrol grubundan ilk başvuruda ve 3. gün kan örnekleri alındı. Her iki grupta da Netrin-1 düzeyleri çalışıldı.*

Bulgular: *Sepsis ve septik şoklu hastaların hastaneye geliş netrin-1 düzeyleri kontrol grubuna göre anlamlı olarak yüksek tespit edildi (p<0,0001). Ancak sepsis ve septik şoklu hastaların acil servise geliş ve 3. gün netrin –1 düzeyleri arasında anlamlı fark yoktu (sırasıyla 0,0522 ve 0,0786) Hem acil servise başvuru Netrin-1 düzeyinin hem de 3. gün netrin-1 düzeyinin istatistiksel olarak mortalite ile ilişkisi yoktu. (p sırasıyla: 0,075, 0,254)*

Sonuçlar: *Sonuçlarımız Netrin-1 'in sepsis ve septik şok tanısında etkili bir biyobelirteç olduğunu göstermektedir. Ancak netrin –1'in sepsis ve septik şok tanılı hastalarda mortalitenin bir gösterisi ve klinik risk skorlamaları için risk faktörü olmadığını gösterdik.*

Anahtar kelimeler: *netrin-1; sepsis; acil servis*

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Introduction

Sepsis is defined as life-threatening organ dysfunction caused by an irregular host response to infection[1]. Sepsis affects approximately 50 million individuals worldwide each year and causes 11 million deaths[2–3]. Therefore, it has become one of the leading causes of critical illness and mortality[3]. The World Health Organization emphasizes sepsis as a health priority due to the growing incidence of this condition every year and its significant societal and economic consequences[3–6]. Despite significant advances in understanding the pathophysiology, making a diagnosis, and providing supportive treatment options for sepsis, the mortality rates associated with sepsis and septic shock in emergency departments and intensive care units remain very high[4–8]. Relevant guidelines recommend using scoring systems, such as the acute physiology and chronic health evaluation (APACHE)-II and the sequential organ failure assessment (SOFA) for the early diagnosis of sepsis and septic shock and predicting mortality[5–9]. Prompt identification and implementation of suitable therapy within the initial hours following the onset of sepsis enhance treatment outcomes[6–9]. Numerous biomarkers have been investigated for the early diagnosis of sepsis and patients' responses to infection and treatment, as well as to help clinicians predict risk and plan treatment[6–13].

Netrins are laminin-like proteins that direct axonal migration and neuronal growth in the central nervous system[14–16]. Netrin-1 has been found to possess chemoattractive or chemo-repulsive properties in various biological processes other than neuronal developmen[14–18]. In addition, netrin-1 has been shown to play an important role in cell adhesion, cell migration, proliferation, and cell survival in tissues[16–21]. In this context, netrin-1 has been reported to regulate organogenesis, angiogenesis, tumorigenesis, and inflammation[18–22]. As in neuronal development, netrin-1 plays an important role in the inflammation process by directing the migration of neutrophils and, in particular, monocytes in inflamed tissue[20–25]. Due to these characteristics of netrin-1, the level of this protein is likely to change infective conditions, such as sepsis and septic shock. Therefore, the current study aimed to determine whether netrin-1 was an effective marker for the diagnosis, treatment follow-up, and prognosis evaluation of patients with sepsis and septic shock.

Material and Method

Study Design and Participants

This observational and prospective study was conducted at the emergency medicine clinic of our hospital from October 2013 to March 2014 after receiving approval from the local ethics committee (approval number: 2013/24). Seventy-one patients with sepsis and 50 volunteers without any disease were included in the study. The control group included people over 18 without acute or chronic disease who came to the hospital for routine screening. Volunteer patients who met the criteria for sepsis or septic shock at the emergency department and were over the age of 18 were included in the sample. The classification of sepsis and septic shock was made according to the most recent definitions (Sepsis-3)[1.] Demographic characteristics, medical history, vital signs, laboratory findings, length of hospital stay, and mortality status were recorded for the patients admitted to the intensive care unit or inpatient ward from the emergency department. The Glasgow Coma Scale (GCS), APACHE II[22], and SOFA[21] scores were calculated to determine the severity of organ dysfunction and clinical condition. Patients with acute and/or chronic kidney disease, a history of cerebrovascular accident, neurological disease, liver failure, or malignancy, pregnant and breastfeeding women, and patients who died or were discharged within 72 hours after presenting to the emergency department were excluded from the study. All patients were treated according to the recommendations of the sepsis guidelines[1].

Laboratory Analysis

To evaluate netrin-1 levels, blood samples were taken within 15 minutes following presentation to the emergency department (day 1) and placed in tubes containing ethylenediaminetetraacetic acid on the third day after presentation. After centrifugation at 2.800 rpm for 20 min at 4°C, plasma samples were placed in Eppendorf tubes and stored at -80°C until analysis. Netrin-1 levels were measured in duplicate assays using enzyme-linked immunosorbent assay kits (MyBioSource MBS044526; MyBioSource, Inc., San Diego, California), and the results were expressed in picograms (pg) per mg.

The netrin-1 levels of the patients were compared according to routinely checked infection markers evaluated on the first and third days, clinical (GCS, APACHE-II, and SOFA) scores, treatment efficacy, and mortality status.

Statistical Analysis

The data obtained from the study were given as median (interquartile range) and mean ± standard deviation values. P values of <0.05 were considered statistically significant. Statistical analyses were undertaken using descriptive statistics, and non-parametric data were compared between groups using the Kruskal-Wallis and Mann-Whitney U tests. The data were transferred to electronic media and analyzed using the IBM Statistical Package for Social Sciences (SPSS) program version 15.0 software package. Numerical data were compared according to the outcome. Multivariate logistic regression analysis revealed the relationship between different parameters and outcomes. Sepsis findings and numerical parameters were evaluated using the Mann-Whitney U test, and the t-test was conducted.

Results

The study included 121 individuals: 71 (58.7%) were patients with sepsis or septic shock, and 50 (41.3%) were healthy controls. Male patients constituted 61.9% (44) of the case group and 56% of the control group. The mean age was 72±22 years for the case group and 67±21 years for the control group. In the evaluation of the case group, 27 (38%) patients were found to have sepsis, while 44 (62%) had septic shock. Table 1 shows the distribution of the demographic data for the case and control groups.

The distribution of the netrin-1 levels of the case and control groups is presented in Figure 1. The netrin-1 levels evaluated at the time of presentation to the hospital were significantly higher among the patients with sepsis and septic shock than the control group (p <0.0001). However, there was no significant difference between the presentation and third-day netrin-1 levels of the patients with sepsis and septic shock (p: 0.0522 and 0.0786, respectively). The laboratory values of the case and control groups are given in Table 2.

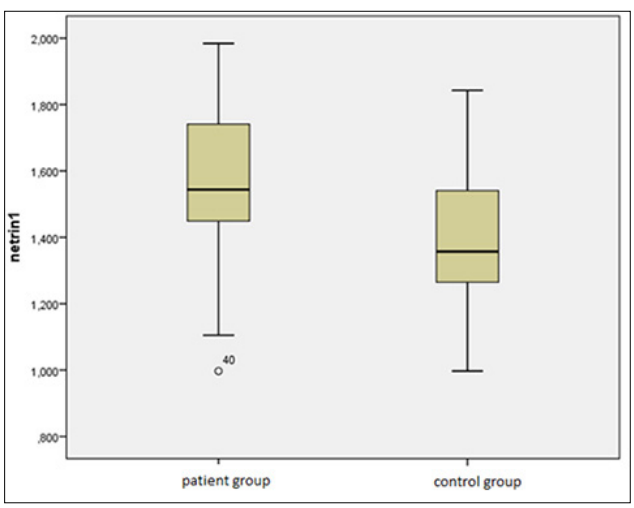

Figure 1. *Distribution of netrin-1 levels in patient and control groups.*

Table 1. *Clinical and demographic data of the sample*

Variables	Control group (n=50)	Case group (n=71)		P-value
Diagnosis [c]		Sepsis (n=27)	Septic shock (n=44)	
Age (years)	67 (21)	71±18	73±20	0.128
Male sex	28 (56%)	18 (25.3%)	26 (36.6%)	0.094
APACHE-II score (at presentation)		19.75±5.81	22.17±7.81	
SOFA (at presentation)		8.22±3.55	9.86±2.69	
GCS score (at presentation)		14.9		
Diabetes mellitus		8 (19.5%)	64 (32.7%)	0.096
Hypertension		13 (31.7%)	28 (14.3%)	0.007*
Coronary artery disease		32 (78.0%)	112 (57.1%)	0.013*
Cerebrovascular accident		11 (26.8%)	68 (34.7%)	0.331
Source of infection: abdomen[c]		11 (43.9%)	24 (25.5%)	0.018*
Source of infection: lungs[c]		10 (61.0%)	21 (25.0%)	<0.001*
Source of infection: soft tissue[c]		3 (61.0%)	2 (25.0%)	<0.001*
Survival status: survival[c]		20	15	<0.001*
Survival status: mortality[c]		1	29	
Treatment: mechanical ventilation[c]		2	22	0.004*
Type of infection: bacterial Gram-negative[c]		12	25	<0.001*
Type of infection: bacterial, Gram-positive[c]		8	17	0.007*
Type of infection: fungal[c]		4	8	0.246
Type of infection: unknown[c]		7	5	0.006*
Mixed infection (2 or more pathogens) [c]		8	9	<0.001*

[a]Mean ± standard deviation, [b]Median (first-third quartile), [c]Number (percentage) of patients. APACHE-II, acute physiology and chronic health evaluation-II; SOFA, sequential organ failure assessment, GCS: Glasgow Coma Scale.

Table 2. *Comparison of the first-day and third-day values of selected parameters between the study groups*

Parameters (evaluation time)	Control (C)	Sepsis (A)	Septic shock (B)	p (C vs. A)	p (C vs. B)	p (A vs. B)	Global p (ranked ANOVA)
Netrin-1 (pg/mL) (day 1)	1.36±0.19	1.57±0.19	1.61±0.28	**<0.0001**	**<0.0001**	0.0522	**<0.0001**
Netrin-1 (pg/mL) (day 3)		1.60±0.19	1.63±0.29			0.0786	
CRP (mg/L)	12.54±9.8	78.12±59.6	158±78.6	**<0.0001**	**<0.0001**	<0.0001	
PCT (µg/L)	0.04±0.01	3.9 (1.9–14.2)	20.9 (7.9–44.2)	**<0.0001**	**<0.0001**	<0.0001	
Lactate (pg/mL)	0.54±0.26	4.1 (3.9–9.1)	8.1 (3.9–19.1)	**<0.0001**	**<0.0001**	<0.0001	

ANOVA, analysis of variance, PCT, procalcitonin; CRP, C-reactive protein. Statistically significant values (p <0.05) are shown in bold.

Table 3. *Evaluation of parameters related to survival status*

	Survival status		
Parameters (evaluation time)	Survival	Mortality	P
Netrin-1 (pg/mL) (day 1)	1.57±0.19	1.61±0.28	0.075
Netrin-1 (pg/mL) (day 3)	1.57±0.19	1.61±0.28	0.254
CRP (mg/L) (day 1)	78.12±59.6	158±78.6	<0.001
PCT (µg/L) (day 1)	3.9 (1.9–14.2)	20.9 (7.9–44.2)	<0.001
Lactate (pg/mL) (day 1)	4.1 (3.9–9.1)	8. 1(3.9–19.1)	<0.001
APACHE-II score (at presentation)	17.45±5.91	23.47±7.94	<0.001
SOFA score (at presentation)	7.72±3.15	9.97±3.49	0.0098
GCS score (at presentation)	14.9(12–15)	13.8(7–15)	0.032

PCT, procalcitonin; CRP, C-reactive protein, APACHE II, acute physiology and chronic health evaluation-II; SOFA, sequential organ failure assessment, GCS: Glasgow Coma Scale. Statistically significant values (p <0.05) are shown in bold.

While the procalcitonin (PCT), C-reactive protein (CRP), and lactate levels and the APACHE II, SOFA, and GCS scores were associated with mortality in the presence of sepsis, neither the presentation nor the third-day netrin-1 level had a statistically significant relationship with mortality (p=0.075 and 0.254, respectively). The relationship of the remaining laboratory values and scoring systems with mortality is shown in Table 3. There was no correlation between netrin-1 levels and the APACHE II, SOFA, or GCS scores.

Discussion

Sepsis, a prevalent condition accompanied by life-threatening organ dysfunction as a result of irregular host response to infection, is responsible for high mortality and morbidity rates as well as decreased quality of life[4,13,28]. In this serious condition, biomarkers guide the diagnosis of infection, prognosis determination, treatment response, and/or clinicians' risk prediction[10–13,26]. Prominent biomarkers used in sepsis include PCT and CRP. In addition, the existing guidelines on the management of sepsis also mention that sepsis biomarkers can complement clinical assessment, and many researchers have investigated novel biomarkers in sepsis[13,27]. Therefore, in the current study, we investigated whether netrin-1 was an effective biomarker in predicting diagnosis, response to treatment, and prognosis in patients with sepsis. To our knowledge, this is the first study in the literature to explore the relationship between netrin-1 and sepsis.

This study revealed high netrin-1 levels in patients with sepsis and septic shock when they presented to the emergency department. However, these patients' netrin-1 levels did not increase in the following days. In addition, neither the presentation nor the third-day netrin-1 level had any significant relationship with mortality. There was also no significant correlation between netrin-1 and clinical scores, such as APACHE II and SOFA.

In the study conducted by Hwang et al. in 29618 intensive care patients, Apache and Sofa scores were significantly higher in those who died compared to those who did not die[28].

Likewise, Kramer et al. found that Apache score was an indicator of mortality in a study conducted on 5000

patients in 13 hospitals, and similar to these studies, we found that Apache and Sofa were an indicator of mortality[29]. Procalcitonin and CRP are the most frequently studied biomarkers in sepsis. They are considered potential sepsis biomarkers and are commonly used in antibiotic selection and evaluation of treatment in critically ill patients[6–12]. They have also been reported as an indicator of mortality[6–10]. In our study, we found that PCT and CRP are strong predictors of mortality in patients with sepsis.

In the pathogenesis of sepsis, there appears to be a complex response that combines pro-inflammatory and anti-inflammatory properties and occurs with impaired homeostasis[2–4,30]. During the initial hyperinflammatory response, organ dysfunction and hypoperfusion develop due to the migration of neutrophils and monocytes to the inflamed tissue and the intense release of inflammatory mediators[4–8,31,32]. Ly et al. reported that netrin-1 could modulate the migration of monocytes and leukocytes into and out of inflamed tissue[23]. In our study, the patients' high levels of netrin-1 at the time of presentation to the emergency department suggest that netrin-1 may have played a role in the hyperinflammatory response that occurred in the first period of sepsis.

Lui et al. found that the expression of netrin-1 and its receptor UNC5B decreased in rats with sepsis through an anti-inflammatory effect[33] In a study conducted by Tui et al. with 150 septic patients, the netrin-1 levels of the patients with sepsis who developed acute renal failure increased within the first 24 hours and then returned to normal[34]. Similarly, in the current study, we observed that netrin-1 increased through the pro-inflammatory effect in the early period of sepsis. Still, this increase was limited in the later period due to the anti-inflammatory effect.

Our study has some limitations. First, it was a single-center pilot study. Second, the relatively small number of patients in the sample may have caused a higher rate of B error. Therefore, the study's findings need to be confirmed with a larger case series. Lastly, netrin-1 levels were only measured in plasma, and further investigations should be undertaken to evaluate the infected tissue and urine levels of this protein.

Conclusions

Our results showed that netrin-1 was an effective biomarker for diagnosing sepsis and septic shock. However, netrin-1 was not a risk factor for mortality or clinical risk scores in these patients. Given the complex nature of sepsis, further studies are needed to investigate the combination of netrin-1 and other biomarkers reflecting different biological pathways in terms of their ability to predict early diagnosis and prognosis.

References

1. Singer M., Deutschman C., Seymour C. W., Shankar-Hari M., Annane D., Bauer, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama,. 2016;315(8), 801–810.
2. Yao R. Q., Zhao P. Y., Li Z. X., Liu Y. Y., Zheng L. Y., DuanY, et al. Single-cell transcriptome profiling of sepsis identifies HLA-DR low S100A high monocytes with immunosuppressive function. Military Medical Research,. 2023;10(1), 27.
3. Rudd, K. E., Johnson, S. C., Agesa, K. M., Shackelford, K. A., Tsoi, D., Kievlan, D. et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet,. 2020;395(10219), 200–211.
4. Reinhart, K., Daniels, R., Kissoon, N., Machado, F. R., Schachter, R. D., & Finfer, S. Recognizing sepsis as a global health priority—a WHO resolution. New England Journal of Medicine,. 2017;377(5), 414–417.
5. Torres LK, Pickkers P, van der Poll T. Sepsis-induced immunosuppression. Annu Rev Physiol. 2022;84:157–81.
6. Venet, F., Demaret, J., Gossez, M., Monneret, G. Myeloid cells in sepsis-acquired immunodeficiency. Annals of the New York Academy of Sciences,. 2021;1499(1), 3–17.
7. Martin-Loeches, I., Perner, A. Focus on infection and sepsis in intensive care patients. Intensive Care Medicine,. 2016;42(4), 491–493.
8. Marshall, J. C., Dellinger, R. P., Levy, M. The Surviving Sepsis Campaign: a history and a perspective. Surgical infections,. 2010;11(3), 275–281.
9. Evans, L., Rhodes, A., Alhazzani, W., Antonelli, M., Coopersmith, C. M., French, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Critical care medicine,. 2021;49(11), e1063–e1143.
10. Póvoa, P., Coelho, L., Dal-Pizzol, F., Ferrer, R., Huttner, A., Conway Morris, et al. How to use biomarkers of infection or sepsis at the bedside: guide to clinicians. Intensive care medicine,. 2023;49(2), 142–153.

11. Póvoa, P., Martin-Loeches, I., Ramirez, P., Bos, L. D., Esperatti, M., Silvestre, J, et al. Biomarker kinetics in the prediction of VAP diagnosis: results from the BioVAP study. Annals of intensive care,. 2016;6, 1–11.
12. de Jong, E., van Oers, J. A., Beishuizen, A., Vos, P., Vermeijden, W. J., Haas, L. et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. The Lancet Infectious Diseases,. 2016;16(7), 819–827.
13. Pierrakos, C., Velissaris, D., Bisdorff, M., Marshall, J. C., Vincent, J. L. Biomarkers of sepsis: time for a reappraisal. Critical Care,. 2020;24, 1–15.
14. Xu, K., Wu, Z., Renier, N., Antipenko, A., Tzvetkova-Robev, D., Xu, Y., et al. Structures of netrin-1 bound to two receptors provide insight into its axon guidance mechanism. Science,. 2014;344(6189), 1275–1279.
15. Cirulli, V.;Yebra, M. Netrins: Beyond the brain. Nat. Rev. Mol. Cell Biol. 2007, 8, 296–306.
16. Bruikman, C. S.;Zhang, H.;Kemper, A. M.;van Gils, J. M. Netrin Family: Role for Protein Isoforms in Cancer. J. Nucleic Acids 2019, 2019, 3947123.
17. Miloudi, K.;Binet, F.;Wilson, A.;Cerani, A.;Oubaha, M.;Menard, et al. Truncated netrin-1 contributes to pathological vascular permeability in diabetic retinopathy. J. Clin. Investig. 2016, 126, 3006–3022.
18. Kruger, R. P.;Lee, J.;Li, W.;Guan, K. L. Mapping netrin receptor binding reveals domains of Unc5 regulating its tyrosine phosphorylation. J. Neurosci. 2004, 24, 10826–10834.
19. Claro, V.;Ferro, A. Netrin-1: Focus on its role in cardiovascular physiology and atherosclerosis. JRSM Cardiovasc. Dis. 2020, 9, 2048004020959574.
20. Castets, M.;Mehlen, P. Netrin-1 role in angiogenesis: To be or not to be a pro-angiogenic factor? Cell Cycle 2010, 9, 1466–1471.
21. Ziegon, L., & Schlegel, M. Netrin-1: A modulator of macrophage driven acute and chronic inflammation. International Journal of Molecular Sciences,. 2021;23(1), 275.
22. Kaya, S., Turhan, U., Dağ, I., Polat, İ. Association of maternal serum Netrin-1 and Netrin-4 levels with placenta accreta spectrum. European Review for Medical & Pharmacological Sciences,. 2023;27(10).
23. Xia, X., Hu, Z., Wang, S., & Yin, K. Netrin-1: An emerging player in inflammatory diseases. Cytokine & Growth Factor Reviews,. 2022;64, 46–56.
24. Schlegel, M.;Kohler, D.;Korner, A.;Granja, T.;Straub, A.;Giera, M.;et al. The neuroimmune guidance cue netrin-1 controls resolution programs and promotes liver regeneration. Hepatology 2016, 63, 1689–1705.
25. Mirakaj, V.;Dalli, J.;Granja, T.;Rosenberger, P.;Serhan, C. N. Vagus nerve controls resolution and pro-resolving mediators of inflammation. J. Exp. Med. 2014, 211, 1037–1048.
26. Azoulay E, Vincent JL, Angus DC, Arabi YM, Brochard L, Brett SJ, et al. Recovery after critical illness: putting the puzzle together-a consensus of 29. Crit Care. 2017;21:296.
27. 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. Crit Care Med. 2017;45:486–552.
28. Hwang, S. Y., Kim, I. K., Jeong, D., Park, J. E., Lee, G. T., Yoo, J., et al. Prognostic Performance of Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation III, and Simplified Acute Physiology Score II Scores in Patients with Suspected Infection According to Intensive Care Unit Type. Journal of Clinical Medicine,. 2023;12(19), 6402.
29. Kramer, A. A., Zimmerman, J. E., Knaus, W. A. Severity of illness and predictive models in society of critical care medicine's first 50 years: a tale of concord and conflict. Critical Care Medicine,. 2021;49(5), 728–740.
30. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. Immunity. 2021;54(11):2450–64.
31. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol. 2013;13(12):862–74.
32. Samudra, D., Santoso, S., Asmoro, A. A., Khotimah, H., Ansori, A. N., Sabdoningrum, E. K. The Effect of Escherichia coli on Pro-Inflammatory Mediators Level and Kidney and Liver Function of Sepsis in Rattus novergicus. Indian Journal of Forensic Medicine & Toxicology,. 2020;14(4).
33. Liu, J., Du, J., Cheng, X., Zhang, X., Li, Y., Fu, X, et al.). Effect of netrin-1 anti-inflammatory factor on acute lung injury in sepsis rats. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research,. 2019;25, 7928.
34. Tu, Y., Wang, H., Sun, R., Ni, Y., Ma, L., Xv, F, et al. Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. Renal failure,. 2014;36(10), 1559–1563.