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Assessment of potential relationships between mortality and the levels of interleukin-6 and 10 in patients with sepsis

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Abstract

Aim: The aim of this study was to investigate whether sepsis-related mortality was associated with serum levels of interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, IL-6/IL-10 ratio and Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation (APACHE-II), Sequential Organ Failure Assessment (SOFA) scores.

Materials and Methods: The sample of the study consisted of 50 patients (median age: 75 years) who were admitted to the Intensive Care Unit of the Emergency Department and were diagnosed with sepsis, between January 2019 and December 2019. Blood samples were drawn on day 1 and day 3 of hospitalization. The IL-6, IL-10, TNF-α levels, APACHE-II, SOFA, and GCS scores were recorded on a data collection form.

Results: The deceased and the survivor groups significantly differed in day-1 ($p = 0.013$) and day-3 IL-6 ($p = 0.016$) levels, day-1 IL-6/IL-10 ratio ($p = 0.029$) and sex. There was no significant difference between the groups in day-1 and day-3 IL-10 levels and day-3 IL-6/IL-10 ratio. The GCS score was significantly lower in deceased subjects compared to survivors ($p < 0.05$).

Conclusion: High IL-6 level and IL-6/IL-10 ratio at sepsis onset were found to be associated with mortality. IL-6 level may be particularly useful for predicting mortality if used in combination with scoring systems such as the GCS and different clinical parameters.

Introduction

Sepsis is a complex clinical syndrome associated with high morbidity and mortality rates. It usually develops due to an underlying infection and is characterized by dysfunctions in multiple organ systems [1,2]. The incidence of sepsis has increased due to the rise in the elderly population, diseases causing immunosuppression, and antibiotic resistance [2]. Although sepsis-related mortality has recently decreased due to improvements in intensive care unit (ICU) care, it is still unacceptably high [3,4]. Early (<3 days) death in sepsis is common due to delayed admission to the ICU, late diagnosis of sepsis, and ineffective ICU treatment. One-third of sepsis deaths occur within three days of admission to ICUs [5]. For these reasons, early diagnosis of sepsis and initiation of antibiotic treatment are critical to decrease sepsis-related mortality rates and the costs and risks associated with prolonged ICU stays [6,7].

There is still no test with explicit reference ranges for early diagnosis of sepsis and monitoring of treatment response. Then again, the inflammatory response triggers the release of various biomarkers as a result of host-microorganism interactions. The use of biomarkers is increasing, especially in elderly patients and those with comorbidities, often due to the lack of specificity of clinical symptoms and inadequate diagnostic tests [8].

Today, C-reactive protein (CRP), procalcitonin (PCT), tumor necrosis factor (TNF)-α, interleukin (IL-6), and IL-10 are the most important biomarkers. Among these, PCT and CRP are the most commonly used; however, PCT and CRP are insufficient to distinguish sepsis from other inflammatory conditions [9]. TNF-α is a representative proinflammatory cytokine. It may trigger the secretion of coagulation proteins and the formation of diffuse endothelial damage [10]. IL-6 is a major proinflammatory cytokine [11] which plays a pivotal role in controlling infection, but its excess production damages organs and tissues

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[12]. It can be detected earlier than CRP and procalcitonin in cases of bacterial infection [13]. IL-10 regulates immune response and prevents excessive secretion of proinflammatory cytokines [14]. Under normal conditions, proinflammatory and anti-inflammatory cytokines work in concert to control systemic inflammation; however, in the event of sepsis, this balance is disturbed [8,15]. A high IL-6/IL-10 ratio indicates multiple organ failure and death [16] and changes in cytokine levels correlate with changes in the patient's clinical condition [17]. The IL-6/IL-10 ratio is important for determining the likelihood of sepsis complications and the success of treatment [18, 19].

Cytokine levels are not the only parameters associated with mortality in patients receiving intensive care. The Acute Physiology and Chronic Health Evaluation (APACHE-II), Glasgow Coma Scale (GCS), and Sequential Organ Failure Assessment (SOFA) were developed to predict prognosis and evaluate the response to treatment [20].

This study was carried out to investigate whether early mortality in sepsis patients was associated with various parameters, including GCS, APACHE-II, and SOFA scores, serum levels of IL-6, IL-10, TNF-α, and the IL-6/IL-10 ratio. Also, we aimed to assess whether IL levels and scoring systems are compatible with each other with respect to mortality.

Materials and Methods

Research design

This study was designed as a prospective, observational study to investigate the difference in serum cytokine levels between patients who died or survived after receiving a diagnosis of sepsis in our ICU. The study protocol was approved by the Ethics Committee of Necmettin Erbakan University (approval number: 14567952-050/865, date: 22/05/2019). Written informed signed consent was obtained from all patients or their legal representatives. The study was carried out in accordance with the principles set forth in the Declaration of Helsinki.

Population and sample

The population of this study consisted of patients admitted to the emergency department between May 2019 and May 2020 with sepsis and had been hospitalized in the ICU. Patients with concomitant malignancy or trauma and those under 18 years of age were excluded from the study. The diagnosis of sepsis was made based on clinical and laboratory findings in accordance with the Surviving Sepsis Campaign 2018 Guidelines [21]. A total of 50 patients constituted the study sample. Patients diagnosed with sepsis were followed up in the ICU of the emergency department for 6-7 days in most cases until they were transferred to the clinical services with respect to the etiology of sepsis. The patients who received treatment in the ICU of the emergency department were divided into two study groups according to early mortality: those who died within one week and those who survived beyond this period. Interleukin levels and scores obtained from the scales were compared between these two groups.

Data collection

tools A standardized data collection form was created prior to the study. Each patient's age, sex and diagnosis information, date of admission to the emergency department, GCS, SOFA and APACHE-II scores, laboratory data, and mortality status (deceased or survivor) were recorded on this form. GCS, SOFA, and APACHE-II scores were calculated within the first 24 hours of admission to the ICU. To assess microorganisms, The VITEK 2 instrument (bioMerieux, Inc., Marcy-l'Étoile, France) was used to identify cultures with bacteria growth.

Blood samples were taken on day 1 and day 3. The blood samples described in this study were only taken to study CRP, PCT, and IL levels and these were not ordered for treatment-related reasons. CRP and PCT were analyzed routinely. The sera obtained from blood samples on day-1 and day-3 were stored at -80°C for subsequent analysis of IL-6, IL-10, and TNF-α levels. IL-6, IL-10, and TNF-α levels were analyzed using the Immulite 2000 XP instrument (Siemens Diagnostics) and a commercial enzyme-linked immunoassay (ELISA) kit (DIAsource, Ottignies-Louvain-la-Neuve, Belgium). Eight different levels of standards were used for IL-6, IL-10, and TNF-α measurements. The reference ranges for the cytokines were as follows: 4.6–12.4 pg/mL for TNF-α, 0–50 pg/mL for IL-6, and 0–3.3 pg/ml for IL-10.

Statistical analysis

All statistical analyses were performed using the SPSS (Statistical Package for Social Sciences for Windows, Version 25.0, IBM Corp. Armonk, NY, U.S., 2017) software package. Q-Q plots and histograms were used to determine whether the data conformed to the normal distribution. Descriptive data were expressed as median (range) in the case of continuous variables and as frequency (percentage) in the case of categorical variables. Continuous variables were analyzed using the Mann–Whitney U test, and the categorical variables were analyzed with the Fisher's exact test. The mortality prediction performance of the variables was assessed by Receiver Operating Characteristic (ROC) curve analysis. Optimal cut-off points were determined by the Youden index. Multiple logistic regression analysis (forward conditional method) was performed to determine the best predictive mortality factors. Probability (p) values of<0.05 were deemed to indicate statistical significance.

Results

Fifty patients, 35 males, and 15 females, with a median age of 75 years (range: 20–80 years), were included in this study. The patients were followed up in the emergency department ICU until the diagnosis of sepsis was made, which took 6-7 days in most cases. Patients were then transferred to the appropriate clinical services. Thirty-five (70%) patients had pneumosepsis, 11 (22%) had urosepsis, and 4 (8%) had uropneumosepsis. While no bacteriological agent was detected in 27 patients, bacterial growth was identified in 23 subjects. Ten (20.0%) patients had died, and forty (80.0%) had survived in the emergency department ICU. Eight of the ten patients had died on day 3, and

Table 1. Patient characteristics and laboratory findings according to mortality status.

		Status		
	Total (N = 50)	Deceased (n = 10)	Alive (n = 40)	p
Age, y	75 (65–80)	77 (38–80)	73 (65–80)	1.000
Sex				
Male	35 (70.0%)	4 (40.0%)	31 (77.5%)	0.048
Female	15 (30.0%)	6 (60.0%)	9 (22.5%)	
Origin				
Pneumosepsis	35 (70.0%)	9 (90.0%)	26 (65.0%)	
Urosepsis	11 (22.0%)	0 (0.0%)	11 (27.5%)	0.171
Urosepsis and pneumosepsis	4 (8.0%)	1 (10.0%)	3 (7.5%)	
Positive culture	23 (46.0%)	5 (50.0%)	18 (45.0%)	1.000
Acinetobacter baumannii	9 (18.0%)	3 (30.0%)	6 (15.0%)	
Candida kefyr	1 (2.0%)	0 (0.0%)	1 (2.5%)	
Escherichia coli	6 (12.0%)	1 (10.0%)	5 (12.5%)	
Enterococcus faecalis	2 (4.0%)	0 (0.0%)	2 (5.0%)	0.914
Klebsiella pneumoniae	1 (2.0%)	0 (0.0%)	1 (2.5%)	
Pseudomonas aeruginosa	1 (2.0%)	0 (0.0%)	1 (2.5%)	
Staphylococcus aureus	3 (6.0%)	1 (10.0%)	2 (5.0%)	
GCS score	10 (6–12)	7.5 (3–10)	11 (6.5–14)	0.044
APACHE-II score	20 (18–24)	23 (18–26)	20 (18–24)	0.195
SOFA score	12 (10–16)	15 (11–18)	12 (10–14)	0.062
C-reactive protein level, mg/L	136 (75–197)	170.5 (120–208)	132 (64–181)	0.291
Procalcitonin, μg/L	3.39 (1.35–5)	3.78 (0.56–6.59)	3.39 (1.36–5)	0.761
IL-6, pg/mL				
Day 1	237 (73–869)	1305 (250–2,087)	164 (36–536)	0.013
Day 3	140 (18–410)	410 (64–2,087)	111 (11–312.5)	0.016
IL-6 (> 50 pg/mL)				
Day 1	38 (76.0%)	9 (90.0%)	29 (72.5%)	0.416
Day 3	34 (68.0%)	10 (100.0%)	24 (60.0%)	0.020
IL-10, pg/mL				
Day 1	88 (40–411)	106 (80–199)	85 (40–500)	0.903
Day 3	101 (27–267)	205 (100–646)	90 (26.5–245)	0.057
IL-10 (> 3.3 pg/mL)				
Day 1	50 (100.0%)	10 (100.0%)	40 (100.0%)	N/A
Day 3	50 (100.0%)	10 (100.0%)	40 (100.0%)	N/A
TNF-α, pg/mL				
Day 1	23 (18–35)	24 (20–35)	23 (17–33)	0.296
Day 3	22 (15–30)	23 (22–31)	20 (14–28.5)	0.091
TNF-α (> 12.4 pg/mL)				
Day 1	44 (88.0%)	10 (100.0%)	34 (85.0%)	0.327
Day 3	42 (84.0%)	10 (100.0%)	32 (80.0%)	0.184
IL-6/IL-10 ratio				
Day 1	2.40 (0.23–6.79)	5.46 (3.13–20.73)	1.19 (0.16–6.43)	0.029
Day 3	1.37 (0.28–3.23)	2.28 (2.00–3.23)	0.79 (0.20–4.93)	0.159
IL-6/IL-10 ratio (> 5)				
Day 1	18 (36.0%)	6 (60.0%)	12 (30.0%)	0.138
Day 3	10 (20.0%)	0 (0.0%)	10 (25.0%)	0.179
TNF-α/IL-10				
Day 1	0.25 (0.01-2.70)	0.26 (0.10-2.36)	0.18 (0.01-2.70)	0.369
Day 3	0.23 (0.01–2.41)	0.20 (0.02-1.19)	0.23 (0.01-2.41)	0.480

Data are median (range) for continuous variables and frequency (percentage) for categorical variables. GCS, Glasgow Coma Scale; APACHE-II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; IL, interleukin; TNF, tumor necrosis factor.

two had died on day 4. No patient had died before day 3. Blood samples were taken from 40 patients who were transferred from the emergency ICU to the clinic services. The IL-6, IL-10, and TNF-α levels of these patients were measured using the said samples, and they were administered the APACHE-II, SOFA, and GCS scales. However, their clinical follow-up could not be continued from 1 week on. The percentage of females was significantly higher in the

Table 2. Performance of variables to predict mortality.

	Glasgow Coma Scale	IL-6, 1st day	IL-6, 3rd day y	IL-6 / IL-10 ratio, 1st da
Cut-off	$\leq$ 10	> 1150	> 300	> 2.5
Sensitivity	80.0%	60.0%	70.0%	90.0%
Specificity	52.5%	90.0%	75.0%	62.5%
Accuracy	58.0%	84.0%	74.0%	68.0%
PPV	29.6%	60.0%	41.2%	37.5%
NPV	91.3%	90.0%	90.9%	96.2%
AUC (95.0% CI)	0.708 (0.543 - 0.872)	0.756 (0.588 - 0.924)	0.747 (0.585 - 0.910)	0.725 (0.578 - 0.872)
p	0.044	0.013	0.016	0.029

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals.

Table 3. Best predictive factors of mortality, multiple logistic regression analysis.

	β coefficient	Standard Error	p	Exp(β)	95.0% CI for Exp(β)
Sex, female	2.586	1.148	0.024	13.280	1.401 125.890
IL-6, 1st day (>1150)	3.432	1.178	0.004	30.943	3.077 311.136
(Constant)	-3.580	1.043	0.001	0.028	

Nagelkerke R^2=0.472, CI: Confidence Interval.

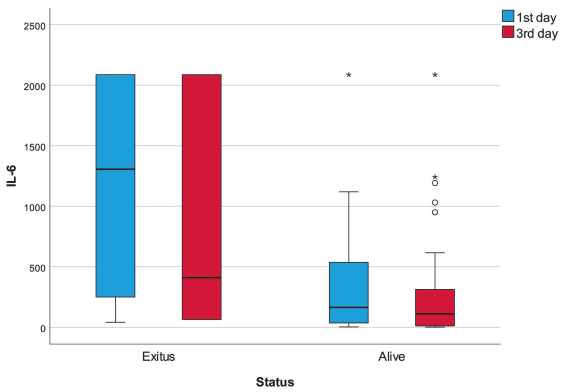

Figure 1. Interleukin (IL)-6 levels according to mortality status.

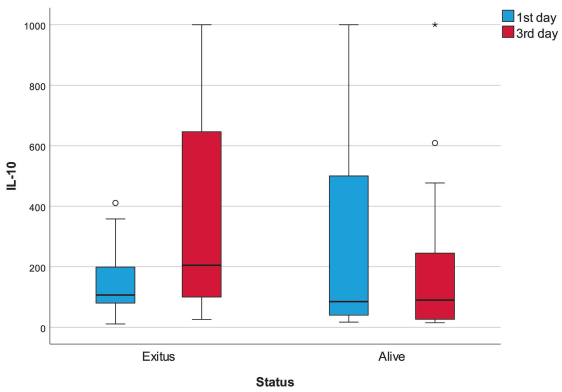

Figure 2. Interleukin (IL)-10 levels according to mortality status.

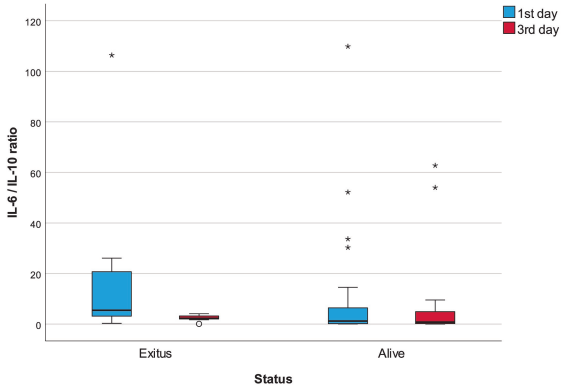

Figure 3. Interleukin (IL)-6/IL-10 ratio according to mortality status.

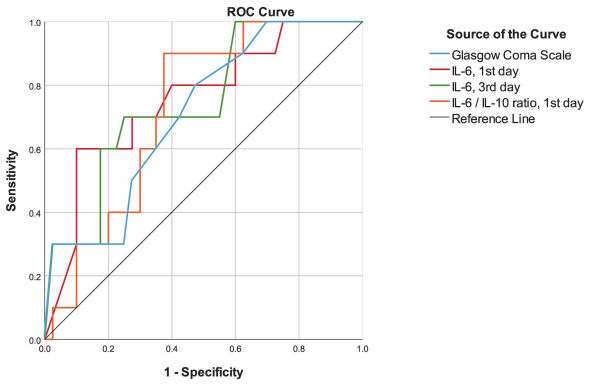

Figure 4. The receiver operating characteristic (ROC) analyses for GCS score, IL-6 level on 1st day, IL-6 level on 3rd day and IL-6/IL-10 ratio on 1st day.

deceased group than in the survivors group (p = 0.048).

The median GCS score was significantly lower in the deceased group than in the survivors group (9 and 12, respectively, p < 0.05). The median APACHE-II and SOFA scores were similar in deceased patients and survivors (p = 0.195 and p = 0.062, respectively). There was also no significant difference between the groups in terms of CRP and PCT levels (Table 1). The day-1 and day-3 IL-6 levels (Figure 1) and day-1 IL-6/IL-10 ratios were significantly higher in the deceased group than in the survivors group (p = 0.013, p = 0.016, and p = 0.029, respectively). There was no significant difference between the groups in day 1 or day 3 levels of IL-10, TNF-α, TNF-α/IL-10 ratio. Also, day 3 values of IL-6/IL-10 ratio were similar. All deceased patients had elevated TNF-α level (>12.4 pg/mL) on both days, and all patients (both groups) had elevated IL-10 level (>3.3 pg/mL) on both days. Although there was no significant difference between the groups in terms of median IL-10 level, the comparison of day 3 IL-10 levels was marginally non-significant (p = 0.057; Figure 2, Table 1).

On day 1, the median IL-6/IL-10 ratio was 5.46 (3.13-20.73) in the deceased group and 1.19 (0.16-6.43) in the survivors group, showing significantly higher value in the deceased group (p = 0.029) (Figure 3).

The analysis of mortality prediction was performed for statistically significant variables. We found that the IL-6 level had the highest specificity, accuracy, positive predictive value, and area under the ROC curve (AUC). On the other hand, day-1 IL-6/IL-10 ratio had the highest sensitivity and negative predictive value (Table 2) (Figure 4). Multiple logistic regression analysis was performed to determine the best predictive factors of mortality. Female patients had 13.280-fold higher risk of mortality than male patients [Odds Ratio (OR): 13.280, 95% Confidence Interval (CI): 1.401 - 125.890, p = 0.024]. Patients with higher day-1 IL-6 (>1150 pg/ml) levels had 30.943-fold higher risk of mortality than other patients (OR: 30.943, 95% CI: 3.077 - 311.136, p=0.004) (Table 3). Other variables analyzed within the scope of the regression analysis were found to be non-significant, including age (p=0.090), Glasgow coma scale score (p=0.295), day-3 IL-6 (p=0.094), and day-1 IL-6/IL-10 ratio (p=0.076).

Discussion

The sepsis process involves an extreme inflammatory response that severely affects those with comorbidities. The early clinical manifestations of sepsis are variable and nonspecific. Clinicians have been searching for novel inflammatory mediators to better understand the inflammatory events that take place during sepsis with a view to facilitate early diagnosis and improve prognosis [15,22]. In recent years, studies have been conducted on IL-6, IL-10 levels, and the IL-6/IL-10 ratio to provide guidance in predicting the progression to organ dysfunction and mortality in sepsis [16]. In parallel, in this study, IL-6 levels and the IL-6/IL10 ratio on day 1 were found to be significantly higher in deceased patients compared to the survivors. Notably, the IL-6 level was significantly higher on day 1 and day 3 in the deceased group than in the survivors group (p < 0.05). The median day-1 IL-6/IL-10 ratio was 5.46 (3.13-20.73) in the deceased group and 1.19 (0.16-6.43) in the survivors group. The median GCS score was significantly lower in the deceased than in the survivors group (9 vs. 12). The results of the multiple logistic regression analysis indicated that mortality risk was higher in female patients and those with elevated day-1 IL-6 levels. The findings of this study suggest that a day-1 IL-6 level of >1150, day-1 IL-6/IL-10 ratio of >2.5, and GCS score of <10 were independently associated with significantly increased likelihood of early mortality in sepsis patients. Particularly, the mortality risk of sepsis patients with day-1 IL-6 levels of >1150 was found to be exceedingly high based on both the ROC curve and multiple logistic regression analyses.

In our study, female sex and IL-6 elevation on the first day of sepsis were found to be risk factors for first-week mortality. Similar results have been reported by previous studies. Song et al. stated that elevated IL-6 was an independent risk factor for 28-day mortality and recommended that clinicians use IL-6 as a prognostic marker in sepsis [12]. Cullberg et al. found that female patients with sepsis had higher 30-day mortality rates compared to males [23]. We believe that this result might be related with the fact that males had received antibiotics earlier compared to females.

In a study conducted with neonatal sepsis patients, serum IL-6 levels of deceased patients were found to be higher than those of survivors. It was determined that an IL-6 level cut-off value of >10 pg/mL at the onset of sepsis had high sensitivity (89%) and a high negative predictive value (91%) for detecting mortality, revealing that it was superior to other cytokines as a biomarker [24]. Similarly, in this study, the median day-1 IL-6 level in deceased patients was found to be 1305 (250-2087) compared to 164 (36-536) in survivors.

In a study by Yende et al., conducted with patients hospitalized for sepsis, it was observed that recovered patients had high IL-6 levels at discharge and that these high levels persisted for an additional 3 months after discharge. These patients subsequently died due to various reasons. This finding was interpreted as suggesting that high IL-6 levels were associated with increased mortality [25].

In patients with sepsis, the immune system initiates a proinflammatory response, followed by an anti-inflammatory one [26]. The IL-6/IL-10 ratio reflects the ability of the immune system to cope with sepsis. A very high IL-6/IL-10 ratio after several days indicates that sepsis remains severe to the extent that the treatment regimen may need to be adjusted [11]. An increase in the IL-6/IL-10 ratio can result in immune system failure, ultimately leading to multiple organ failure and death [27,28]. On the other hand, a decrease in the IL-6/IL-10 ratio can result in the progression of systemic inflammatory response syndrome (SIRS) to compensatory anti-inflammatory response syndrome (CARS), reflecting an immune system deficiency and increased proneness to secondary infections and mortality [13,29]. Hence, accurate interpretation of the IL-6/IL-10 ratio is very important for management of such patients. Analysis of the IL-6/IL-10 ratio may be an important marker of the severity of infection at the time of hospitalization, and may support the prediction of prognosis as a screening test. A high IL-6/IL-10 ratio, especially

on the third day of antibiotic therapy, indicates persistent severe infection, prompting further testing of the patient and possibly adjusting the treatment protocol [30,31].

In a study conducted with patients with HIV and pneumocystis carinii pneumonia, the IL-6/IL-10 ratio was found to be high in the acute period of infection. The ratio was significantly higher in severe pneumonia patients with low oxygen pressure compared to the convalescent group [31]. In comparison, in this study, nine of the ten patients who died were diagnosed with pneumosepsis, and they had a significantly higher IL-6/IL-10 ratio compared to the survivors ($p = 0.029$).

In our study, although TNF-α levels of deceased patients were higher on both day 1 and day 3, there was no significant difference between the two groups. There are also some studies investigating TNF-α/IL-10 ratio in infection and inflammatory diseases. For instance, Tsurumi et al. reported that the TNF-α/IL-10 ratio decreased in patients with severe burns [32]. In our study, no significant correlation was found between mortality and TNF-α/IL-10 ratio.

In addition to cytokines, scoring systems are also important for predicting mortality in sepsis. Mortality likelihood is increased in the presence of higher APACHE-II score and lower GCS score. The APACHE-II is used to assess the mortality risk of patients based on various parameters, including laboratory and clinical findings [33]. The SOFA is used to determine the severity of organ failure in patients receiving intensive care. The GCS is used in neurological evaluations for determining mortality risk [2,20]. Although the GCS was found to be useful for determining neurological status, its prognostic power for predicting mortality is questionable [20]. In contrast, in this study, patients with a low GCS score died within the first week, indicating a significant relationship between the GCS score and mortality.

Limitations

There were some limitations to this study. First, patients could be monitored only for one week, that is, until they were transferred to specialized ICUs according to their clinical condition. Secondly, patients' treatment regimens could not be modified and clinical changes could not be observed beyond a pre-determined follow-up period.

Conclusion

In conclusion, it was determined that serum levels of IL-6 (at onset and during treatment) could be used to predict early prognosis in patients with sepsis, thereby supporting the decision-making process regarding during management. Furthermore, it was determined that high day-1 IL-6 levels and high day-1 IL-6/IL-10 ratios in these patients might serve as risk factors showing greater likelihood for early mortality. It appears that IL-6 level may be particularly useful for predicting mortality if used in combination with scoring systems (such as the GCS) and different clinical parameters. The use of combined approaches (with GCS and other clinical parameters) may be particularly important since IL-6 level predicts mortality with low sensitivity.

Ethics approval

The study protocol was approved by the Ethics Committee of Necmettin Erbakan University (approval number: 14567952-050/865, date: 22/05/2019). The study was carried out in accordance with the principles set forth in the Declaration of Helsinki.

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