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RESEARCH ARTICLE

Pan-immune-inflammation value and platelet indices as mortality markers in intensive care patients with sepsis

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ABSTRACT

Objective: Sepsis remains a major global health problem with high morbidity and mortality rates, mostly in intensive care unit (ICU) settings. The Pan-Immune Inflammation Value (PIIV), a composite marker derived from neutrophil, monocyte, platelet, and lymphocyte counts, has recently emerged as a potential indicator of systemic inflammation. This study aimed to evaluate the prognostic performance of PIIV and platelet-derived indices, including mean platelet volume (MPV) in predicting 30-day mortality among ICU-admitted sepsis patients.

Methods: This retrospective study included 191 adult patients with sepsis admitted to the ICU of a tertiary care hospital. Laboratory parameters, including PIIV, MPV, PLR, and lactate, along with various clinical and laboratory parameters were recorded within the first 24 hours of ICU admission. Logistic regression analysis (LRA) and receiver operating characteristic curve (ROC) analysis were performed to determine predictors of 30-day mortality.

Results: Of the total cohort, 96 patients (50.3%) died within 30 days after ICU admission. PIIV, MPV, and lactate levels were found to be elevated in non-survivors (p=0.001, p=0.003, and p=0.001, respectively). In multivariate LRA, PIIV (OR: 1.235; 95% CI: 1.086–1.404; p=0.001), MPV (OR: 1.346; 95% CI: 1.111–1.630; p=0.002), lactate, and urea were independently associated with mortality. ROC analysis showed that PIIV had an AUROC of 0.643 at a cut-off value of ≥1.2, while MPV had an AUROC of 0.623 at a cut-off of ≥11.5 fL.

Conclusion: Integrating PIIV and MPV into the clinical assessment of sepsis patients may improve decision-making in the management of critically ill septic patients in intensive care units.

Keywords: Sepsis, prognosis, mortality, pan-immune-inflammation value, platelet indices

ÖZET

Yoğun bakım ünitesinde sepsis tanılı hastalarda mortalitenin belirteçleri olarak pan-immün-inflamasyon değeri ve trombosit indeksler

Amaç: Sepsis, çoğunlukla yoğun bakım ünitesi (YBÜ) ortamlarında yüksek morbidite ve mortalite oranlarına sahip önemli bir küresel sağlık sorunu olmaya devam etmektedir. Nötrofil, monosit, trombosit ve lenfosit sayımlarından türetilen bir bileşik belirteç olan Pan-İmmün İnflamasyon Değeri (PIIV), son zamanlarda sistemik inflamasyonun potansiyel bir göstergesi olarak ortaya çıkmıştır. Bu çalışma, YBÜ'ye yatırılan sepsis hastalarında 30 günlük mortaliteyi tahmin etmede PIIV ve ortalama trombosit hacmi (MPV) dahil olmak üzere trombosit kaynaklı endekslerin prognostik performansını değerlendirmeyi amaçlamaktadır.

Yöntem: Bu retrospektif çalışmaya, üçüncü basamak bir hastanenin YBÜ'süne yatırılan 191 yetişkin sepsis hastası dahil edilmiştir. YBÜ'ye yatışın ilk 24 saati içinde PIIV, MPV, PLR ve laktat gibi laboratuvar parametreleri ile çeşitli klinik ve laboratuvar parametreleri kaydedilmiştir. 30 günlük mortalitenin öngörücülerini belirlemek için lojistik regresyon analizi (LRA) ve alıcı işletim karakteristik eğrisi (ROC) analizi yapıldı.

Bulgular: Toplam kohorttan 96 hasta (%50,3) yoğun bakım ünitesine yatışından sonraki 30 gün içinde öldü. PIIV, MPV ve laktat düzeylerinin hayatta kalamayan hastalarda yüksek olduğu bulundu (sırasıyla p=0,001, p=0,003 ve p=0,001). Çok değişkenli LRA'da, PIIV (OR: 1,235; %95 GA: 1,086-1,404; p=0,001), MPV (OR: 1,346; %95 GA: 1,111-1,630; p=0,002), laktat ve üre mortalite ile bağımsız olarak ilişkiliydi. ROC analizi, PIIV'in ≥1,2 kesme değerinde 0,643 AUROC değerine sahip olduğunu, MPV'nin ise ≥11,5 fL kesme değerinde 0,623 AUROC değerine sahip olduğunu göstermiştir.

Sonuç: PIIV ve MPV'nin sepsis hastalarının klinik değerlendirmesine entegre edilmesi, yoğun bakım ünitelerinde kritik septik hastaların yönetiminde karar verme sürecini iyileştirebilir.

Anahtar kelimeler: Sepsis, prognoz, mortalite, pan-immün inflamasyon değeri, trombosit indeksleri

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INTRODUCTION

Sepsis is a critical condition resulting from a systemic inflammatory response to infections, related with increased morbidity and mortality. It poses a serious economic healthcare burden, particularly in patients admitted to intensive care units (ICUs), with significant clinical and social consequences [1]. In recent years, there has been an ongoing effort to develop prognostic scoring systems, integrated with novel biomarkers, to enable early risk stratification and guide clinical decision-making in the initial hours following diagnosis.

The inflammatory response plays a critical role in the sepsis pathogenesis, and these processes are regulated by the production of pro-inflammatory and anti-inflammatory mediators, as well as platelet-induced activation of blood leukocytes. In this context, several hematologic and biochemical parameters that reflect the severity of the inflammatory response may be critical in determining the prognosis of sepsis [2]. Currently, the most investigated hematologic parameters are the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV), along with biomarkers such as lactate, procalcitonin, and C-reactive protein (CRP) and all of which have been found to be associated with mortality in sepsis patients [3-7]. However it is obvious that these parameters alone cannot reflect the prognosis of a complex and multifactorial pathophysiological condition such as sepsis.

In recent years, studies have been conducted to develop more comprehensive inflammatory indices, and among these, the Pan-Immune Inflammation Value (PIIV) has been found to be a promising index to reflect prognosis in various disease states including, coronary artery diseases, rectal cancer, appendicitis, heart failure, pneumonia and rheumatoid arthritis [8-11]. PIIV is a composite biomarker that combines neutrophil, monocyte, platelet, and lymphocyte counts and offers a broad evaluation of immune and inflammatory activity [12,13]. Although the evidence regarding the relationship between PIIV and distinct disease states is accumulating, there is scarce evidence exploring the prognostic value of PIIV in sepsis patients [14]. The existing studies are often limited to small patient groups and show heterogeneity in outcomes. On the other hand, the ease of calculating the PIIV score—derivable from complete blood count (CBC) analysis—and its potential to reflect systemic inflammation in many ways suggest that this index may be a promising biomarker in sepsis prognosis.

This study investigates the potential predictive role of PIIV measured at the time of ICU admission in sepsis patients. Additionally, the comparative performance of PIIV was also evaluated with platelet-derived indices such as PLR and MPV, which have been shown to reflect inflammatory burden. Therefore, the present study aims to analyze whether PIIV is an effective prognostic biomarker in predicting early mortality in critically ill sepsis patients and will discuss the feasibility of this value being put into clinical use.

MATERIALS and METHODS

Patient selection

This retrospective case-control study was conducted in the ICU department of Çanakkale Onsekiz Mart University Medical Faculty Hospital, January 2021 to December 2024 after ethical authorization from the local institutional ethical committee (Ethical board No: 2025-YÖNP-0129). Patients over 18 years of age, with an exact diagnosis of sepsis based on Sepsis-3 criteria, were included in the study. Sepsis was defined as the presence of an infection together with signs of organ failure, indicated by a SOFA score of 2 or more points [15]. Patients were excluded if they had been transferred from another hospital, were pregnant, had recently undergone surgery, had non-sepsis diagnoses (like trauma, myocardial infarction, or pulmonary embolism), or if lab results for neutrophil, lymphocyte, monocyte, platelet counts, or MPV were missing within the first day of ICU admission. Patients who stayed in the ICU or hospital for less than 24 hours and those with cancer, including blood-related cancers, were also excluded.

Data extraction

Data on demographic, clinical and laboratory parameters collected within 24 hours of admission were all extracted from electronic health files of study participants. Laboratory parameters included complete blood count (WBC, platelet, neutrophil, lymphocyte and MPV), biochemical tests (LDH, ALT, AST, glucose, albumin, urea, creatinine), inflammatory markers (CRP, sedimentation and procalcitonin) and PIIV (calculated as [neutrophil count × platelet count × monocyte count] / lymphocyte count). NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, while PLR was obtained by dividing the absolute platelet count by the absolute lymphocyte count. In cases where a laboratory parameter was measured more than once within the first 24 hours of ICU admission, the first available result was used in the analysis. The primary endpoint was 30-day all-cause mortality after ICU admission.

Statistical analysis

The statistical evaluation was done using SPSS software version 20 (IBM, Armonk, NY). First, all the collected parameters were tested for normal distribution by using the Shapiro-Wilk test. Continuous variables were presented as median with interquartile range (IQR) because most of them did not follow a normal distribution. Categorical data were given as numbers and percentages. Comparisons between survivors and non-survivors were made using the Mann–Whitney U test for continuous variables and the Chi-square test for categorical variables. A p-value of less than 0.05 was considered statistically significant. To analyze the predictive value of the studied parameters for 30-day mortality, univariate and multivariate logistic regres-

sion analyses (LRA) were performed. Variables with significant p-values in univariate analysis were included in multivariate logistic regression to identify independent predictors of mortality. Receiver Operating Characteristic (ROC) curve analysis was also done for selected markers like PIIV, MPV, lactate, and albumin to determine their sensitivity, specificity, and overall diagnostic performance. Area under the curve (AUC) values were calculated, and optimal cut-off points were chosen based on Youden's index.

RESULTS

A total of 191 sepsis patients admitted to internal medicine ICU of Çanakkale Onsekiz Mart University hospital were included in the study. The median age was 76.0 years (64.5-85.0), and 47.6% of the patients were female. Intubation was required in 40.8% of patients. Clinical, laboratory and demographic characteristics of study participants are presented in table 1.

Parameters	All Patients (n = 191)
Baseline characteristics	
Age (years), median (IQR)	76.0 (64.5–85.0)
Female sex, n (%)	91 (47.6%)
Intubation, n (%)	78 (40.8%)
ICU Admission Vital Signs	
Heart rate (/min), median (IQR)	102.0 (88.0–120.0)
Respiratory rate (/min), median (IQR)	22.0 (20.0–24.0)
Systolic blood pressure (mmHg), median (IQR)	99.0 (88.0–118.5)
Mean arterial pressure (mmHg), median (IQR)	76.0 (66.8–87.5)
Body temperature (°C), median (IQR)	36.5 (36.3–36.7)
Complete Blood Count	
WBC (x10^3/uL)	13.8 (10.0-18.9)
Hemoglobin(g/dL)	10.0 (8.5-11.3)
Hemotocrit(%)	31.0 (26.7-35.2)
Platelet(x10^3/uL)	205.0 (129.0-295.0)
PLR	253.8 (146.1-433.1)
Mean Platelet Volume	10.8 (9.8-12.4)
Biochemical measurements	
Blood glocose (mg/dL)	134.0 (109.0-189.0)
Urea (mg/dL)	93.0 (60.0-144.0)
Creatinine (mg/dL)	1.81 (0.96-2.84)
ALT (U/L)	16.0 (9.2-40.5)
AST (U/L)	26.0 (15.0-65.5)
LDH (U/L)	256.0 (188.0-394.0)
Inflammatory parameters	
CRP (mg/L)	170.0 (103.0-259.5)
Procalcitonin(ng/mL)	4.1 (1.0-21.0)
Lactate (mmol/L)	1.7 (1.2-2.9)
PIIV	1634.1 (691.2-3504.6)

IQR, Interquartile Range; ICU, Intensive Care Unit; WBC, White Blood Count; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; LDH, Lactate Dehydrogenase; CRP, C-Reactive Protein; PIIV, pan-immune-inflammation value; PLR, Platelet-to-Lymphocyte Ratio

Table 1. Demographic, clinical and laboratory characteristics of sepsis patients

Among the patients that were analyzed for 30-day mortality, 95 (49.7%) survived while 96 (50.3%) of the patients died. Compared to survivors, non-survivors had significantly higher levels of MPV (p=0.003), WBC (p<0.001), neutrophils (p<0.001), and monocytes (p=0.019). Laboratory parameters, including urea (p<0.001), creatinine (p=0.028), lactate (p=0.001), and LDH (p=0.002), were found to be elevated in non-survivor group. Mean PIIV levels in survivor and non-survivor group were 1150.2 (494.6-2559.0) and 2076.4 (838.9-5537.6) (p=0.001) respectively. In contrast, serum albumin levels were found to be decreased among non-survivor group (p=0.001) (Table 2). The comparison of selected inflammatory and prognostic markers between survivors and non-survivors ara graphically presented in Figure 1. Non-survivors exhibited significantly elevated levels of PIIV, MPV and lactate. Although PLR levels were higher in deceased patients, the difference did not reach statistical significance.

Parameters	**Survivors** n=95 (49.7)	**Deceased** n= 96 (50.3)	**P value**
Demographics			
Age (years), median (IQR)	75.0 (62.5-83.0)	78.0 (65.5-87.0)	0.029
Female sex, n (%)	44 (48.4)	47 (51.6)	0.715
Intubation, n (%)	14 (17.9)	64 (82.1)	<0.001
Complete Blood Count			
WBC (x10^3/uL)	11.4 (8.2-15.9)	16.1 (12.6-21.9)	<0.001
Hemoglobin(g/dL)	9.4 (8.3-11.0)	10.2 (9.1-11.5)	0.062
Hemotocrit(%)	30.5 (26.5-35.0)	31.6 (28.4-35.7)	0.147
Platelet(x10^3/uL)	174.0 (121.0-285.0)	226.5 (131.5-301.0)	0.105
Neutrophil (x10^3/uL)	9.8 (6.6-14.0)	14.0 (10.2-20.5)	<0.001
Lymphocyte (x10^3/uL)	0.73 (0.50-1.21)	0.92 (0.53-1.39)	0.310
Monocyte (x10^3/uL)	0.54 (0.31-0.77)	0.69 (0.41-0.94)	0.019
PLR	233.3 (146.1-441.8)	261.5 (148.9-419.9)	0.478
Mean Platelet Volume	10.7 (9.7-11.5)	11.2 (9.9-13.4)	0.003
Biochemical measurements			
Blood glocose (mg/dL)	130.0 (108.0-173.5)	138.5 (109.5-207.5)	0.334
Urea (mg/dL)	76.0 (51.0-122.0)	112.0 (76.0-170.0)	<0.001
Creatinine (mg/dL)	1.34 (0.87-2.63)	2.04 (1.08-3.25)	0.028
Total bilirubin (mg/dL)	0.6 (0.4-1.0)	0.6 (0.4-1.1)	0.546
ALT (U/L)	18.0 (9.0-36.5)	15.0 (10.0-44.0)	0.738
AST (U/L)	24.0 (14.0-47.5)	29.0 (16.0-116.5)	0.106
LDH (U/L)	227.0 (167.5-369.0)	277.5 (211.5-509.0)	0.002
Albumin (g/dL)	2.9 (2.6-3.2)	2.6 (2.3-2.9)	0.001
Fibrinogen (mg/dL)	432.0 (357.0-592.5)	423.5 (280.0-615.5)	0.270
D-dimer (ug/mL)	4.4 (1.7-8.3)	5.2 (2.1-11.3)	0.154
CRP (mg/L)	161.0 (101.5-264.0)	171.5 (104.5-254.5)	0.697
Procalcitonin(ng/mL)	2.9 (0.7-18.0)	5.0 (1.3-23.5)	0.129
PIIV	1150.2 (494.6-2559.0)	2076.4 (838.9-5537.6)	0.001
Lactate (mmol/L)	1.6 (1.1-2.1)	2.4 (1.3-4.2)	0.001

IQR, Interquartile Range; ICU, Intensive Care Unit; WBC, White Blood Count; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; LDH, Lactate Dehydrogenase; CRP, C-Reactive Protein; PIIV, pan-immune-inflammation value; PLR, Platelet-to-Lymphocyte Ratio

Table 2. Comparison of Demographic and Laboratory Parameters Between Survivors and Non-Survivors in ICU Patients With Sepsis

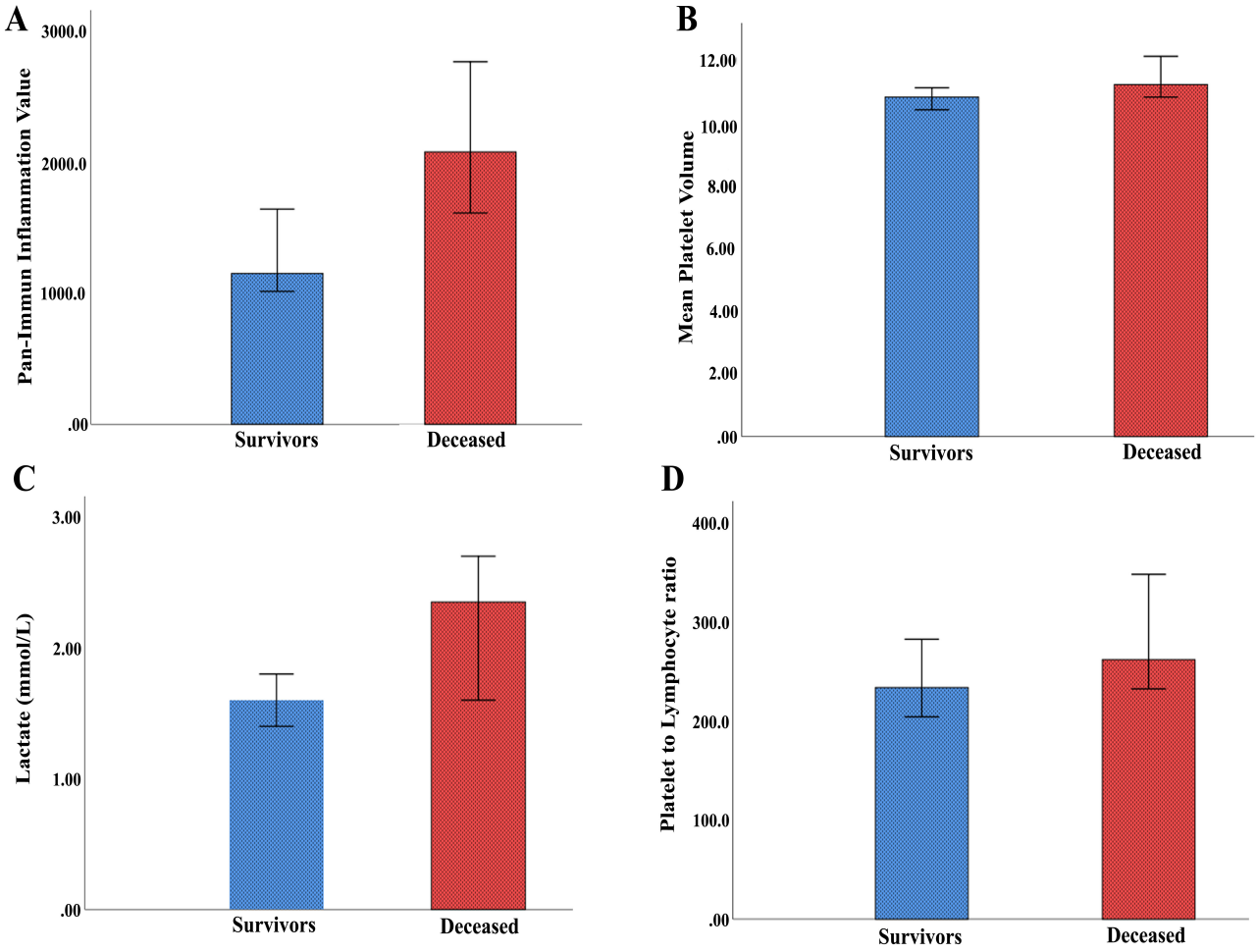

Figure 1. Comparison of inflammatory and prognostic biomarkers between survivors and non-survivors in ICU sepsis patients; (A) Pan-Immune Inflammation Value, (B) Mean Platelet Volume, (C) Lactate, (D) Platelet-to-Lymphocyte Ratio. (Each bar represents the median and interquartile range (IQR) of the corresponding parameter)

In this study we also performed logistic regression analysis for prediction of mortality. In univariable logistic regression analysis several predictors of 30-day mortality was demonstrated: advanced age (OR: 1.023, 95% CI: 1.001–1.047, p=0.041), elevated PIIV (OR: 1.222, 95% CI: 1.088–1.374, p=0.001), increased NLR (OR: 1.023, 95% CI: 1.004–1.041, p=0.016), higher urea (OR: 1.009, 95% CI: 1.004–1.014, p<0.001), AST (OR: 1.002, 95% CI: 1.000–1.003, p=0.037), MPV (OR: 1.341, 95% CI: 1.136–1.583, p=0.001), and lactate (OR: 1.239, 95% CI: 1.078–1.424, p=0.003). Lower albumin levels were associated with decreased survival (OR: 0.376, 95% CI: 0.207–0.685, p=0.001). In multivariable analysis, PIIV (OR: 1.235, 95% CI: 1.086–1.404, p=0.001), MPV (OR: 1.346, 95% CI: 1.111–1.630, p=0.002), urea (OR: 1.007, 95% CI: 1.002–1.013, p=0.011), and lactate (OR: 1.218, 95% CI: 1.056–1.405, p=0.007) remained independently associated with increased mortality (Table 3).

ROC curve analysis demonstrated that PIIV had moderate discriminative ability with an area under the curve (AUC) of 0.643 (95% CI: 0.565–0.721), at a cutoff value of ≥1.2, yielding a sensitivity of 67.7% and specificity of 51.6%. MPV with a cut-off level of ≥11.5 fL, exhibited high specificity (83.2%) with an AUC of 0.623 (Table 4).

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age (years)	1.023 (1.001-1.047)	0.041		
Gender M[F(ref)]	1.112 (0.630-1.962)	0.715		
Comorbidities (n=177)	1.379 (0.460-4.139)	0.566		
PIIV/10^6	1.222 (1.088-1.374)	0.001	1.235 (1.086-1.404)	0.001
NLR	1.023 (1.004-1.041)	0.016		
Urea	1.009 (1.004-1.014)	<0.001	1.007 (1.002-1.013)	0.011
AST	1.002 (1.000-1.003)	0.037		
LDH	1.001 (1.000-1.001)	0.060		
Albumin	0.376 (0.207-0.685)	0.001	0.370 (0.189-0.721)	0.003
Mean Platelet volume	1.341 (1.136-1.583)	0.001	1.346 (1.111-1.630)	0.002
Lactate	1.239 (1.078-1.424)	0.003	1.218 (1.056-1.405)	0.007
Platelet lymhocyte ratio	1.000 (0.999-1.001)	0.908		

PIIV, Pan-Immune-Inflammation Value; NLR, Neutrophil-to-Lymphocyte Ratio; PLR,Platelet-to-Lymphocyte Ratio; MPV, Mean Platelet Volume; AST, Aspartate Aminotransferase; LDH, Lactate Dehydrogenase; ICU, Intensive Care Unit; CI, Confidence Interval; OR, Odds Ratio

Table 3. Univariable and Multivariable Logistic Regression Analysis of Risk Factors Associated With 30-Day Mortality in ICU Patients With Sepsis

Biomarker (Cut-off)	**AUROC (95% CI)**	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**	**PPV % (95% CI)**	**NPV % (95% CI)**	**Accuracy % (95% CI)**
PIIV (≥1.2)	0.643 (0.565–0.721)	67.7 (57.4–76.9)	51.6 (41.1–62.0)	58.6 (52.4–64.5)	61.3 (52.7–69.2)	59.7 (52.4–66.7)
Urea (≥85.5)	0.658 (0.581–0.735)	67.7 (57.4–76.9)	59.0 (48.4–68.9)	62.5 (55.8–68.8)	64.4 (56.4–71.6)	63.4 (56.1–70.2)
Lactate (≥2.0)	0.639 (0.560–0.718)	55.2 (44.7–65.4)	73.7 (63.7–82.2)	68.0 (59.1–75.6)	62.0 (55.8–67.7)	64.4 (57.2–71.2)
Albumin (≤2.7)	0.639 (0.560–0.718)	64.6 (54.2–74.1)	60.0 (49.4–70.0)	62.0 (55.1–68.5)	62.6 (55.0–69.7)	62.3 (55.0–69.2)
MPV (≥11.5)	0.623 (0.544–0.702)	39.6 (29.8–50.1)	83.2 (74.1–90.1)	70.4 (58.8–79.8)	57.7 (53.1–62.1)	61.3 (54.0–68.2)

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; MPV, mean platelet volume; PIIV, pan-immune-inflammation value.

Table 4. *Diagnostic Performance of Selected Biomarkers for Predicting 30-Day Mortality in Sepsis Patients*

DISCUSSION

In this study, the effect of PIIV and other CBC-derived parameters on 30-day mortality was investigated in patients diagnosed with sepsis at the time of ICU admission. Our findings revealed that non-survivor sepsis patients had elevated PIIV in comparison with survivors. Elevated levels of PIIV were found to give high sensitivity, specificity and predictive values for predicting mortality, which suggests its potential as a prognostic marker in sepsis patients. Moreover, MPV levels were found to be elevated in non-survivors and were independently associated with mortality in multivariate analysis, supporting its role as a reliable prognostic marker. Although PLR levels were numerically higher in non-survivors, this difference did not show statistical significance, and PLR was not identified as an independent predictor of mortality in our study.

Sepsis is a systemic inflammatory condition resulting from the dysregulation of the host response and is associated with increased rates of mortality, even with appropriate and timely antimicrobial therapy [16]. Therefore, early prognosticators are essential for early and effective implementation of diagnostic and treatment algorithms PIIV has the potential to meet this need by evaluating various hematological parameters derived from CBC counts and representing the systemic inflammatory response as a whole. The PIIV, which uses the counts of four types of blood cells—monocytes, neutrophils, platelets, and lymphocytes—can express the immunological complexity of sepsis with a single numerical value, particularly reflecting the imbalances that occur between immune cell subpopulations. It might offer a more consistent and precise prediction of poor prognosis [13]. The results obtained in this study revealed that PIIV is strongly associated with mortality. The PIIV value was found to be significantly higher in the exitus group and was independently associated with mortality in multivariate regression analysis, regardless of other clinical and biochemical factors (AUROC 0.643, 95% CI 0.565–0.721, OR: 1.235, p = 0.001). In addition, according to ROC analysis, PIIV values above 1.2 were able to predict 30-day mortality with 67.7% sensitivity and 51.6% specificity with a PPV of 58.6% and NPV of 61.3%, respectively. These rates are at a level that may hold clinical significance, considering the heterogeneous nature of sepsis.

PIIV was initially reported as a novel systematic inflammatory marker as a predictor of survival outcomes, demonstrating superior performance compared to other inflammatory biomarkers in metastatic colorectal cancer patients [17]. Because of its promising capacity to broadly reflect a patient's immunity and systemic inflammation, PIIV has gained more interest from researchers around the globe. Consequently, PIIV has been demonstrated to be a promising marker of prognosis in several disease states, including tumors, pulmonary embolism, inflammatory conditions, rheumatologic disorders, and coronary heart diseases [8-11,18-22]. The underlying pathophysiology of sepsis, including inflammation and immune dysregulation, led us to investigate the relation between PIIV and the prognosis of septic patients. In this context, the study by Xu et al. [23] is one of the largest studies to date, including 11,331 septic patients and exploring the relationship between PIIV and mortality. Authors demonstrated a non-linear association between PIIV and 28-day mortality risk in sepsis patients. Contrary to this finding, Turan et al. [14] found PIIV as a potential marker that could predict longer survival in septic shock patients, however in multivariate analysis this association with mortality was not statistically significant.

Apart from traditional inflammatory markers, this study also explored MPV as a platelet-derived index as a marker of mortality prediction solely and in conjunction with PIIV. We demonstrated that MPV was a significant predictor in both univariate and multivariate LRA (p=0.002) and reached an AUROC of 0.623 in ROC analysis. MPV is a readily accessible marker of platelet function and activation that can be obtained from CBC counts with no additional cost and is influenced by inflammatory conditions [24,25]. MPV is evaluated as a parameter reflecting the activation status of platelets and as a marker of processes such as endothelial damage and microthrombosis in sepsis [24]. Increased MPV levels are determined in conditions such as acute pancreatitis (AP), ulcerative colitis, tumoral diseases, myocardial infarction, and diabetes mellitus [26-29]. Furthermore, accumulating evidence suggests that MPV is also increased in sepsis patients. In a recent study by Gupta et al. [30], it was shown that MPV and platelet distribution width increased, while plateletcrit decreased as the severity of sepsis increased. Similarly, in an elegant study by Djordjevic et al. [31] MPV was shown to be very good independent predictor of lethal outcome in sepsis patients. Taken together, these findings emphasize the capacity of MPV as a valuable and independent prognostic biomarker in patients with sepsis.

This study additionally explored the role of NLR and PLR in mortality prediction in sepsis patients and found only NLR as significant predictor of mortality only in univariate (OR: 1.023, p = 0.016) analysis. Ratios such as NLR and PLR also stand out as simple and rapid markers reflecting the immune system balance in sepsis. NLR is especially important in terms of evaluating neutrophil increase and lymphocytopenia together and is thought to reflect the proinflammatory load in sepsis patients [32]. Although PLR did not exhibit a significant association with mortality in either univariate or multivariate analysis, it remains a widely studied inflammatory marker that has been associated with prognosis in various diseases. An

elevated PLR reflects both an increased platelet count, which is related with thrombosis and pro-inflammatory activity, and a decreased count of lymphocytes indicates suppressed adaptive immune response during systemic inflammation. This dual alteration makes PLR a valuable indicator of the balance between pro-inflammatory and regulatory immune mechanisms [33]. In our study, NLR was found to be independently associated with sepsis associated mortality similar to the studies by Barekatain et al. [34] and Wang et al. [35]. These findings support the evidence that suggests NLR not only readily available and cost-effective a laboratory biomarker, but also a valuable tool for early risk stratification in sepsis patients.

There are some limitations of the study that need to be mentioned. First of all, the retrospective design is a restrictive factor that limits the ability to understand cause-effect relationships. Second, the generalizability of the results may be limited due to the single-center nature of the study. Third, the alterations in PIIV over time were not evaluated; whether this value becomes more significant with dynamic follow-up should be investigated in prospective studies. Finally, various potential confounding factors (e.g., treatment protocols used, infectious agents) could not be controlled, which may have affected the final results.

In conclusion, PIIV and MPV in conjunction with other traditional inflammatory markers stand out as a significant and independent marker in predicting sepsis related mortality. All of the studied parameters have high applicability in clinical practice due to their easy calculation and their reliance on commonly used hematological parameters. Additionally, PIIV may contribute to early risk stratification and treatment planning by providing a more comprehensive immune response assessment compared to existing inflammation markers.

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