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Diagnostic and prognostic value of procalcitonin and sTREM-1 levels in sepsis*

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Background/aim: Sepsis is still a major cause of morbidity and mortality despite the improvements in diagnosis and treatment. The aim of this study was to investigate the values of procalcitonin and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in the differential diagnosis of patients with sepsis and noninfectious systemic inflammatory response syndrome (NI-SIRS) and measure their importance in the prognosis of patients with sepsis.

Materials and methods: This prospective study included 41 NI-SIRS and 33 sepsis patients hospitalized in Celal Bayar University Hospital, Manisa, Turkey. Blood samples were taken from NI-SIRS patients on days 0 and 3 and from sepsis patients on days 0, 3, 4, 7, and 14. Clinical status of the patients was determined with the SOFA scoring system.

Results: The SOFA scoring system and procalcitonin and sTREM-1 measurements were significant in the differential diagnosis of sepsis and NI-SIRS patients. The SOFA scoring system was considered the most important indicator in determining the prognosis of sepsis patients. Procalcitonin and sTREM-1 levels increased progressively in nonsurvivors and decreased in survivors, but changes were statistically insignificant.

Conclusion: In the differentiation of sepsis and NI-SIRS, and evaluation of the prognosis of sepsis, combined measurements of procalcitonin and sTREM-1 levels are important.

Key words: Procalcitonin, sepsis, SIRS, SOFA, sTREM-1

1. Introduction

Sepsis is a fatal infectious disease that involves multiple organ systems, leads to hemodynamic changes, and causes shocks, organ dysfunction, and organ failure. It is ranked as the thirteenth leading cause of death in the US and the second leading cause of death in intensive care units (ICUs) other than coronary ICUs. In recent years, due to the increases in aggressive therapies and invasive procedures, sepsis incidence and sepsis-associated mortality rates have increased (1,2).

Nonspecific clinical signs in the initial period of sepsis may lead to unnecessary or delayed use of antibiotics. Therefore, laboratory investigations yielding rapid and accurate results to support the diagnosis are needed. Blood culture growth, the differential diagnosis criterion, cannot be achieved in all patients, and the results cannot be obtained earlier than 24 h. On the other hand, when attempting to confirm the absence of infection in patients suspected to have sepsis but in fact not having sepsis, serious diagnostic problems arise (3).

In recent years, studies conducted on the early diagnosis of sepsis have focused not only on the rapid diagnosis of the causative microorganisms but also on some indicators of host inflammatory response triggered by these microorganisms. However, to date, to achieve early, quick, and accurate diagnosis of sepsis, no single laboratory test with high sensitivity and specificity has been found. For this purpose, the efficacy of several immunological, hematological, and biochemical diagnostic indicators alone or in combination has been investigated (4,5).

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Procalcitonin, the precursor molecule of the calcitonin hormone, was defined in neonatal sepsis for the first time and has been one of the most-studied molecules in the early diagnosis of sepsis (6). It is a useful marker used in the determination of the severity of the infection, the prediction of prognosis, and monitoring the response to the treatment (5,7).

In addition to procalcitonin, triggering receptor expressed on myeloid cells-1 (TREM-1) has been another studied molecule in recent years. TREM-1 is a member of the immunoglobulin superfamily released from phagocytic cells in the presence of bacterial and fungal infections. Soluble TREM-1 (sTREM-1) is released from activated phagocytes and can be detected in body fluids (8). Therefore, it is important to investigate sTREM-1 plasma levels for the diagnosis of patients with severe infection and to differentiate the infectious inflammatory response from the noninfectious inflammatory response (8,9). In several studies, a correlation between sTREM-1 and procalcitonin, both of which are important markers in the prognosis of patients with sepsis, has been determined (5,10,11).

This study aimed to investigate the role of procalcitonin and sTREM-1 in differentiating patients with sepsis from patients with noninfectious systemic inflammatory response syndrome (NI-SIRS) and to determine procalcitonin and sTREM-1 values in the prognosis of patients with sepsis.

2. Materials and methods

The study was designed as a prospective study including 74 patients (41 with NI-SIRS and 33 with sepsis) who were hospitalized and treated in Celal Bayar University (CBU) Hospital.

Of the NI-SIRS and sepsis patients, those who met at least two of the SIRS criteria (core temperature >38 °C or <36 °C; heart rate >90 beats/min; respiratory rate >20 breaths/min or arterial partial pressure of carbon dioxide <32 mmHg or requirement for mechanical ventilation for an acute pathological process; white blood cell count >12,000 /mm^3 or <4000 /mm^3 or more than 10% immature neutrophils) were included in the study (12). In addition, in order not to not cause any diagnostic confusion, only sepsis patients with microbiological evidence were included in the sepsis group. Those with immunodeficiency and/or malignancy, having undergone organ transplantation, taking corticosteroids more than 1 mg/kg per day, younger than 18 years old, or older than 80 years old were not included in the study.

The patients in the study group were visited at regular intervals and assessed clinically, and the demographic data and clinical and laboratory findings related to them were recorded on a follow-up form prepared in advance. For the clinical follow-up of the patients, the sepsis-related organ failure assessment (SOFA) scoring system was used (12,13).

In order to determine the role of procalcitonin and sTREM-1 markers in differentiating sepsis and NI-SIRS cases from each other, blood samples were taken from the patients in both groups on days 0 and 3. The role of these immunological markers in the prognosis of patients with sepsis was investigated by taking blood samples from the sepsis patients on days 4, 7, 14, and 21, in addition to days 0 and 3. After the sera were separated, all the blood samples taken from the patients were stored at –80 °C. While plasma procalcitonin concentrations were investigated with the enzyme-linked fluorescent assay method (VIDAS BRAHMS PCT, France), sTREM-1 levels were investigated with the enzyme-linked immunosorbent assay method (R & D Systems Human TREM-1 ELISA, USA) in the biochemistry laboratory of CBU.

Blood samples and other clinical samples taken to determine the focus of infection were examined in the bacteriology laboratory of CBU. Standard microbiological methods for the identification of the isolated microorganisms and the determination of antimicrobial susceptibility of these microorganisms were used (14).

The statistical analysis of the study was performed with the SPSS for Windows 11.0. To assess the role of procalcitonin and sTREM-1 in the differential diagnosis of sepsis and NI-SIRS, Student's t-test, the Mann–Whitney U-test, and ROC analysis were used. The Mann–Whitney U-test and ROC analysis were also used for the assessment of prognostic values of SOFA, sTREM-1, and procalcitonin in the patients with sepsis, and repeated measures analysis of variance was used to determine the changes in each variable during follow-up.

3. Results

While the demographic and clinical data of the patients are given in Table 1, causes of sepsis and NI-SIRS are summarized in Table 2. Statistically significant differences were determined between the sepsis and NI-SIRS patients in terms of age, being inpatient or outpatient, ICU admission, antibiotic usage history, and underlying diseases (liver failure, kidney failure, diabetes, chronic lung disease, cardiovascular disease) ($P < 0.05$) (Table 1). Of the microorganisms that cause sepsis, gram-negative bacteria were determined to take the lead (60.6%) (Table 3).

In this study, the overall mortality rate was 54.54% in the sepsis group (n = 18 patients) and of them, 16 (88.9%) were followed in the ICU and 2 (11.1%) in the surgical wards. On the other hand, the mortality rate in the SIRS group was 21.9% (n = 9 patients).

When the SOFA scores and procalcitonin and sTREM-1 markers were assessed to differentiate sepsis cases from NI-SIRS cases, they were significantly higher

Table 1. Demographic and clinical data of the patients.

	Sepsis n (%)	NI-SIRS n (%)	P-value
Age (Mean ± SD)	58.1 ± 18.1	44 ± 17.53	0.001*
Sex			
Male	17 (51.5)	27 (65.9)	0.2**
Female	16 (48.5)	14 (34.1)	
Total	33 (100.0)	41 (100.0)	
Being inpatient or outpatient			
Outpatient	16 (48.5)	38 (92.7)	0.001**
Inpatient	17 (51.5)	3 (7.3)	
Total	33 (100.0)	41(100.0)	
Operation			
Yes	9 (27.3)	9 (22.0)	0.5**
No	24 (72.7)	32 (78.0)	
Total	33 (100.0)	41(100.0)	
Other Interventions[#]			
Yes	0 (0.0)	4 (9.8)	0.1**
No	33 (100.0)	37 (90.2)	
Total	33 (100.0)	41(100.0)	
Department			
Intensive care	23 (69.7)	16 (39.0)	
Internal medicine	7 (21.2)	13 (31.7)	0.02**
Surgery	3 (9.1)	12 (29.3)	
Total	33 (100.0)	41(100.0)	
Antibiotic usage history			
Yes	12 (36.4)	2 (4.9)	
No	21 (63.6)	39 (95.1)	0.001**
Total	33 (100.0)	41(100.0)	
Underlying disease			
Hepatic failure	5 (15.2)	0 (0.0)	0.015***
Renal failure	12 (36.4)	3 (7.3)	0.002**
Neurologic disorder	13 (39.4)	8 (19.5)	0.059**
Diabetes mellitus	10 (30.3)	4 (9.8)	0.025**
COPD[x]	5 (15.2)	0 (0.0)	0.015**
CVD[ƒ]	8 (24.2)	2 (4.8)	0.020**

* Student's t test.
** χ^2 test.
*** Fisher's exact χ^2 test.
[#] Other interventions: endoscopy, endoscopic retrograde cholangiopancreatography, thoracentesis, paracentesis, stent placement, angiography.
[x] COPD: Chronic obstructive pulmonary disease.
[ƒ] CVD: Cardiovascular disease.

in the patients with sepsis than were those in the NI-SIRS patients on days 0 and 3 (P = 0.001, Mann–Whitney U-test and Student's t-test) (Table 4).

In order to determine the role of all the three parameters in the differentiation of sepsis from NI-SIRS, ROC analysis was performed. The results of ROC analysis were presented as area under the curve (AUC), P-values, cut-off values, sensitivity, specificity, positive predictive values, and negative predictive values (Table 5). We found that the AUC, sensitivity, and specificity values of SOFA, procalcitonin, and sTREM-1 were quite high for differential diagnosis of sepsis and NI-SIRS.

Table 2. Clinical diagnosis of NI-SIRS and sepsis cases.

NI-SIRS cases	n (%)	Clinical diagnosis
Polytrauma	16 (39.02)	
Neurological disease	8 (19.51)	Ischemic stroke (5), intracerebral hemorrhage (3)
Gastroenterological disease	6 (14.63)	Gastrointestinal bleeding (2), pancreatitis (3), subileus (1)
Burns	3 (7.31)	
Malignant disease	3 (7.31)	
Heatstroke	3 (7.31)	Pulmonary embolism (1), pulmonary edema (1)
Respiratory disease	2 (4.87)	
Sepsis cases		
Respiratory tract	13 (39.39)	Pneumonia (13)
Gastrointestinal tract	8 (24.24)	Seconder peritonitis (6), intraabdominal abscess (2)
Urinary tract	7 (21.21)	Pyelonephritis (7)
Skin/soft tissue	3 (9.09)	Diabetic foot (2), cellulitis (1)
Central nervous system	2 (6.06)	Meningitis (2)

Table 3. Distribution of microorganisms isolated in the clinical samples of sepsis patients.

Microorganisms (n)		n (%)
Gram-negative	*Escherichia coli* (11) *Acinetobacter* spp.(6) *Pseudomonas aeruginosa* (1) *Klebsiella* spp. (2)	20 (60.6)
Gram-positive	*Staphylococcus aureus* (2) Coagulase negative staphylococcus (2) *Enterococcus* spp. (2) *Streptococcus pneumoniae* (1)	7 (21.2)
Other	Polymicrobial	6 (18.2)

Table 4. The SOFA scores and procalcitonin and sTREM-1 markers of the sepsis and NI-SIRS cases.

	Sepsis		NI-SIRS		P-value
	Median (min–max)	Mean ± SD	Median (min–max)	Mean ± SD	
SOFA (day 0)	6 (0–16)	7.12 ± 3.95	1 (0–9)	1.73 ± 2.23	0.001*
SOFA (day 3)	7 (0–16)	7.67 ± 4.67	0 (0–10)	1.07 ± 2.33	0.001*
PCT[#] (day 0)	7.31 (0.16–201)	34.37 ± 51.79	0.41 (0.05–18.93)	2.65 ± 4.94	0.001**
PCT[#] (day 3)	10.55 (0.28–201)	37.13 ± 55.42	0.21 (0.4–17.39)	1.20 ± 2.92	0.001**
sTREM-1[f] (day 0)	268.41 (43.5–137.7)	398.96 ± 308.37	154.43 (9.91–519.8)	162.12 ± 86.36	0.001**
sTREM- 1[f] (day 3)	307.23 (53.68–1442.88)	417.60 ± 332.17	118.81 (3.88–221.6)	118.61 ± 52.30	0.001**

[#] (ng/mL)
[f](pg/mL)
* Mann–Whitney U-test.
**Student's t-test.

Table 5. The predictive value of procalcitonin and sTREM-1 for differential diagnosis of sepsis and SIRS.

	Cut-off value	AUC*	P	Sensitivity (%)	Specificity (%)	PPV$^{\chi}$	NPV$^{\delta}$
SOFA (day 0)	3.5	0.891	0.001	81.8	80.5	77.1	84.6
SOFA (day 3)	1.5	0.907	0.001	90.3	85.4	82.4	92.1
PCT$^{\#}$ (day 0)	1.63	0.837	0.001	81.8	70.7	69.2	82.9
PCT$^{\#}$ (day 3)	1.26	0.894	0.001	80.6	80.0	75.8	84.2
sTREM-1^{f} (day 0)	199.72	0.826	0.001	81.8	73.2	71.1	83.3
sTREM-1^{f} (day 3)	159. 52	0.883	0.001	80.6	80.5	75.8	84.6

*AUC: Area under the curve.
$^{\chi}$PPV: Positive predictive value.
$^{\delta}$NPV: Negative predictive value.
$^{\#}$ (ng/mL)
^{f}(pg/mL)

In order to determine the prognostic values of SOFA scores, procalcitonin, and sTREM-1 levels in patients with sepsis, the values for survivors and nonsurvivors during the follow-up on days 0, 3, 4, 7, and 14 were compared. A decrease in the survivors and an increase in the nonsurvivors were determined. Significant differences were observed between the SOFA scores on all the days, between the procalcitonin values only on days 7 and 14, and between the sTREM-1 values on days 4, 7, and 14 ($P < 0.05$, Mann–Whitney U-test) (Table 6).

Table 6. The values of the SOFA scores and procalcitonin and sTREM-1 values for survivors and nonsurvivors.

	Survivors	Nonsurvivors	P*
SOFA score			
(Mean ± SD)	4.33 ± 2.15	9.44 ± 3.60	<0.05
day 0	4.30 ± 2.95	10.10 ± 4.17	<0.05
day 3	3.69 ± 2.59	12.00 ± 3.38	<0.05
day 4	2.83 ± 2.44	11.80 ± 3.08	<0.05
day 7	2.20 ± 2.30	12.75 ± 2.70	<0.05
day 14	2.66 ± 1.15	-	
PCT			
(Mean ± SD) ng/mL	31.69 ± 46.40	36.61 ± 57.1	>0.05
day 0	29.11 ± 51.10	42.92 ± 59.1	>0.05
day 3	19.96 ± 37.30	45.38 ± 57.7	>0.05
day 4	3.76 ± 5.92	39.91 ± 55.4	<0.05
day 7	1.63 ± 3.08	40.58 ± 57.8	<0.05
day 14	1.08 ± 0.35	-	
sTREM-1			
(Mean ± SD) pg/mL	386.67 ± 244.20	409.20 ± 360.06	>0.05
day 0	320.02 ± 221.81	488.08 ± 383.98	>0.05
day 3	278.28 ± 172.08	655.75 ± 684.65	<0.05
day 4	216.43 ± 146.80	600.30 ± 414.49	<0.05
day 7	208.52 ± 163.16	552.36 ± 214.37	<0.05
day 14	85.54 ± 54.84	-	

*Mann–Whitney U-test.

ROC analysis was also performed to determine the prognostic value of these parameters. AUC, P-values, sensitivity, specificity, positive predictive values, and negative predictive values are presented in Table 7. It was found that procalcitonin and sTREM-1 values were not as significant as SOFA values in the estimation of prognosis of sepsis cases in the early stage. Of these two indicators, the procalcitonin value became significant from day 7 onwards and the sTREM-1 value became significant from day 4 onwards.

Repeated measures analysis of variance was performed to determine the changes in SOFA, procalcitonin, and sTREM-1 values during follow-up. According to the results of this analysis, the values for each variable were higher in the nonsurvivors than in the survivors; however, the only statistically significant difference was determined for the SOFA values ($P < 0.001$, repeated measures multivariate variance analysis) (Figures 1–3; Table 8).

4. Discussion

Sepsis is SIRS developing due to infection. Using only SIRS criteria, it is difficult to differentiate sepsis cases from NI-SIRS patients. In addition to the SIRS criteria, laboratory findings play a very important role in the early differential diagnosis of these patients (1,12). Studies conducted on the differential diagnosis of sepsis and NI-SIRS in recent years have focused on the indicators which yield results more rapidly in the early period. Among them, clinical scoring systems such as the SOFA and immunological markers such as procalcitonin and sTREM-1 are the leading ones (3,7,13).

In their clinical study, Endo et al. (15) observed higher procalcitonin levels in patients with sepsis, which they considered important in differentiating severe sepsis from NI-SIRS. The results obtained were consistent with the SOFA scores. In a metaanalysis, in which 30 studies involving 3244 patients were evaluated, procalcitonin

Table 7. The prognostic values of SOFA, sTREM-1, and procalcitonin in the patients with sepsis.

	Cut-off value	AUC*	P	Sensitivity (%)	Specificity (%)	PPVx	NPVδ
SOFA score							
day 0#	7.5	0.885	0.001	77.8	100.0	100.0	78.9
day 3#	7.5	0.865	0.001	77.8	92.3	93.3	75.0
day 4#	8.5	0.981	0.001	91.7	100.0	100.0	92.9
day 7#	7.5	1.000	0.001	100.0	100.0	100.0	100.0
day 14#	8.5	1.000	0.005	100.0	100.0	100.0	100.0
PCT (ng/mL)							
day 0#	6.56	0.520	0.842	50.0	46.7	52.9	43.8
day 3#	10.80	0.577	0.471	61.1	69.2	73.3	56.3
day 4#	14.78	0.686	0.115	75.0	76.9	75.0	76.9
day 7#	4.46	0.833	0.008	80.0	75.0	72.7	81.8
day 14#	1.44	0.950	0.011	100.0	80.0	66.7	100.0
sTREM-1 (pg/mL)							
day 0#	254.67	0.444	0.588	50.0	40.0	50.0	40.0
day 3#	310.72	0.658	0.139	66.7	76.9	80.0	62.5
day 4#	292.33	0.763	0.026	66.7	69.2	66.7	69.2
day 7#	307.09	0.896	0.002	80.0	83.3	80.0	83.3
day 14#	375.27	0.925	0.016	100.0	90.0	80.0	100.0

# $P < 0.05$
*AUC: Area under the curve.
xPPV: Positive predictive value.
δNPV: Negative predictive value.

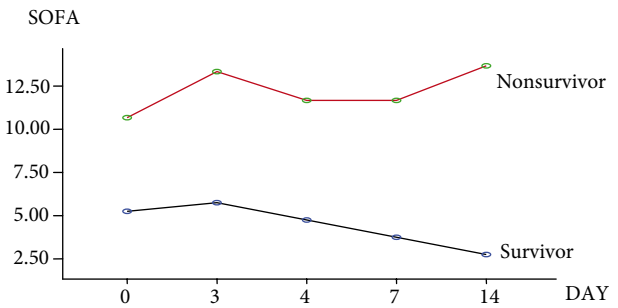

Figure 1. Repeated measures multivariate variance analysis for SOFA scores.

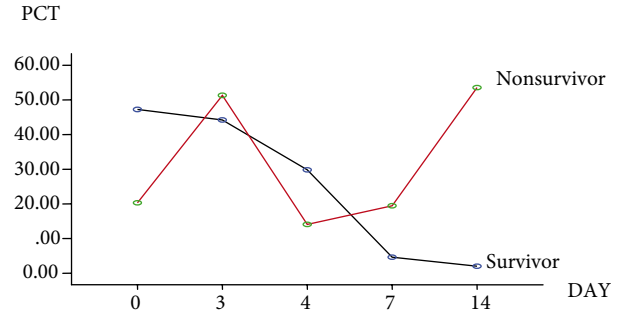

Figure 2. Repeated measures multivariate variance analysis for procalcitonin.

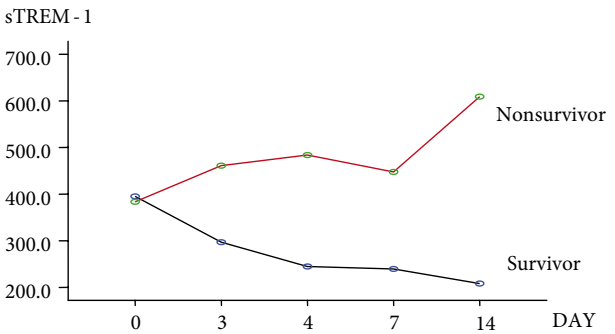

Figure 3. Repeated measures multivariate variance analysis for sTREM-1.

Table 8. The results of repeated measures multivariate variance analysis of SOFA, procalcitonin, and sTREM-1.

	SOFA	PCT	sTREM-1
Group (nonsurvivor/survivor)	P = 0.001	P = 0.7	P = 0.7
Time (days 0, 3, 4, 7, 14)	P = 0.2	P = 0.3	P = 0.1
Group × time	P = 0.07	P = 0.2	P = 0.1

sensitivity in differentiating NI-SIRS patients from sepsis patients was 77%, while the specificity was 79%. It was emphasized that procalcitonin was useful in the early diagnosis of sepsis both in surgical and in medical patients (16). In Gibot et al.'s study conducted to investigate the diagnostic values of both procalcitonin and sTREM-1, laboratory findings of both markers were higher in patients with sepsis (10). In another study investigating the diagnostic value of the sTREM-1 in patients with sepsis and NI-SIRS, sTREM-1 levels were significantly higher in patients with sepsis than in patients with NI-SIRS (17). In a metaanalysis of 13 studies, it was concluded that sTREM-1 levels could be considered a reliable biological marker in bacterial infections (18). In another metaanalysis, 11 studies involving 1795 patients were evaluated, and sTREM-1's sensitivity and specificity in differentiating NI-SIRS patients from sepsis patients were determined to be 79% and 80%, respectively (9). In our study too, both the SOFA scores and the procalcitonin and sTREM-1 levels were found to be significantly higher in the patients with sepsis than in the NI-SIRS patients. In the differentiation of NI-SIRS from sepsis, the sensitivity and specificity of SOFA were 81.8% and 80.5%, respectively, the sensitivity and specificity of procalcitonin were 81.8% and 70.7%, respectively, and the sensitivity and specificity of sTREM-1 were 81.8% and 73.2%, respectively. These results were consistent with those in the literature.

Despite the developments in the early diagnosis and treatment of sepsis, it still leads to high mortality. In several clinical trials conducted on mortality resulting from sepsis

in different patient groups, the mortality rate ranged between 22% and 50% (1,5,19). In our study, the mortality rate in the sepsis group was 54.54%. Determination of the prognosis of the disease in sepsis patients is as important as its early diagnosis. However, it is difficult to predict mortality, or in other words, to determine the prognosis. As in studies on the differential diagnosis of sepsis and NI-SIRS, in studies conducted to determine the prognosis of sepsis, the focus is on clinical scoring systems such as the SOFA and immunological markers such as procalcitonin and sTREM-1 (7,20,21).

Kenzaka et al. (20) indicated that mean SOFA scores in patients with sepsis, severe sepsis, and septic shock were directly proportionate to the severity of the disease. Innocenti et al. (22) investigated the importance of various clinical scores and biological parameters in the prognosis of patients who presented to the emergency room with sepsis and septic shock. The SOFA score had the best mortality prediction ability (AOC 0.80, 95% confidence interval 0.70–0.91) compared with other clinical scores and biologic parameters. In our study too, similar results were obtained for the SOFA scores. During the entire follow-up of patients with sepsis, sensitivity and specificity values of SOFA scores were high and the prognostic value of the SOFA score was statistically significant.

Several studies conducted on the same topic report that both procalcitonin and sTREM-1 are reliable indicators in determining prognosis. Studies conducted in various centers determined that procalcitonin and sTREM-1 levels were higher in nonsurviving sepsis patients than in surviving sepsis patients (7,15,21,23). In another study, it was emphasized that sTREM-1 had a prognostic value particularly in the long-term follow-up (24). In our study too, although the difference was not statistically significant, procalcitonin and sTREM-1 values obtained during follow-up decreased in the survivors but gradually increased in the nonsurvivors. The statistical insignificance might be due to the fact that the number of people in the groups decreased as the follow-up period lengthened. When the data obtained in this study were evaluated in the light of the data in the literature, not only the SOFA scores but also procalcitonin and sTREM-1 values were important indicators in determining the prognosis of patients with sepsis.

In the literature, different sensitivity and specificity results have been reported regarding the prognostic value of procalcitonin and sTREM-1 (5,7,11,15,21,23). However, there is no clinical study indicating that they are the single biological indicator with sufficient sensitivity and specificity. In general, clinical studies have been conducted on the use of these biological indicators in combination with each other or with clinical indicators such as SOFA scores. In this present clinical study, the prognostic values of procalcitonin and sTREM-1 were not as significant as those of SOFA during the early stage of sepsis. Since the sensitivity and specificity of procalcitonin and sTREM-1 increase markedly in later stages, these immunological indicators can be used along with the SOFA in this stage.

Many risk factors related to interventions performed for diagnosis and treatment, the host, and microorganisms play a role in the development of sepsis. Of the factors related to the host, age and underlying disease are the most important risk factors (1,2,5,25). The findings of our study regarding demographic data and risk factors were consistent with those in the literature we reviewed. Age, being inpatient or outpatient, ICU admission, antibiotic usage history, and underlying diseases (liver failure, kidney failure, diabetes, chronic lung disease, and cardiovascular disease) were identified as the most significant risk factors.

In line with the data obtained, in order to make an early diagnosis and to determine the prognosis of patients suspected to have sepsis, monitoring procalcitonin and sTREM-1 values would be useful. However, further clinical studies are needed in order to determine the diagnostic and prognostic values of these markers in sepsis.

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