RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2021.31032
Ankara Üniversitesi Tıp Fakültesi Mecmuası 2021;74(3):289-295

MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Efficacy of Prognostic Scoring Systems and Neutrophil-to-Lymphocyte Ratio (NLR) Among Critically Ill Elder Sepsis Patients

Yaşlı Sepsis Hastalarında Prognostik Puanlama Sistemlerinin ve Nötrofil-Lenfosit Oranının (NLO) Etkinliği

Bilgin Bahadır Başgöz[1], Musa Barış Aykan[2], Ramazan Acar[2], İlker Taşçı[1]

[1]University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey
[2]University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey

Abstract

Objectives: Several scoring models and biomarkers are available to predict survival among critically ill patients. However, their accuracy among older adults with sepsis has been questioned. In this study, we aimed to evaluate the currently used prognostic scoring scales and neutrophil-to-lymphocyte ratio (NLR) in the prediction of survival among older adults with sepsis.

Materials and Methods: The study prospectively included older adults who were admitted to the intensive care unit (ICU) with sepsis. On admission, Acute Physiology And Chronic Health Evaluation (APACHE)-II, Sequential (sepsis-related) Organ Failure Assessment (SOFA), Glasgow coma scale (GCS) score, and NLR were calculated. By the end of a 28-day follow-up period, survivors and non-survivors were compared for the study parameters.

Results: Overall, the data of 36 patients were analyzed (mean age: 80.00±6.37 years, female: 58.3%). The rate of mortality was 47.3% (n=17). The mean SOFA score and the median NLR on admission were significantly lower in survivors [SOFA: 10.37±2.91, and NLR: 9.64 (11.25)] vs non-survivors [SOFA: 12.82±3.21 and NLR: 14.95 (35.53)] ($p<0.05$) but the mean APACHE-II and the median GCS score were comparable. Using ROC curve analysis, we determined that only the SOFA score and NLR could predict mortality.

Conclusion: The present study showed that, among older adults with sepsis admitted to the ICU, baseline SOFA score and NLR but not APACHE-II or GCS score could successfully predict mortality. Further studies are required to evaluate the utility of existing prognosis scales in older people.

Key Words: Organ Dysfunction Scores, Sepsis, APACHE, Survival, Intensive Care Units, Aged

Öz

Amaç: Yoğun bakım hastalarında mortaliteyi tahmin eden birçok puanlama sistemi ve biyobelirteç mevcuttur. Ancak yaşlı sepsis hastalarında kullanılabilirlikleri konusunda netlik bulunmamaktadır. Bu çalışmada, yaşlı sepsis hastalarında sağkalımı öngörmede şu anda kullanılan prognostik skorlama ölçeklerini ve nötrofil lenfosit oranını (NLO) değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya yoğun bakım ünitesine sepsis tanısı ile yatırılan yaşlı hastalar prospektif olarak dahil edildi. Başvuru anında Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II (APACHE), Sıralı (sepsisle ilişkili) Organ Yetmezliği Değerlendirmesi (SOFA) ve Glasgow koma skoru (GKS) puanı ve NLO hesaplandı. 28 günlük bir takip süresinin sonunda, hastalar "hayatta kalanlar" ve "hayatta kalmayanlar" olarak iki gruba ayrıldı ve çalışma parametreleri yönünden karşılaştırıldı.

Bulgular: Otuz altı hastanın verileri analiz edildi (ortalama yaş: 80,00±6,37 yıl, kadın: %58,3). Ölüm oranı %47,3 (n=17) idi. Başvuru anındaki ortalama SOFA skoru ve medyan NLO, hayatta kalanlarda [SOFA: 10,37±2,91 ve NLR: 9,64 (11,25)], hayatta kalmayanlara [SOFA: 12,82±3,21 ve NLR: 14,95 (35,53)] ($p<0,05$) göre anlamlı olarak daha düşüktü, ancak ortalama APACHE-II ve medyan GKS skoru benzerdi. ROC eğrisi analizini kullanarak, sadece SOFA skorunun ve NLO'nun mortaliteyi tahmin edebileceğini belirledik.

Address for Correspondence/Yazışma Adresi: Bilgin Bahadır Başgöz
University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey
Phone: +90 532 623 73 44 E-mail: bbbasgoz@gmail.com **ORCID ID:** orcid.org/0000-0002-5795-533X
Received/Geliş Tarihi/: 14.09.2020 **Accepted/Kabul Tarihi: 23.07.2021**

Öz

Sonuç: Bu çalışma, yoğun bakım ünitesine kabul edilen sepsisli yaşlı hastalar arasında, APACHE-II veya GKS skorunun değil, başlangıç SOFA skorunun ve NLO'nun mortaliteyi başarıyla tahmin edebileceğini gösterdi. Yaşlılarda mevcut prognoz ölçeklerinin faydasını değerlendirmek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Organ İşlev Bozukluğu Puanları, Sepsis, APACHE, Hayatta Kalma, Yoğun Bakım Üniteleri, Yaşlı

Introduction

Sepsis is characterized by the development of organ failure as a result of the systemic inflammatory response of the host to infection (1). Almost 3% of all hospitalized patients have sepsis, 51% of sepsis patients were admitted to the intensive care unit (ICU), and all-cause mortality rate of sepsis patients is around 28% (2). With the advancing age, the incidence of sepsis is disproportionately increased, and the rate of mortality dramatically increases with age, up to 26.2% and 38.4%, respectively, in those over 85 years old (2,3).

In patients admitted to the ICU, prognostic scoring models are used to assess the severity of disease and to predict the risk of mortality. These include sequential (Sepsis-related) organ failure assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE)-II, and Glasgow coma scale (GCS) (4-6). The predictive power of these scoring systems in the determination of in-hospital mortality has been reported by many authors (7-9). Interestingly, studies comparing SOFA, APACHE-II, and GCS with each other in estimating the probability of adverse events in the ICU yielded contradictory results (10-13).

In addition to scoring models, the predictive power of neutrophil-to-lymphocyte ratio (NLR) on mortality is also studied in sepsis patients (14,15). However, the results of such studies focused on the association of NLR and mortality show discrepancies due to several confounders.

With the increased proportion of aged people in the population, more patients are hospitalized due to sepsis and admitted to the ICU (2). Nevertheless, the utility of existing prognostic scoring systems and NLR in critically ill older adults has not been studied extensively. A study with a small sample size published in 1993, and a large one published recently both suggested that APACHE was a better predictor of survival (16,17). However, many other studies failed to propose the utility of any tool in the clinical practice for patients aged 65 and over to estimate prognosis in the short term or long term (18).

Therefore, in this study, we aimed to evaluate the predictive value of prognostic scoring systems and NLR on mortality among older adult patients admitted to the ICU with the diagnosis of sepsis.

Materials and Methods

Setting and Participants

We prospectively included patients diagnosed with sepsis or septic shock aged 65 and over who were hospitalized in the ICU of a tertiary care hospital. The diagnosis of sepsis was made using the criteria in the 3rd Sepsis Consensus (Sepsis-3) report (19) and the International Sepsis and Septic Shock Management Guidelines (1) published jointly by the Society of Critical Care Medicine and European Society of Intensive Care Medicine. Subjects with a history of advanced dementia, end-stage cancer, cirrhosis, aged under 65 years, requiring urgent surgery, a history of recent trauma and lack of written consent from the patients or caregivers. The Health Sciences University Non-Invasive Research Ethics Committee approved the study protocol (no: 46418926-18/55). Written informed consent was obtained for each participant. All procedures followed the standards of the Turkish Medicine and Medical Devices Agency Good Clinical Practices Guidelines and per the Declaration of Helsinki.

Patient Characteristics and Procedures

On ICU admission, demographic and clinical characteristics, anthropometric variables, and comorbid conditions including diabetes mellitus, dyslipidemia, hypertension, congestive heart failure, coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease were noted from electronic health records of the participants. Then, we calculated SOFA, APACHE-II and GCS scores to determine the severity of sepsis. In addition, we recorded neutrophil and lymphocyte counts and calculated the NLR. The predicted mortality rate of each patient was calculated by APACHE-II risk of death equation using the following information: The diagnosis leading to ICU admission, APACHE-II score, and requirement of emergency surgery (5). The duration of follow-up was 28 days, and the primary outcome was mortality from any cause. We divided the patients into two groups as "non-survivors" and "survivors" based on the 28-day death records.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) (Version 23.0, Chicago, Illinois) program was used for statistical analysis. The distribution of the data was evaluated by the Shapiro-Wilk test. Results were expressed as the mean ± standard deviation for continuous variables or as the percentage for categorical variables. Skewed variables were presented as median interquartile range (IQR). The differences between the continuous variables in the non-survivor and survivor groups were compared Student's t-test or Mann-Whitney U test according to the distribution of variables. Chi-square test was used to compare categoric variables. Pearson correlation coefficients were calculated to evaluate potential correlations. The power of SOFA, APACHE-II and GCS score in the prediction of the 28-day mortality rate was tested with the receiver operator characteristics (ROC) area under curve (AUC) analysis. ROC analysis was also used to determine cut-off values and their sensitivity and specificity to estimate the risk of mortality in the ICU. Statistical significance was accepted at the level of $p<0.05$.

Results

The study included 36 patients with a mean age of 80.0±6.37 years (65 to 90 years) and female predominance (n=21, 58.3%). The rate of mortality during the 28-day follow-up was 47.3% (n=17). Non-survivor and survivor groups showed no statistical difference in terms of age, gender, body mass index, diabetes mellitus, dyslipidemia, hypertension, congestive heart failure, coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease (Table 1). Baseline laboratory findings other than NLR were also similar. However, the NLR was significantly higher among non-survivors (p=0.04) (Table 1).

The non-survivor group had significantly higher mean SOFA score on admission (Table 2). However, APACHE-II score, predictive mortality rate, and GCS score showed no significant difference between the two groups (Table 2).

As shown in Table 3, a higher SOFA score and NLR showed a significant correlation with mortality (p=0.022, and p=0.034,

Table 1: General characteristics and baseline laboratory findings of patients

	Total (n=36)	Survivors (n=19)	Non-survivors (n=17)	p-value
Age, mean (SD)	80.00 (6.37)	80.95 (5.48)	78.94 (7.25)	0.361
Gender, n (%) **Female**	21 (58.3)	12 (33.3)	9 (25.0)	0.535
Body mass index, median (IQR)	24.97 (5.95)	26.04 (8.16)	23.66 (3.95)	0.086
Diabetes mellitus, n (%)	11 (30.6)	5 (13.9)	6 (16.7)	0.559
Dyslipidemia, n (%)	5 (13.9)	2 (5.6)	3 (8.3)	0.650
Hypertension, n (%)	26 (72.2)	15 (41.7)	11 (30.6)	0.463
Congestive heart disease, n (%)	18 (50.0)	11 (30.6)	7 (19.4)	0.317
Coronary artery disease n, (%)	6 (16.7)	3 (8.3)	3 (8.3)	1.000
Chronic kidney disease, n (%)	10 (27.8)	4 (11.1)	6 (16.7)	0.463
COPD, n (%)	8 (22.2)	4 (11.1)	4 (11.1)	1.000
WBC (cells/uL), mean (SD)	1,6134 (9,747)	1,5210 (8,718)	17,231 (11,034)	0.558
Neutrophil (N) (cells/uL), median (IQR)	1,1600 (13,300)	10,400 (9,100)	12,300 (15,350)	0.562
Lymphocyte (L) (cells/uL), median (IQR)	1,100 (1,000)	1,400 (1,200)	850 (1,000)	0.127
NLR, median (IQR)	12.89 (12.77)	9.64 (11.25)	14.95 (35.53)	**0.040**
Hemoglobin (g/dL), mean (SD)	10.45 (2.74)	10.58 (3.32)	10.30 (1.92)	0.759
Platelets (cellsx10^3/uL), median (IQR)	212 (204)	212 (153)	196 (289)	0.960
Glucose (mg/dL), median (IQR)	149 (138)	142 (162)	150 (134)	0.917
Urea (mg/dL), mean (SD)	141.71 (69.26)	149.79 (79.43)	132.13 (55.86)	0.447
Creatinine (mg/dL), median (IQR)	1.88 (1.44)	1.88 (1.36)	1.93 (1.80)	0.529
AST (U/L), median (IQR)	29.50 (25.25)	33.50 (28.25)	27.50 (27.25)	0.214
ALT (U/L), median (IQR)	19.50 (20.00)	20.00 (31.00)	33.50 (28.25)	0.129
Potassium (mmol/L), mean (SD)	4.61 (1.00)	4.76 (0.91)	4.44 (1.10)	0.370
Sodium (mmol/L), mean (SD)	140.66 (7.16)	139.05 (6.79)	142.56 (7.32)	0.154
Procalcitonin, (ng/mL) median (IQR)	2.01 (9.95)	1.95 (2.96)	6.72 (21.43)	0.138
CRP (mg/L), mean (SD)	144.94 (84.51)	137.69 (94.06)	154.13 (72.78)	0.569

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range, NLR: Neutrophil-to-lymphocyte ratio, WBC: White blood cell count, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein

respectively). However, there was no relationship between mortality of older sepsis patients and any of the APACHE-II score, predictive mortality rate, or GCS score (p=0.289 for APACHE-II score; p=0.331 for predicted mortality rate, and p=0.187 for GCS Score) (Table 3).

ROC-AUC analysis of these prognostic scoring models and NLR showed that both SOFA score and NLR have predictive power on the mortality of elderly patients with sepsis in the ICU (p=0.029, and p=0.040, respectively) (Table 3). However, APACHE-II score, predictive mortality rate, GCS score showed no utility in the prediction of mortality (p=0.311; p=0.303; and p=0.138 respectively) (Table 3). ROC curve diagrams are displayed in Figure 1.

The median values of SOFA, APACHE-II, predicted mortality rate, GCS and NLR are given in Table 4. The mortality rate of patients with a SOFA scores higher than the median value was significantly higher compared to those with a SOFA scores below the median (p=0.043). However, the mortality rate of patients with the above-median value of APACHE-II score, predicted mortality rate, GCS score and NLR at the day of admission were not different from the participants having below-median values (p=0.317; p=0.317; p=0.692 and p=0.130 respectively) (Table 4).

Discussion

Despite improvements in diagnostic approaches and therapeutic interventions in recent years, sepsis and septic shock are still the leading causes of death among adults hospitalized in the ICU (1). Several scoring systems and also NLR are used

Table 2: Study parameters and their comparisons

	Total (n=36)	Survivors (n=19)	Non-survivors (n=17)	p-value
SOFA, mean (SD)	11.53 (3.26)	10.37 (2.91)	12.82 (3.21)	**0.023**
APACHE-II, mean (SD)	36.03 (6.37)	34.95 (6.01)	37.24 (6.72)	0.292
Predicted mortality rate (%)*, mean (SD)	81.89 (12.04)	80.02 (12.59)	83.98 (11.40)	0.328
GCS, median (IQR)	10 (6)	10 (6)	10 (7)	0.128

*Calculated by using the APACHE II risk of death equation.
SD: Standard deviation, SOFA: Sequential organ failure assessment, APACHE-II: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow coma score, IQR: Interquartile range

Table 3: Pearson Correlation and ROC analyses of patient survival across SOFA, APACHE-II, predicted mortality rate, GCS and NLR

	Pearson correlation		ROC				
	r	p-value	Cut-off	Sensitivity (%)	Specificity (%)	AUC, CI	p
SOFA	-0.382	**0.022**	11.5	63.2	70.6	0.714, 0.542-0.885	**0.029**
APACHE-II	-0.182	0.289	35.5	57.9	58.8	0.559, 0.409-0.789	0.311
Predicted mortality rate (%)*	-0.167	0.331	84.6	57.9	58.8	0.601, 0.411-0.791	0.303
GCS	0.236	0.187	9.5	66.7	40.0	0.652, 0.464-0.840	0.138
NLR	-0.359	**0.034**	12.92	63.2	62.5	0.704, 0.526-0.882	**0.040**

*Calculated by using the APACHE II risk of death equation.
SOFA: Sequential Organ Failure Assessment, APACHE-II: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow coma score, NLR: Neutrophil-to-lymphocyte ratio, ROC: Receiver operator characteristics, AUC: Area under curve, CI: Confidence interval

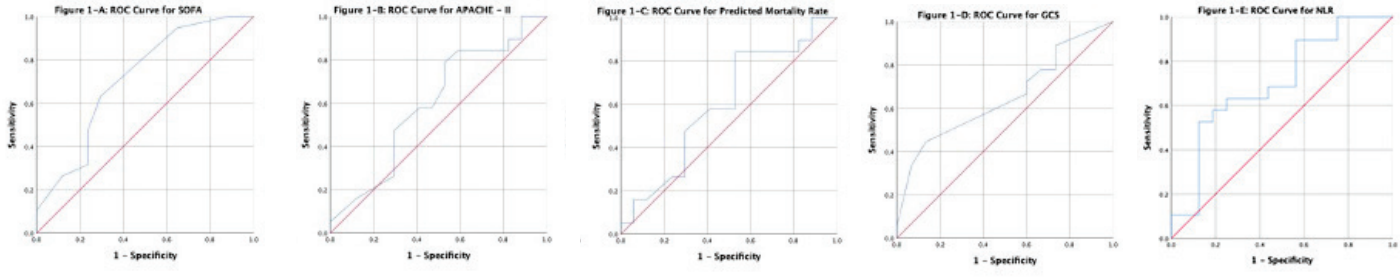

Figure 1A-E: ROC curves of patient survival across SOFA, APACHE-II, Predicted Mortality Rate, GCS, and NLR

ROC: Receiver operator characteristics, SOFA: Sequential Organ Failure Assessment, APACHE-II: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow coma score, NLR: Neutrophil-to-lymphocyte ratio

Table 4: Survival rates of patients with above and below median values

	Median values		Survivors (n=19)	Non-survivors (n=17)	p
SOFA, n (%)	12	Above median	7 (19.4)	12 (33.3)	0.043
		Below median	12 (33.3)	5 (13.9)	
APACHE-II, n (%)	35.5	Above median	8 (22.2)	10 (27.8)	0.317
		Below median	11 (30.6)	7 (19.4)	
Predicted mortality rate, n (%)	84.6	Above median	8 (22.2)	10 (27.8)	0.317
		Below median	11 (30.6)	7 (19.4)	
GCS, n (%)	10	Above median	12 (36.4)	9 (27.3)	0.692
		Below median	6 (18.2)	6 (18.2	
NLR, n (%)	12.89	Above median	7 (20.0)	10 (28.6)	0.130
		Below median	12 (34.3)	6 (17.1)	

N: Absolute number, %: Percentage of the total, SOFA: Sequential Organ Failure Assessment, APACHE-II: Acute Physiology and Chronic Health Evaluation, GCS: Glasgow coma score, NLR: Neutrophil-to-lymphocyte ratio

to determine the severity of illness and to predict in-hospital mortality among critically ill patients (7-9,20). However, their usefulness among older patients has not been thoroughly identified and studies may reveal inconsistent results (14,15,18). Given the growing number of aged individuals in the community, the requirement of robust prediction tools to use in older adults is more critical. In this study, we evaluated the predictive value of prognostic scoring models SOFA, APACHE-II, GCS and NLR, on 28-day mortality among older adults with sepsis admitted to the ICU. We demonstrated that higher SOFA scores and higher NLR on admission were associated with increased mortality in patients with sepsis aged 65 years and over. However, APACHE-II score and GCS score did not show a similar association with mortality. In addition, we did not observe a relationship between mortality and predicted mortality rate derived from the APACHE-II score.

Given the mortality rate of 47.2% in the present work is comparable with the findings in a much larger study published recently with a mortality rate of 48.8% (17). Our patient group can be considered, at least in the regional context, representative of older adults admitted to the ICU with sepsis.

Prognostic scoring systems guide clinicians to determine the severity of patients and also help them to establish a standardized approach in the management of critically ill patients. One of the essential features expected from a scoring system is its ability to discriminate survivors from non-survivors consistently. Also, it is expected to be easy to use by all healthcare professionals. The SOFA score was developed to evaluate organ dysfunctions in sepsis and validated in adult ICU patients (4,21). If the SOFA score is calculated periodically after admission to the ICU, it is called as "SOFA" score, and a 30% increase in the SOFA score during follow-up is associated with an increase in mortality (22). It is easy to calculate the SOFA score by using simple surrogate indicators related to major organ functions. Even though the patient's age is not a criterion in the calculation of the SOFA score, older people tend to die earlier following sepsis-induced hospitalization, and survivors need longer-term rehabilitation after discharge (23). In addition, although the applicability of the SOFA score has been demonstrated in adults, its relevance in the elderly should be investigated (18,21).

The SOFA score calculated on admission to the ICU had a positive correlation with mortality, suggesting that it can be used effectively to estimate mortality rate (24). However, more the evidence is required for the older adults as only 11% of patients enrolled in that study were aged 65 and over. In our study, all patients were elderly with a mean age of 80.00±6.37 years, and the relationship between the SOFA scoring system and survival was significant. Our results suggest that the SOFA score that is determined on admission can be used to estimate the survival rate among older adult sepsis patients. In another study that included almost 400 elderly patients aged 80 years or older admitted to the ICU due to all causes, authors identified an association between higher SOFA scores and in-hospital mortality rate, along with age, higher SAPS II score, multiple trauma with a head injury, and requirement mechanical ventilation (25).

It has been shown that NLR is a more reliable inflammatory biomarker for predicting mortality than neutrophils or lymphocytes alone (26,27). In addition to its reliability, the calculation of NLR is simple, easy to obtain, and inexpensive. Regardless of different ethnicities, studies conducted with Belgian and South Korean adults to determine a reference value for healthy patients showed a similar result with the value of 1.65 (28,29). In our study, median NLR values were six times higher in the survivors [median=9.64 (11.25)] and nine times higher in the non-survivors [median=14.95 (35.53)]. It has been revealed that NLR can be used as an independent predictor of mortality in several clinical conditions, such as malignancies, fibrotic liver disease, and cardiovascular diseases (30-32). In a meta-analysis that published in 2020, authors evaluated 14

studies (n=11,564) focused on the predictive value of NLR for sepsis, and the results of this meta-analysis showed that NLR was significantly higher in non-survivors than in survivors (random-effects model: Standard mean differences=1.18, 95% confidence interval; 0.42-1.94) (20). Similarly, NLR values of non-survivors in our study are significantly higher than survivors [median (IQR)]=14.95 (35.53) vs. 9.64 (11.25), respectively.

Another widely used and validated predictor of survival is the APACHE-II scoring system. The APACHE-II score is calculated upon ICU admission using various variables such as age, history of severe organ failure or immunocompromise, current vital findings, and laboratory test results to calculate the APACHE-II score (5). Although it is recommended to use the worst values recorded in the first 24 hours in the ICU to calculate the initial score, the variables recorded on admission can be used for practical reasons. The rational use of APACHE-II score is to help determine the patient's mortality risk. It is not calculated sequentially and does not have a utility to follow clinical improvement or response to interventions. APACHE-II scoring system could be used successfully among the adult population (10,33).

Baseline APACHE-II score was not associated with the risk of 28-day mortality in our study on exclusively older adults. In contrast, a recently published prospective study with a patient population similar to us concluded that the APACHE-II score predicting mortality in addition to the age of patients. However, the mean APACHE-II score was markedly lower than we report in the present study (22.6±7.0 vs 36.03±6.37) (17). Indeed, mean APACHE-II score in both the non-survivor and survivor subjects was marginally high, suggesting an estimated in-hospital mortality rate exceeding 85% (5,34,35). Likely, such extreme scores did not allow successful discrimination between the non-survivors and survivors in the present study.

According to the results of another study including 50 adult sepsis patients, while the SOFA score was successful in predicting mortality, the APACHE II score was not countable for predicting mortality rate (11). Similar to our study, this research was accomplished with limited participants and also the APACHE II score of the non-survivor group were higher than the survivor group, but the difference did not reach a statistical significance.

The mental state evaluated by GCS has an important place in the calculation of scoring systems. Sepsis-associated encephalopathy is a clinical reflection of neurological dysfunction in the host's impaired response to infection. Although GCS has been reported in some studies as a good predictor for sepsis, it is still considered unreliable and uncertain (36). Mohammad (37) demonstrated that GCS score reliably predicts the outcomes of elder ICU patients. In our study, however, median GCS scores showed no difference between the non-survivor and survivor groups. Nevertheless, our study population consisted of only sepsis patients, and we did not include any ICU patients with a history of trauma or need for emergency surgery. Besides, patients included in our study are not just over 65 years old but also at advanced ages. Thus, the GCS score could have been influenced by age-related cognition disorders other than sepsis, weakening its predictive power in the case of severe illnesses. A previous study that focused on the importance of GCS in assessing the severity of brain injury among trauma patients demonstrated that older moderate brain trauma patients had a higher GCS score than younger ones (38). Thus, it couldn't determine the disease severity in older adults, unlike younger patients (38). Besides, several other studies have also suggested that more research on GCS are needed to prove its utility in older adults (38-40).

Study Limitations

Our study has several limitations. First, as we did not have a control group without sepsis, it remains unclear as to whether our findings apply to only sepsis patients. Second, the number of participants in our study was limited, and we were not able to perform either subgroup analyses or adjusted analyses. Third, the originating site and responsible microbial source of sepsis are unclear due to the lack of blood culture results, which has a critical impact on survival.

Conclusion

The present study showed that a lower SOFA score and NLR is significantly associated with survival among elderly sepsis patients admitted to the ICU. Unlike the SOFA or NLR, the present study showed no significant differences in baseline APACHE-II score and GCS between survivors and non-survivors of sepsis. Future studies are warranted to confirm the current findings and to validate the use of scoring systems among patients at advance ages.

Ethics

Ethics Committee Approval: The Health Sciences University Non-Invasive Research Ethics Committee approved the study protocol (code: 46418926-18/55).

Informed Consent: Written informed consent was obtained for each participant.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.B.B., R.A., Concept: B.B.B., Design: B.B.B., Data Collection or Processing: B.B.B., R.A., İ.T., Analysis or Interpretation: B.B.B., İ.T., Literature Search: B.B.B., M.B.A., Writing: B.B.B., M.B.A.

Conflict of Interest: We declare that there are no conflicts of interest associated with this publication.

Financial Disclosure: We declare that we have not received any financial support to perform this study.

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