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Evaluation of Factors Associated with Adult Sepsis Prognosis

Erişkin Sepsis Prognozu ile İlişkili Faktörlerin Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study was to evaluate the factors affecting the prognosis of sepsis in patients admitted to the intensive care unit (ICU).

Materials and Methods: We retrospectively included all adult patients admitted to the ICU, who were diagnosed with sepsis according to the Sepsis 3 criteria between September 2013 and February 2021. Demographic, clinical data and laboratory results were recorded.

Results: Of the 245 patients in the ICU, 100 (40.8%) died during the 30-day follow-up. In univariate logistic regression analysis, Sequential Organ Failure Assessment (SOFA) score, vasopressor need, immunosuppressive treatment, neutropenic fever, hematological malignancy, pneumonia, urinary tract infection, lactate, ferritin, lactate dehydrogenase (LDH), and albumin levels were found to be independently associated with mortality. When evaluated in terms of prognostic significance in ROC curve, the optimal cutoff values for 30-day mortality were 7 for SOFA score (AUC=0.713, p<0.001), 1518 µg/L for ferritin (AUC=0.732, p<0.001), 324 U/L for LDH (AUC=0.593, p=0.035), and 2.9 g/dL for albumin (AUC=0.632, p=0.001), in mortality. Using these values, in multivariate logistic regression analysis, we determined that a SOFA score >7 [odds ratio (OR): 95% confidence interval (CI): 9.66 (1.16-80.82), p=0.036], history of immunosuppressive treatment [OR 95% CI: 12.41 (1.45-106.17), p=0.021], and ferritin levels >1518 µg/L [OR 95% CI: 9.46 (1.36-65.79), p=0.023] were independent risk factors for 30-day mortality.

Conclusion: In our single-center study, serum ferritin level was determined to be a valuable prognostic biomarker in patients with sepsis.

Keywords: Sepsis, prognosis, mortality, ferritin, critical care

ÖZ

Amaç: Yoğun bakım ünitesinde (YBÜ) takip edilen sepsis tanılı erişkin hastalarda prognozu etkileyen faktörleri değerlendirmektir.

Gereç ve Yöntem: Eylül 2013 ile Şubat 2021 arasında Sepsis-3 kriterlerine göre sepsis tanısı almış tüm yetişkin hastalar retrospektif olarak değerlendirildi. Demografik, klinik veriler ve laboratuvar sonuçları kaydedildi.

Bulgular: YBÜ'de 245 hastadan 100'ü (%40,8) 30 günlük takip süresi içinde öldü. Tek değişkenli lojistik regresyon analizinde; ardışık organ yetmezlik değerlendirme (SOFA) skoru, vazopresör ihtiyacı, immünsupresif tedavi öyküsü, nötropenik ateş, hematolojik malignite, pnömoni, üriner sistem enfeksiyonu, laktat, ferritin, laktat dehidrogenaz (LDH) ve albümin seviyelerinin 30 günlük mortalite ile ilişkili olduğu saptandı. ROC eğrisinde; 30 günlük mortalite için optimal kesme değerleri SOFA skoru için 7 (AUC=0,713, p<0,001), ferritin için 1,518 µg/L (AUC=0,732, p<0,001), LDH için 324 U/L (AUC=0,593, p=0,035), ve albümin için 2,9 g/dL (AUC=0,632, p=0,001) olarak belirlendi. Bu değerleri kullanarak yapılan çok değişkenli lojistik regresyon analizinde; SOFA skoru >7 [odds oranı (OR) %95 güven aralığı (GA): 9,66 (1,16-80,82), p=0,036], immünsüpresif tedavi öyküsü [OR %95 GA: 12,41 (1,45-106,17), p=0,021] ve ferritin seviyesinin >1,518 µg/L [OR %95 GA: 9,46 (1,36-65,79), p=0,023] olması 30 günlük mortalite için bağımsız risk faktörleri olarak saptandı.

Sonuç: Tek merkezli çalışmamız sonucunda, serum ferritin seviyesi, sepsis hastalarında değerli bir prognostik biyobelirteç olarak saptandı.

Anahtar Kelimeler: Sepsis, prognoz, mortalite, ferritin, yoğun bakım

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INTRODUCTION

Sepsis is characterized by an excessive immune response to an infectious agent, leading to multiple organ failure with a high mortality rate[1]. Sepsis is a major concern in public health due to its widespread impact, with over 19 million individuals diagnosed each year globally[2]. Despite advances in supportive care and intensive care technologies, the mortality rate in septic shock remains approximately 40%[3]. Sepsis involves the release of high levels of proinflammatory cytokines due to microbial agents, accompanied by the release of anti-inflammatory cytokines. The initial hyperinflammatory phase can lead to early mortality[4]. Numerous studies have been conducted on various laboratory parameters to evaluate the severity of the increased inflammatory response and to predict mortality. Mortality predictor parameters can help identify patients who, in addition to supportive therapies, may benefit from potentially effective additional treatments by predicting early mortality. Recently, in addition to commonly used parameters such as C-reactive protein (CRP), procalcitonin, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), studies have been conducted on numerous new markers such as N-terminal pro b-type natriuretic peptide (NT-proBNP), ferritin, and presepsin. Some of these studies have yielded significant results for these parameters[5-10]. However, none of these parameters have been accepted as additional mortality predictive markers in scoring systems such as Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) according to international guidelines[11]. In this study, we aimed to evaluate the capability of certain inflammatory markers to predict prognosis independently of general patient characteristics and parameters already associated with disease severity and mortality, such as the SOFA score and serum lactate levels.

MATERIALS AND METHODS

Patient Selection and Study Design

This retrospective study was conducted in a single-center internal medicine intensive care unit (ICU) between September 2013 and February 2021. The Institutional Ethical Review Board of Ege University Hospital approved the study (decision no: 21-6.1T/54, date: 10.04.2016). This study was conducted in accordance with good clinical practice guidelines and adhered to the principles of the Declaration of Helsinki. Patients or their relatives provided written informed consent. We included all adult patients (≥18 years old) diagnosed with sepsis. The diagnosis of sepsis and septic shock was made according to the Sepsis-3 criteria[12].

Demographic characteristics and clinical features were extracted from patients' medical records. In addition, the following laboratory parameters were obtained on admission and 48 h after hospitalization: neutrophil count, lymphocyte count, platelet count, CRP at admission and 48 h, procalcitonin, albumin, ferritin, NT-proBNP, troponin-T, lactate, and LDH. The primary endpoint of the study was 30-day mortality. Secondary endpoints included factors associated with prognosis.

Statistical Analysis

Descriptive statistics were used to summarize the data. For continuous (numerical) variables, depending on the distribution, either mean±standard deviation or median, minimum, and maximum values were presented. Categorical variables are summarized as counts and percentages. The normality of the numerical variables was assessed using the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. For comparisons between two independent groups, the Independent Samples t-test was used when numerical variables were normally distributed, and the Mann-Whitney U test was used when they were not. Risk factors affecting 30-day mortality were investigated using univariate and multivariate logistic regression models. To identify the ideal cutoff level to evaluate 30-day mortality, receiver operating characteristic curve (ROC), in which the Youden J index was considered in determining the threshold value, was performed. Statistical analyses were performed by Jamovi project (2020), Jamovi (version 1.8.4.0) [computer software], and JASP with a significance level set at 0.05 (p value).

RESULTS

During the study period, 245 patients diagnosed with sepsis were followed up in the ICU. The 30 day-mortality rate was 40.8%. Demographic information, comorbid conditions, and infection sites, laboratory data along with the differences between the survivors and non-survivors are presented in Table 1. Within comorbidities, vasculitis, hematologic malignancy, and the use of immunosuppressive therapy were significantly more frequent in the non-survivor group (p values 0.009, <0.001, 0.004 respectively). Among the sources of infection, pneumonia was more commonly observed in the non-survivor group (p=0.001), whereas urinary tract infections were more frequent in the survivor group (p=0.003). Neutropenic fever, high SOFA scores, and the need for vasopressors were more common in the non-survivor group (p values <0.001, <0.001, 0.004 respectively). Among baseline data, albumin, LDH, lactate, and ferritin levels at admission as well as the changes in CRP and LDH levels at the 48 h of hospitalization compared with their admission values were found to be statistically different between the non-survivor and survivor groups (p values 0.002, 0.034, 0.005, <0.001, 0.002, 0.012, respectively).

Logistic regression analysis was performed to determine the parameters that were significantly different between the survivor and non-survivor groups. In the evaluation based

Table 1. Patient characteristics and laboratory parameters of surviving and non-surviving septic patients

	30 days mortality		p value
	Survivors (n=145)	Non-survivors (n=100)	
Age	60.0±17.8	62.2±15.9	0.306
Gender (%)			
Male	71 (49.0)	50 (50.0)	0.977
Female	74 (51.0)	50 (50.0)	
Comorbidity	100 (69.0)	70 (70.0)	0.975
Diabetes mellitus	51 (35.2)	32 (32.0)	0.705
Chronic heart failure	24 (16.6)	21 (21.0)	0.474
Cardiovascular disease	23 (15.9)	23 (23.0)	0.215
COPD/asthma	11 (7.6)	11 (11.0)	0.489
Chronic renal disease	12 (8.3)	12 (12.0)	0.456
Vasculitis	1 (0.7)	7 (7.0)	**0.009**
Connective tissue disease	7 (4.8)	8 (8.0)	0.455
Hematological malignancy	16 (11.0)	35 (35.0)	**<0.001**
Solid organ malignancy	8 (5.5)	2 (2.0)	0.206
History of immunosuppressive therapy	10 (6.9)	20 (20.0)	**0.004**
Site of infection			
Pneumonia	33 (22.8)	44 (44.0)	**0.001**
Urinary tract	51 (35.2)	17 (17.0)	**0.003**
Biliary system	12 (8.3)	3 (3.0)	0.155
Abdomen (other than biliary system)	14 (9.7)	5 (5.0)	0.273
Catheter	21 (14.5)	19 (19.0)	0.445
Infective endocarditis	4 (2.8)	2 (2.0)	0.999
Meningitis	0 (0.0)	1 (1.0)	0.408
Skin and soft tissue	10 (6.9)	10 (10.0)	0.526
Septic arthritis	3 (2.1)	1 (1.0)	0.647
Primary bacteremia	1 (0.7)	4 (4.0)	0.162
Spondylodiscitis	1 (0.7)	0 (0.0)	0.999
Neutropenic fever	15 (10.3)	35 (35.0)	**<0.001**
Vasopressor need	69 (47.6)	66 (66.0)	**0.004**
SOFA score	6.0 [2.0-15.0]	9.0 [2.0-16.0]	**<0.001**
Biochemical results			
CRP mg/L	240.0 [7.0-619.0]	230.0 [18.0-471.0]	0.402
CRP D2-D0	-6.4 [-87.5-564.3]	7.9 [-86.4-566.7]	**0.002**
Albumin g/dL	3.1±0.6	2.8±0.7	**0.002**
CRP/albumin ratio mg/g	79.6 [1.5-238.1]	81.2 [4.4-261.7]	0.397
LDH U/L	277.0 [85.0-3798.0]	320.5 [99.0-4730.0]	**0.034**
LDH D2-D0	-4.5 [-48.2-258.5]	6.4 [-76.0-1344.3]	**0.012**
Procalcitonin µg/L	19.5 [0.3-100.0]	7.7 [0.3-100.0]	0.069
NT-proBNP ng/L	8299.5 [113.0-70000.0]	5536.0 [262.0-70000.0]	0.941
Troponin-T ng/L	51.0 [13.0-604.0]	61.0 [13.0-1824.0]	0.090
Lactate mmol/L	2.3 [0.6-24.0]	3.0 [0.6-11.0]	**0.005**
Ferritin µg/L	705.0 [104.0-76893.0]	2337.0 [291.0-44258.0]	**<0.001**

COPD: Chronic obstructive pulmonary disease, SOFA score: Sequential Organ Failure Assessment Score, CRP: C-reactive protein, LDH: Lactate dehydrogenase, NT-proBNP: N-terminal pro b-type natriuretic peptide

on 30-day mortality outcomes, univariate regression analysis identified SOFA score, use of immunosuppressive therapy, neutropenic fever, pneumonia, urinary tract infection, lactate, albumin, ferritin, and LDH as statistically significant factors. CRP D2-D0, LDH D2-D0, NLR, PLR, and NPAR were not found to be statistically significant in univariate analysis. Because the SOFA score and lactate levels are already established parameters used in determining the severity of sepsis and in diagnosing septic shock, model-1 was formed incorporating these along with other patient characteristics found to be associated with mortality. Ferritin, LDH, and albumin were added to the existing model to perform a multivariate regression analysis. After the modeling yielded inconclusive results, ROC curve was conducted on the relevant parameters (Figure 1). The cutoff values obtained from the ROC curve are shown in Table 2. Using the cutoff values obtained from the ROC curve, logistic regression analysis was repeated (Table 3). Initially, the univariate logistic regression model revealed that the following factors individually had a significant impact on 30-day mortality: a SOFA score above 7, the need for vasopressors at admission, administration of immunosuppressive therapy, the presence of neutropenic fever, hematologic malignancy, pneumonia, urinary tract infection, an albumin level below 2.9 g/dL, an LDH level over 324 U/L, and a ferritin level exceeding 1.518 µg/L. When examining the results of the multivariate logistic regression analysis, it was observed that a SOFA score

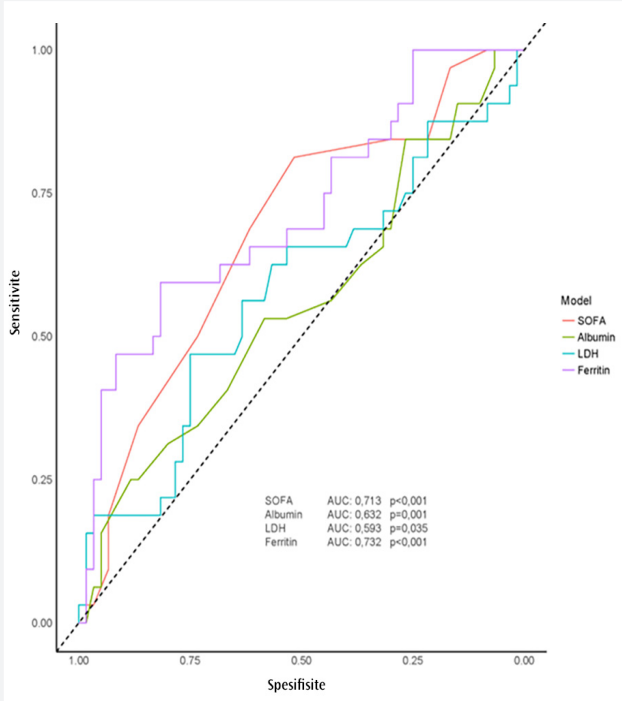

Figure 1. ROC curve analysis

SOFA score: Sequential Organ Failure Assessment Score, LDH: Lactate dehydrogenase

Table 2. ROC curve results

	AUC	Sensitivity	Specificity	Cutoff value	95% CI	p value
SOFA score	0.713	73	64.83	>7	0.652-0.769	**<0.001**
Albumin	0.632	64.95	58.27	≤2.9	0.567-0.694	**0.001**
LDH	0.593	50	71.58	>324	0.517-0.667	**0.035**
Ferritin	0.732	61.54	80.9	>1518	0.646-0.806	**<0.001**

SOFA score: Sequential Organ Failure Assessment Score, ROC: Receiver operating characteristic, LDH: Lactate dehydrogenase, CI: Confidence interval

Table 3. Results of the logistic regression analysis following the ROC curve

	Univariate LR		Multivariate LR	
	OR [95% CI]	p value	OR [95% CI]	p value
SOFA score: >7 vs ≤7	4.98 [2.85-8.70]	**<0.001**	9.66 [1.16-80.82]	**0.036**
Vasopressor need yes vs no	2.14 [1.26-3.62]	**0.005**	0.14 [0.02-1.16]	0.068
History of immunosuppressive therapy: yes vs no	3.37 [1.50-7.57]	**0.003**	12.41 [1.45-106.17]	**0.021**
Neutropenic fever: yes vs no	4.67 [2.38-9.16]	**<0.001**	4.94 [0.60-40.51]	0.137
Hematological malignancy: yes vs no	4.34 [2.24-8.42]	**<0.001**	1.21 [0.12-11.97]	0.872
Pneumonia: yes vs no	2.67 [1.53-4.64]	**<0.001**	0.95 [0.16-5.68]	0.954
Urinary tract infection yes vs no	0.38 [0.20-0.70]	**0.002**	1.58 [0.23-10.86]	0.639
Lactate mmol/L	1.13 [0.97-1.30]	0.111	1.51 [0.92-2.49]	0.103
Albumin: >2,9 vs ≤2,9 g/dL	0.39 [0.23-0.66]	**<0.001**	0.47 [0.12-1.90]	0.288
LDH: >324 vs ≤324 U/L	2.52 [1.35-4.71]	**0.004**	3.81 [0.89-16.18]	0.070
Ferritin >1518 vs ≤1518 µg/L	6.78 [2.94-15.60]	**<0.001**	9.46 [1.36-65.79]	**0.023**

SOFA score: Sequential Organ Failure Assessment Score, LDH: Lactate dehydrogenase, LR: Logistic regression, OR: Odds ratio, CI: Confidence interval

above 7 [odds ratio (OR): 95% confidence interval (CI): 9.66 (1.16-80.82) p=0,036], history of immunosuppressive therapy [OR 95% CI: 12.41 (1.45-106.17) p=0.021], and a ferritin level over 1.518 µg/L [OR 95% CI: 9.46 (1.36-65.79) p=0.023] were independent risk factors for 30-day mortality (p=0.036, p=0.021, and p=0.023).

DISCUSSION

In the current study, which included patients with sepsis, the 30-day mortality was 40.8%. High SOFA score (>7), history of immunosuppressive therapy, and ferritin levels >1.518 µg/L were significantly associated with 30-day mortality.

Ferritin is a protein composed of heavy and light chain structures that are responsible for iron binding and storage. It prevents the free circulation of iron in the body, thereby protecting proteins, lipids, and DNA structures from potential iron toxicity. Serum ferritin is also known as an acute phase reactant, which is regulated by proinflammatory cytokines. An increase in ferritin levels is often observed in inflammatory processes following the stimulation of heme oxygenase-1. This rise in ferritin levels plays a protective role aimed at preventing oxidative damage that occurs during inflammatory processes[13-15]. In adults, hyperferritinemia can be seen in various conditions, including hemophagocytic lymphohistiocytosis, in patients undergoing hemodialysis, having hemochromatosis, receiving frequent transfusions, having liver failure, antiphospholipid antibody syndrome, adult-onset still's disease, and patients with sepsis. Each of these conditions has unique mechanisms and implications related to elevated ferritin levels, emphasizing the importance of ferritin as a marker in diverse clinical scenarios[16]. High ferritin levels are increasingly being recognized as valuable biomarkers for the prognosis of several conditions, including cancer, connective tissue diseases, and notably, Coronavirus disease-2019 infection[17,18].

Studies on the relationship between ferritin levels and mortality in sepsis have particularly been conducted in the pediatric patient group. In a study conducted on pediatric patients, it was found that a ferritin level greater than 500 µg/L significantly increased the mortality risk by 3.2 times[6]. In another study conducted with pediatric patients, it was found that a ferritin level above 3.000 µg/L was associated with a 4.32-fold increase in the risk of mortality[19]. Studies conducted on elderly inpatients with ferritin levels above 1.000 µg/L have demonstrated the prognostic significance of high ferritin levels in sepsis and their importance in the recognition of malignancies[20]. In another study conducted on sepsis patients, ferritin levels exceeding 4.420 µg/L g/ml were found to be associated with a diagnosis of macrophage activation-like syndrome and related to 28-day mortality. Furthermore, a reduction of less than 15% in ferritin levels within three days compared to the initial value has been found to be associated with 28-day mortality[21]. In a recent study among adult septic patients, high ferritin levels were found to be associated with mortality. In this study, the cutoff value for ferritin was determined to be 591 µg/L[22]. In our study, the cutoff value for ferritin was found to be 1.518 µg/L. The different cutoff values obtained in these studies may be attributable to variations in the comorbid conditions of the patients. As previously mentioned, patients with malignancies, those undergoing hemodialysis, and those receiving frequent transfusions tend to have higher ferritin levels compared to other patients[16].

In addition to ferritin, univariate analysis in our study also found that low serum albumin levels and high LDH levels were predictors for mortality. In studies conducted on patients with abdominal sepsis, albumin levels below 2.9 g/dL were associated with high SOFA and APACHE scores, although no direct relationship with mortality was established[23]. In a prospective study investigating the relationship between low albumin levels and 28-day mortality, albumin levels below 2.9 g/dL were identified as an independent risk factor[24]. In our study, similar to other studies, the cutoff value for albumin was determined to be 2.9 g/dL in the ROC curve; however, in the multivariate analysis, it was not identified as an independent risk factor. In previous studies, LDH levels exceeding the upper limit of local laboratory standards were reported as to be associated with mortality[25]. In our study, the ROC curve identified a cutoff value of 324 U/L for LDH. However, LDH was not determined to be an independent predictive factor in the multivariate analysis.

Study Limitations

The present study has some limitations. First, this was a retrospective and observational study. Second, it is a single-center study and has limited generalizability. Serial determination of biomarkers will be more useful than single measurements. However, changes were not evaluated in this study.

CONCLUSION

In conclusion, many biomarkers have been studied in the prognosis of sepsis. How to guide the therapy is still a question for the clinicians. The findings of our study suggest that ferritin can be a useful bedside prognostic biomarker with clinical evaluation.

Ethics

Ethics Committee Approval: The Institutional Ethical Review Board of the study center (Ege University Faculty of Medicine), approved the study (decision no: 21-6.1T/54, date: 10.04.2016). The study was conducted in accordance with Good Clinical

Practice guidelines and adhered to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: C.A., Concept: C.A., Ş.M.K.B., D.B., Design: C.A., Data Collection or Processing: C.A., Analysis or Interpretation: C.A., Ş.M.K.B., D.B., Literature Search: C.A., Writing: C.A., Ş.M.K.B., D.B.

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