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The Preseptic Period and Inflammatory Markers in the Prediction of the Course of Sepsis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Literature Search F
Funds Collection G

ABEF 1 **Ömer Faruk Boran**
CDE 2 **Fatih Mehmet Yazar**
BDF 3 **Maruf Boran**
BDF 1 **Aykut Urfaloğlu**
CDE 4 **Zeyneb Bakacak**
CDE 5 **Mürşide Yıldız**
ADE 5 **Fethi Gül**
ABD 6 **Selma Güler**

1 Department of Anesthesiology and Reanimation, Sütçü Imam University School of Medicine, Kahramanmaraş, Turkey
2 Department of General Surgery, Sütçü Imam University School of Medicine, Kahramanmaraş, Turkey
3 Department of Internal Medicine, Sabuncuoğlu Serafettin University, Faculty of Medicine, Amasya, Turkey
4 Department of Obstetrics and Gynecology, Private Vatan Hospital, Kahramanmaraş, Turkey
5 Department of Anesthesiology and Reanimation, Marmara University, Pendik Educational Research Hospital, İstanbul, Turkey
6 Department of Infectious Disease, Sütçü Imam University School of Medicine, Kahramanmaraş, Turkey

Corresponding Author: Zeyneb Bakacak, e-mail: zeynebbakacak@gmail.com
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Background: The aim of this study was to find a simple and easily accessible scoring system that could predict the development of sepsis in the preseptic period.


Material/Methods: The study included 161 patients with a basal sequential organ failure assessment (SOFA) value of 2 or more. The sepsis group (n=83) comprised patients with infection reported in culture results; the control group (n=78) comprised patients not showing evidence of infection in blood, urine, and phlegm cultures; samples were taken on three consecutive days.

Results: The patients in both groups were divided into subgroups of non-survivor and survivor patients. The preseptic and septic SOFA score, neutrophil lymphocyte ratio (NLR), and procalcitonin (PRC) and lactate (Lac) values were determined to be statistically significantly higher in the sepsis group than in the control group. When the values related to sepsis were examined, a strong relationship was determined between sepsis and SOFA score, PRC values, and Lac values in the preseptic period and a weak relationship with NLR. In the model formed using multiple regression analysis with defined cutoff values for the preseptic and the septic periods, we found that in the septic period, a diagnosis of sepsis could be made with 83.8% accuracy. The diagnostic value of the same parameters evaluated in the preseptic period was 77.9%.

Conclusions: The diagnostic value of the combination of Lac, PRC, SOFA, and NLR were found to be similar in the preseptic period as the sepsis period; thus these combined values could safely be used for the early diagnosis of sepsis.

MeSH Keywords: **Early Diagnosis • Intensive Care • Sepsis**

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Background

Sepsis is the cause of 23–39% of hospital-based mortality, and despite developments in treatment approaches, it is still one of the most frequent causes of deaths occurring in intensive care units (ICUs) [1]. There are many factors that affect morbidity and mortality in the process of a disease. The severity and process of sepsis varies from patient to patient, according to underlying etiological factors, the presence of comorbidities, and the resistance and response of the patient to the disease. For many years, it has been the goal of many studies to develop a rapid and simple algorithm to be used in the diagnosis and treatment of sepsis to reduce morbidity and mortality [2–4].

With new information available in the literature related to the mechanisms of sepsis pathophysiology, we now have a better understanding of the cellular damage caused by the response of a host to a pathogen. However, there continues to be debate regarding the behavior of the host in sepsis, the mechanism of the development of organ dysfunction, the increased antibiotic resistance, the heterogeneity of patients, and the contribution of technology for the identification of sepsis.

In a 2016 consensus report, sepsis was defined as the development of organ dysfunction related to a dysregulated response of the host to infection [5]. Many studies have attempted to identify the ideal biomarker to show the severity of a disease, organ failure, and/or mortality [2–4]. Various biomarkers that have been studied include serum albumin [2], C-reactive protein (CRP) [3], procalcitonin (PRC) [3], lactate (Lac) [6], and the neutrophil lymphocyte ratio (NLR) [4]. The aim of these studies was to evaluate the utility of specific parameters that could be used for diagnostic purposes in patients diagnosed with sepsis [2–6].

Despite advances since the 1990s [7], most clinicians find identifying sepsis in clinical practice challenging, and this can cause a delay in initiation of treatment, thus the need for more sensitive markers for early diagnosis [2–6]. Kumar et al. suggest that for each hour delay in treatment, there is an increase in mortality of approximately 7.6% [8]. In our study, one of the considerations was that sepsis is an ongoing process and that there could be a window of time in which clinicians could be forewarned of the sepsis process by development of an early sepsis warning system and a scoring methodology to predict the onset of the disease. Through comparison of CRP, PRC, Lac, NLR, and SOFA (sequential organ failure assessment) values in the pre-septic and septic periods, the aim of our study was to find a simple and readily available scoring system that could predict the development of sepsis.

Material and Methods

Setting and Patients

Approval for the study was granted by the Local Ethics Committee and all procedures were in accordance with the 1975 Helsinki Declaration. This prospective study included 161 consecutive patients treated in the ICU between March 2016 and April 2017.

In accordance with the 2016 consensus report [9], patients with an increase of ≥ 2 in the basal SOFA value and evidence of infection in culture, were evaluated as having sepsis (sepsis group, $n=83$). Patients were excluded if they had stage C liver failure findings according to Child-Pugh classification at the time of admission, surgery-related sepsis where a drain was not applied, AIDS, pregnancy, trauma, or if cardiac arrest developed before sepsis and resuscitation was applied. All the patients were treated according to the 2012 Surviving Sepsis Guidelines [10]. A control group was formed of patients admitted to the ICU during the same period and who, despite an increase of ≥ 2 in the basal SOFA value, showed no evidence of infection in the blood, urine, and bronchoalveolar lavage (BAL) cultures taken on three consecutive days (control group, $n=78$).

A record was made of the clinical, biochemical, and hematological parameters of the patients on admittance to ICU, and of the daily follow-up measurements. The power of the study and sufficiency of patient numbers were evaluated with a power analysis. When the sample size reached 161 according to X parameters, the power of the hypothesis test was 89% at a significance level (p value) of 0.05. To avoid errors in the study, the team that diagnosed, treated, and collected the data (FG, MY) was separate from the team that conducted the data analyses (ÖFB, MY).

Before the study, a detailed anamnesis was taken from each patient, including information about cardiac and metabolic diseases and use of medications. In cases where patients could not give an anamnesis, the information was obtained from primary relatives of the patient. A record was made of age, gender, and comorbidities of the patient, clinical scoring systems such as the SOFA score, biochemical parameters such as PRC and Lac, and hematological variables such as NLR. For those in the sepsis group, the day of sepsis diagnosis and the day of starting antibiotics were recorded; other details were recorded prospectively throughout the length of the patient's stay in the hospital.

In the control group, an increase of 2 units on the SOFA score compared to the basal value was accepted as significant according to the new definition of sepsis. The day on which there was a 2-unit increase in the SOFA value was accepted as equal

Table 1. Demographic data of patients in the sepsis group and the control group.

Characteristic	Sepsis (n=83)			Control (n=78)		
	Nonsurvivor (n=63)	Survivor (n=20)	P	Nonsurvivor (n=27)	Survivor (n=51)	P
Age (years)	56.58±16.88	57.73±16.79	0.794	56.27±14.53	57.81±15.45	0.683
Gender (F/M)	19/44	7/13	0.908	11/16	16/35	0.274
Hospitalizasyon time (days)	10.46±8.77	6.65 ±9.91	0.562	7.60±3.71	6.95 ±6.09	0.640

Data are expressed as the mean ±SD, unless other wise noted. Independent T Test (Bootsrap).

to the sepsis day for the sepsis group, and calculations were made accordingly. The patients in sepsis group and control group were divided into two subgroups of survivors and non-survivors to evaluate more objectively the reasons for differences which developed between the groups. In the control group, patients with a previous infection and/or antibiotic use within one month before admission were excluded from the study. Variables were investigated for patients in the sepsis group on the day of admission to intensive care (day 0), on the day of a 2-unit increase in SOFA value and identification of infection foci on culture results (septic), 24 hours before the day of sepsis development (preseptic) and 24 hours after sepsis development (post septic). In the control group, the SOFA values for patients on the day with a 2-unit increase were compared with the septic day

Statistical analysis

Statistical analyses were performed using IBM SPSS for Windows, version 22.0 software (IBM Corporation, Armonk, NY, USA). Data were stated as mean ± standard deviation (SD). The variance analysis of repeated measures ANOVA with Bonferroni was applied for repeated measurements. Linear regression models were used for the evaluation of factors related to sepsis. The optimal cutoff value was determined for each value in the preseptic period and in the septic period using receiver operating characteristic curves (ROC). The area under the curve (AUC) was stated as 95% confidence interval (CI). A value of $p < 0.05$ was accepted as statistically significant.

The combination of biomarkers with SOFA scores was determined with ROC curves; the AUC values of these were re-evaluated using the prognostic value of a multiple multimarker approach.

In the reclassification analyses using net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for evaluation of the additional value of the multi-marker approach together with the SOFA score, analysis was made of the CRP, and WBC, NRI and IDI values at 95% CI. Statistical analyses were applied using MedCalc Software v. 15.8 (MedCalc, Mariakerke, Belgium) and R version 3.3.1 (The R Foundation

for Statistical Computing, Vienna, Austria). For multiple comparisons, p values were not adjusted and were, therefore, only descriptive.

Results

The clinical characteristics of the patients included in the study are summarized in Table 1. In the analysis of the 161 patients, the mean age was 57.01 ± 16.81 years in the sepsis group ($n=83$) and 57.26 ± 15.05 years in the control group ($n=78$). Both groups were divided into subgroups of survivors and non-survivors. The SOFA, NLR, PRC, and Lac values in the preseptic period and on the day that sepsis was diagnosed were observed to be significantly higher in the sepsis group than in the control group. In the subgroup analyses, this difference in the sepsis group was determined to originate from the non-survivors group. The values of the sepsis survivor group were not determined to be any different from those of the control survivor group and control non-survivor group (Figure 1).

When the values related to sepsis were examined, a strong relationship was determined between sepsis and SOFA score, PRC value, and Lac value in the preseptic period and a weak relationship between sepsis and NLR in the preseptic period (Table 2). In the ROC analyses, the cutoff values in the preseptic period and the septic periods were calculated as 6.5 for SOFA score ($p < 0.001$), 14.5 for NLR ($p < 0.001$), 1.65 mmol/L for Lac ($p < 0.001$), and 4.2 ng/mL for PRC ($p < 0.001$). The cutoff value of 6.5 for the SOFA score in the septic period had a 59.8% sensitivity and a 78.7% specificity in the diagnosis of sepsis ($AUC=0.757 \pm 0.039$). The cutoff value of NLR in the septic period had a 85.4% sensitivity and a 71.4% specificity ($AUC=0.764 \pm 0.041$), and the cutoff value of PRC had a 94.5% sensitivity and a 75.2% specificity ($AUC=0.863 \pm 0.030$). The cutoff value of Lac in the septic period had a 79.3% sensitivity and a 63.4% specificity ($AUC=0.717 \pm 0.042$). The results of these values in the preseptic period were similar (Figure 2).

The model formed using multiple logistic regression analysis examined the preseptic and septic periods separately with the independent variables of SOFA, NLR, PRC, and Lac in the

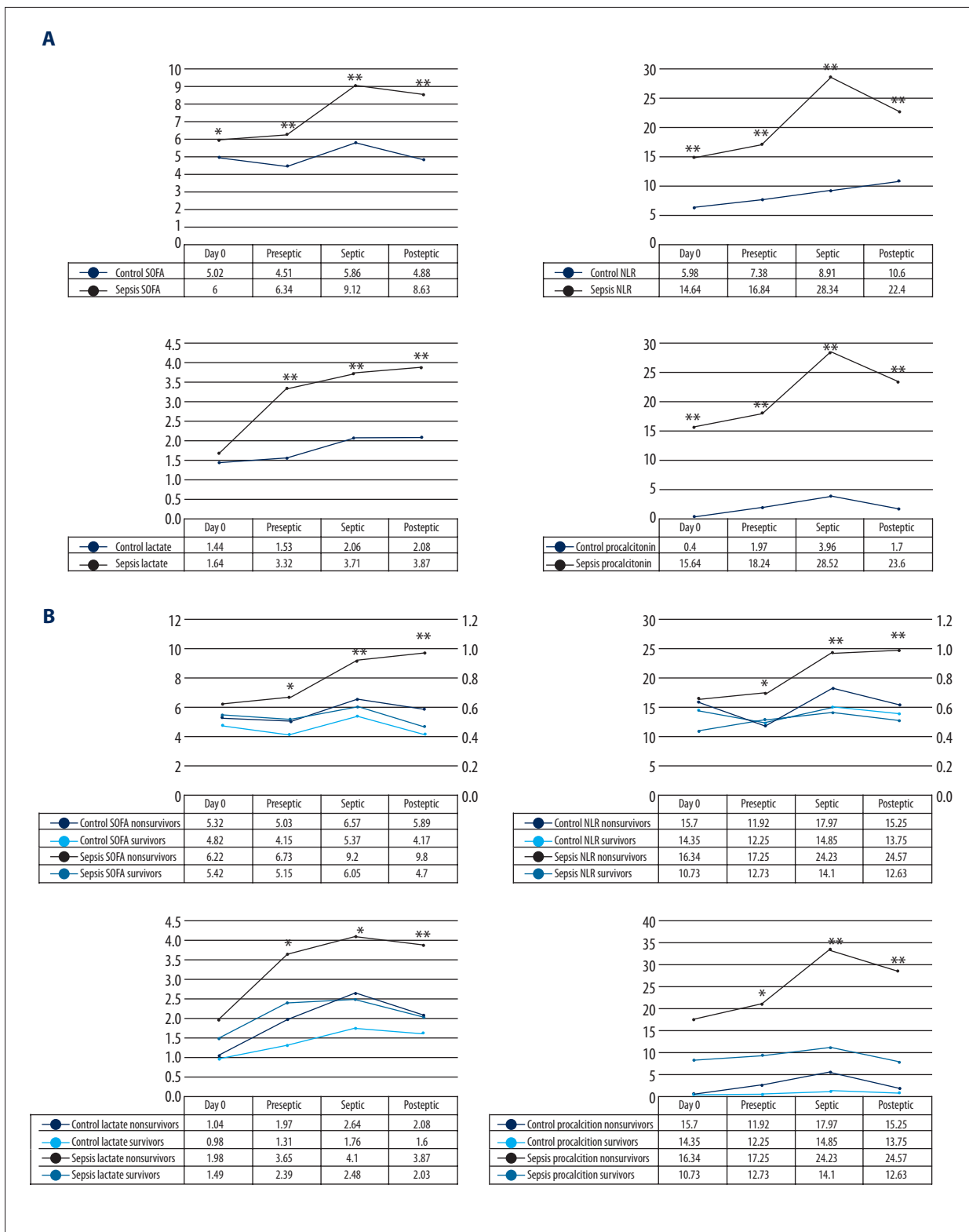


Figure 1. Changes in the biomarkers according to the day of admittance to the ICU, pre-septic and septic days and the day of discharge from the ICU (A); changes in the biomarkers according to the subgroups (B). ICU – intensive care unit.

Table 2. The relationship of sepsis and biomarkers in the preseptic period and septic period.

Sepsis	r	P
Preseptic SOFA	0.275**	0.001
Septic SOFA	0.446**	0.001
Preseptic NLR	0.182*	0.026
Septic NLR	0.455**	0.001
PresepticPrc	0.646**	0.001
SepticPrc	0.626**	0.001
PresepticLac	0.457**	0.001
SepticLac	0.374**	0.001

* Correlation is significant at the 0.05 level (2-tailed);
** correlation is significant at the 0.01 level (2-tailed).
SOFA – sequential organ failure assessment;
NLR – neutrophil lymphocyteratio; Prc – procalcitonin;
Lac – lactate

diagnosis of sepsis. The statistically significant results of the model are shown in Table 3. When the defined cutoff values of these four variable parameters were taken into consideration in the statistically significant model ($p < 0.001$), it was seen that sepsis could be diagnosed with an 83.8% accuracy. The diagnostic value was 77.9% when the same parameters were evaluated for the preseptic period (Table 3).

In the reclassification analyses, NLR, Lac, and PRC values added to the SOFA score and showed higher prognostic value than the SOFA score alone and the SOFA score + NLR value in the septic period. When the SOFA, NLR, Lac, and PRC values were examined in the preseptic period, a similar prognostic value was determined for the SOFA score, NLR, Lac value and PRC value (Figure 3). Among patients in the sepsis group, 31 patients had proliferation in blood and BAL cultures, 23 patients had proliferation in blood and urine cultures, 14 patients had proliferation in BAL and urine culture, and 15 patients had

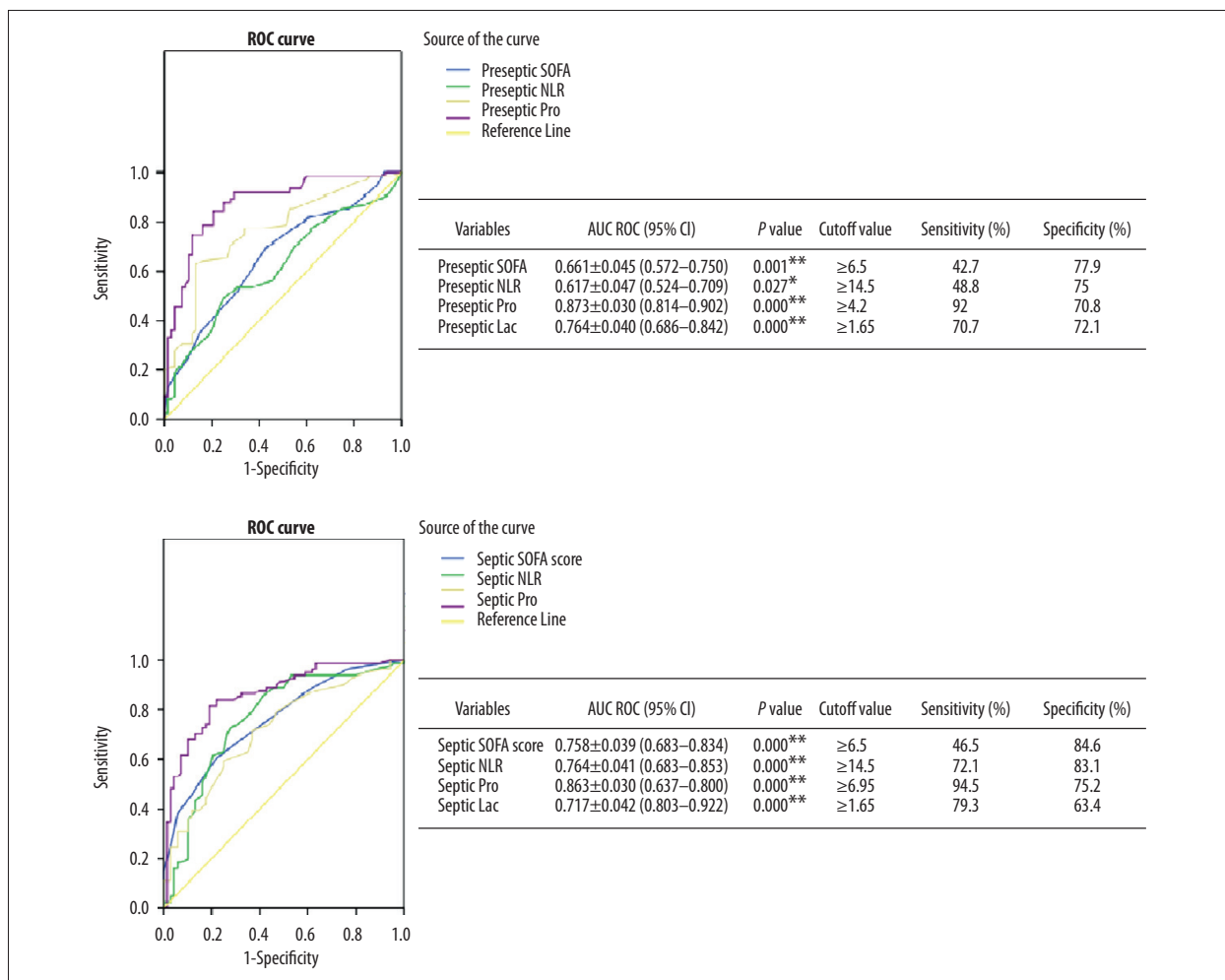


Figure 2. Comparison of the ROC curves of the SOFA, NLR, PRC, and Lac values in the preseptic and septic periods. SOFA – sequential organ failure assessment; NLR – neutrophil lymphocyte ratio; PRC – procalcitonin; Lac – lactate.

Table 3. Results of multiple logistic regression analysis of sofa score, procalcitonin level, lactate level, and neutrophil lymphocyte ratio to determine independent predictors of sepsis.

	Independent variables	B ±SE	p	Oddsratio (95% CI)	
Sepsis	Preseptic SOFA	0.058±0.070	0.411	0.944 (0.823–1.083)	
	Preseptic Prc	0.055±0.025	0.022	0.924 (0.898–0.992)	
	Preseptic Lac	0.654±0.198	0.001	0.520 (0.352–0.767)	
	Preseptic NLR	0.048±0.021	0.019	0.953 (0.915–0.992)	
	Constant	2.634±0.588	0.001	13.931	
	Dependent variable: groups Nagelkerke R ² =0.426 Predicted (%): 77.9 p<0.001				
	Septic SOFA	0.213±0.069	0.002	0.808 (0.706–0.925)	
	Septic Prc	0.024±0.012	0.044	0.976 (0.349–0.774)	
	Septic Lac	0.253±0.131	0.053	0.776 (0.601–1.003)	
	Septic NLR	0.028±0.013	0.034	0.972 (0.948–0.998)	
	Constant	2.955±0.624	0.001	19.211	
	Dependent variable: groups Nagelkerke R ² =0.438 Predicted (%): 83.8 p<0.001				

SOFA – sequential organ failure assessment; NLR – neutrophil to lymphocyteratio; Prc – procalcitonin; Lac – lactate.

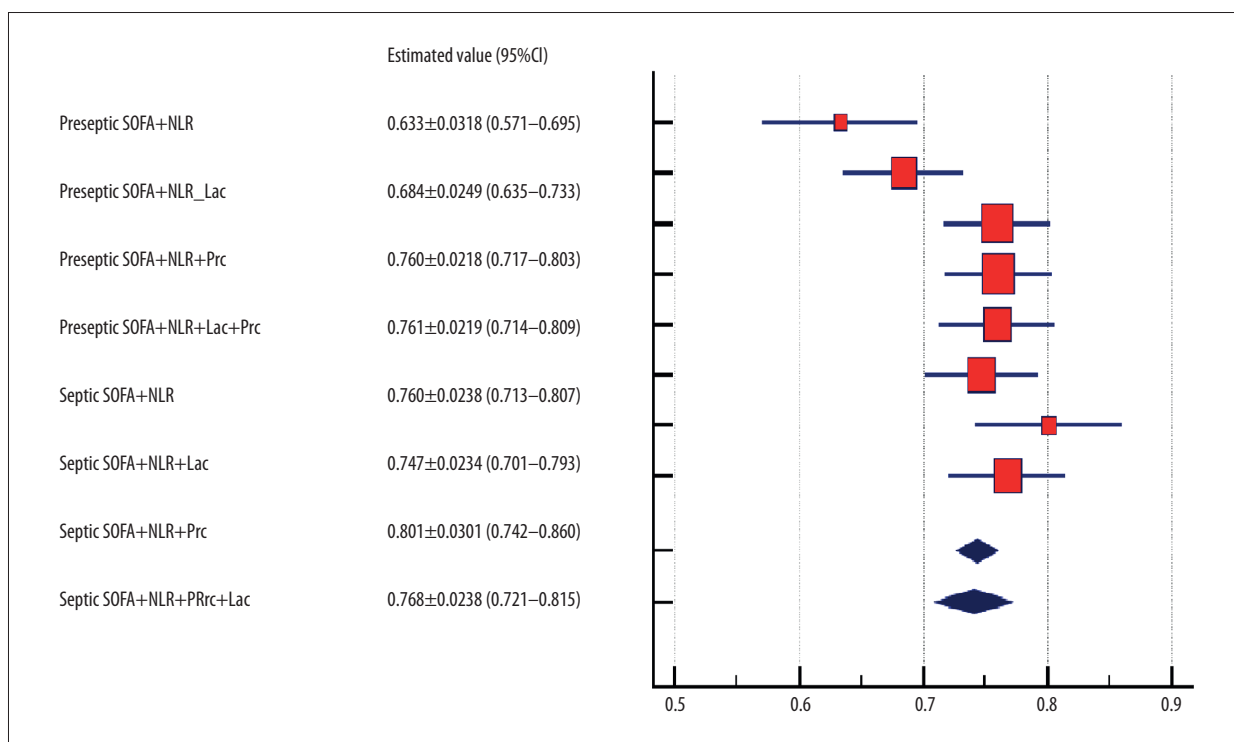


Figure 3. Evaluation of the factors related to sepsis with a multimarker approach. The biomarkers were reclassified using NRI and IDI. The rhombi mean values and lines are at 95% CI. IDI – integrated discrimination improvement; NRI – net reclassification index.

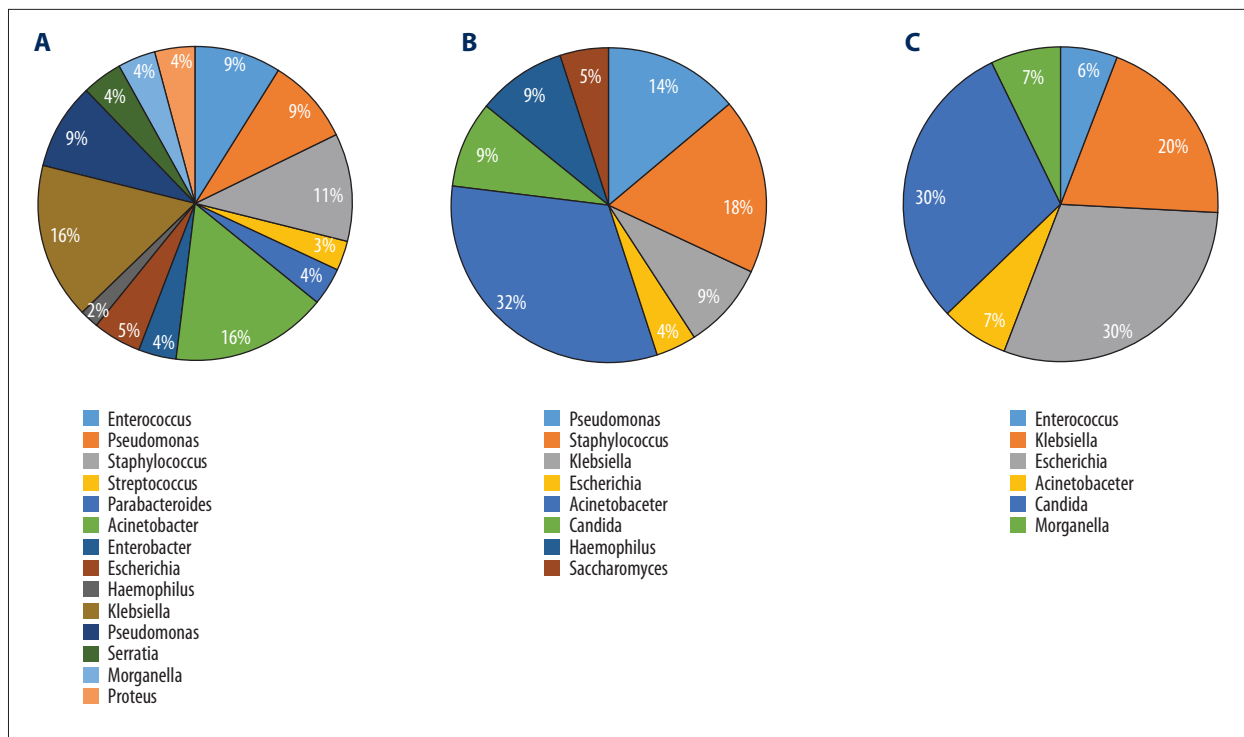


Figure 4. Microorganisms proliferating in blood, bronchoalveolar lavage and urine cultures.

proliferation in all cultures. The distribution of proliferative microorganisms is shown in Figure 4.

Discussion

In this study, an evaluation was made to determine if the SOFA score (which is known to have a place in sepsis diagnosis) and the parameters of NLR, Lac, and PRC values (which have been shown to have diagnostic value in several studies) could be used for diagnostic purposes before the patient has entered the sepsis phase. The results of our study showed a strong correlation between sepsis and SOFA score, PRC values, and Lac values in the preseptic period. The relationship with NLR was determined to be weak. In the multiple logistic regression analysis with cutoff values defined for each parameter, we found that sepsis could be diagnosed with a 83.8% accuracy using the defined values in the septic period, and furthermore, when the evaluation was made with the same parameters in the preseptic period, the diagnostic value was at 77.9% accuracy. In the reclassification analyses, the diagnostic value of the combination of SOFA score and NLR was relatively better in the septic period and lower in the preseptic period. However, the diagnostic value of the combination of preseptic SOFA score with NLR, PRC, and Lac values was seen to be similar to that of the septic period SOFA score with NLR, PRC, and Lac values.

Despite increasing clinical experience and technological developments in ICU conditions, sepsis remains the most important cause of deaths occurring in ICUs [1]. Of the several factors determined in the process of sepsis, a proportion of these are invariable factors such as the presence of an underlying etiology or comorbid disease [2–4]. The most important factors determining the survival rate include diagnosis in as short a time as possible, fluid treatment, and early initiation of antibiotherapy [8]. However, as sepsis is a process, some pathophysiological changes occur in the body before entering the septic phase and defense mechanisms start to work. The aim of this study was to evaluate the contribution of the SOFA score in combination with different biomarkers in the early diagnosis of sepsis.

SOFA is a simple scoring system that can be easily applied at the bedside and has a place in the new definition of sepsis. Compared to the basal value, an increase of 2 points in SOFA score in the presence of infection is defined as sepsis [11]. SOFA is a scoring system used in the determination of organ dysfunction related to sepsis, and is used to evaluate the severity of disease in critical patients and to predict results. By evaluating the level of functional impairment of six systems (respiratory, cardiovascular, coagulation, renal, neurological), SOFA focuses on organ function impairment in bedside clinical changes and thus is a simple scale which calculates morbidity rather than mortality [12]. If the score is 0–6, mortality is expected to be <10%; for scores 13–14, the expected mortality

is 50%; and for scores >15 the expected mortality is 90% [13]. Seymour et al. compared the predictive value of SOFA, SIRS (systemic inflammatory response syndrome), LODS (logistic organ dysfunction system), and the recently developed qSOFA in an analysis of 706,399 patient in 165 hospitals; 148,907 of the patients were suspected to have sepsis, The analysis showed that SOFA and LODS provided similar results in respect of potential ICU infections and hospital mortality, and both scoring systems were found to be superior to SIRS [11].

Shi et al. reported that SOFA scores of a non-survivor group were significantly higher than those of a survivor group (8.9 ± 2.1 versus 5.4 ± 2.2) [14]). In another recent study by Kim et al., the mean SOFA score of the non-survivor group was reported as 5 (range, 3–8) which was significantly higher than that of the survivor group [3]. In our study, the SOFA scores of the non-survivor group were seen to be statistically significantly high in both the preseptic and septic periods ($p=0.041$, $p=0.001$, respectively). Kim et al. reported that a SOFA cutoff value of >7 for 30-day mortality had a 32.4% sensitivity and a 96.8% specificity [3]. In the ROC analysis of our study, it was seen that sepsis diagnosis could be made with a SOFA score of >6.5 in the septic period with a 46.5% sensitivity and an 84.6% specificity, and in the preseptic period, sensitivity was 42.7% and specificity was 77.9%. However, in the logistic regression analysis, despite the diagnostic value of the SOFA score alone in the septic period ($p=0.002$), there was no diagnostic value to the SOFA score alone in the preseptic period ($p=0.411$) (Table 3).

The Lac level is used as a global marker of the sufficiency of perfusion and oxygenation and of impaired microvascular function. Hyperlactatemia (>1 mmol/L) is associated with reduced capillary filling. Just as in all markers, the trend of numerous Lac values are more important than one Lac value. Elevated Lac has prognostic value independent of the underlying cause [15]. It has been reported that in the first eight hours in the ICU, a fall of 20% every two hours in the Lac level after targeted treatment, shortened the duration of the ICU stay, and reduced damage to organs, mortality rates, and the time to removal from a ventilator [16,17].

In a study by Khater et al., the serum Lac levels were determined to be statistically significantly higher at 3 ± 2.52 mmol/L in the sepsis group than the mean value of 1.2 ± 0.5 mmol/L in the control group, and at the cutoff value of 1.95 mmol/L, sepsis diagnosis could be made with 67.5% sensitivity and 87.5% specificity [18]. Singer et al. reported an ideal cutoff value of 2 mmol/L for optimal diagnosis [9]. In the current study, the Lac values of the sepsis group were statistically significantly higher than those of the control group on the day of sepsis diagnosis (3.71 ± 3.01 mmol/L versus 2.06 ± 1.39 mmol/L) ($p<0.001$), and diagnosis was made with a cutoff value of 1.65 mmol/L with 79.3% sensitivity and 63.4% specificity. When the same cutoff value was examined in the preseptic period, the sensitivity

was 70.7% and specificity was 72.1% in the diagnosis of sepsis. The results were seen to be consistent with the literature.

NLR is a simple test, which does not incur any extra cost for the patient or the hospital and does not require specialist interpretation, as it uses blood parameters included in the full blood count workup and is therefore easily accessible [19]. Despite various reports related to the use of the NLR in patients with sepsis, no consensus has yet been reached on the efficacy of its use. In a recent study of 333 sepsis patients, the mean NLR was reported to be 17.85 (range, 9.61–28.19).

Patients were grouped according to the development of mortality and the NLR value of the non-survivor group was statistically significantly higher than that of the survivor group (25.49 [16.64–47.15] versus 15.03 [8.94–24.67]) ($p<0.001$). NLR over the cutoff value of 23.8 was reported to have a sensitivity of 81.3% and a specificity of 53.6% in the diagnosis of sepsis [20]. In our study, the cutoff value in the septic period was defined as ≥ 14.5 (sensitivity 85.4%, specificity 71.4%), but the same value in the preseptic period was seen to have a low sensitivity in the diagnosis of sepsis (sensitivity 48.8%, specificity 75%). The results for the septic period were similar to results reported in the literature.

PRC, which is a biomarker showing early inflammation that develops associated with sepsis, has a half-life of 24 to 36 hours and the highest levels can be measured in the plasma at between 6 and 24 hours. PRC increases specific to bacterial infections and shows a positive correlation with the severity of sepsis. A trend of increased PRC levels within the first 72 hours is closely related to mortality [21,22]. PRC levels, which are relatively low in healthy individuals, increase in bacterial infections or in sepsis patients and significantly decrease following appropriate antimicrobial treatment [23].

In a study of 112 patients by Shi et al., SOFA scores and PRC levels were evaluated in SIRS, sepsis, severe sepsis, and septic shock patients and the highest levels were reported in the septic shock patients ($n=41$). When the SOFA scores were grouped, the highest PRC values of mean 28.7 ng/mL (19.98–37.56 ng/mL) were reported to be in the infectious patients with SOFA scores of 19–24 (14). Yin et al. compared the PRC values in 116 patients being followed for sepsis and reported that values were higher in the non-survivor group ($n=31$) than the survivor group ($n=85$) but the difference was not statistically significant (16.1 ± 27.8 ng/mL versus 7.7 ± 20.7 ng/mL) [2].

In our study, patients in the sepsis and control groups were separated into subgroups of survivors and non-survivors. The highest PRC values of mean 33.64 ± 38.14 ng/mL were found in the non-survivor group and these were statistically significantly higher than the values in the survivor group ($p<0.001$). In the septic

period, the PRC cutoff value of ≥ 6.95 ng/mL was defined using ROC analysis and was seen to have a sensitivity of 94.5% and a specificity of 75.2% in the diagnosis of sepsis; and in the preseptic period, a sensitivity of 92% and a specificity of 70.8%. In the multiple logistic regression analysis using the defined cutoff values for SOFA, NLR, PRC, and Lac, sepsis could be diagnosed in the septic period with 83.8% accuracy and when the same parameters were evaluated for the preseptic period, accuracy of diagnosis was 77.9%. In the reclassification analyses, the combination of SOFA, NLR, and Lac parameters had the optimal diagnostic value in the septic period (AUC ROC=0.747 \pm 0.0234), and the diagnostic value of the combination of SOFA score, the NLR and PRC values and SOFA score, and the NLR, Lac, and PRC was seen to be similar in both the preseptic and septic periods (Figure 3).

One of the limitations of the current study was that no investigation was made of the biological markers used for diagnostic purposes related to specific bacterial identification or antibiotic consumption. However, as the aim of the study was to determine inexpensive diagnostic criteria that would be easily accessible in all centers and which would allow the possibility of diagnosis in the preseptic period, this point was not included to avoid confusion.

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Conclusions

The diagnostic value of the combination of preseptic period SOFA, NLR, Lac, and PRC was seen to be similar to that of the same combination during the septic period, and therefore, can be considered to be safe for use in the early diagnosis of sepsis.