



The Predictive Value of Systemic Immune Inflammation Index in Patients Hospitalized in the Intensive Care Unit

Yoğun Bakım Ünitesinde Yatan Hastalarda Sistemik İmmün Enflamasyon İndeksinin Prediktif Değeri

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ABSTRACT

Objective: The systemic immune-inflammation index (SII), predicated on peripheral platelet, neutrophil, and lymphocyte counts, has been shown to be an effective predictive tool in different illnesses. We examined the role of the baseline SII in predicting short-term outcomes in patients hospitalized in the intensive care unit (ICU).

Methods: The data of patients followed in the ICU between January 01, 2019 and December 31, 2019, were included in the study. Demographic data, the length of stay in the ICU, additional diseases, Acute Physiology and Chronic Health Evaluation-II score, presence of comorbidity and mortality, and complete blood count test results were recorded from electronic files. The SII was calculated as platelet \times neutrophil/lymphocyte counts. The predictive value of SII on the clinical outcomes (length of stay, and 30-day mortality) were investigated retrospectively.

Results: Based on the inclusion and exclusion criteria, 201 patients (104 female and 97 male) were selected to be included. The median age [interquartile range (IQR): 61-82] was 73. The median length of stay in the hospital was 19 days (IQR: 8-32). Fifty-nine (n=59) patients (29.3%) died, leaving 142 patients (70.64%) who were discharged alive. Non-survivors had significantly higher SII values, (median; 1,566; IQR: 812-3,455 vs. 1,019; IQR 599-1,771, p=0.037) compared to survivors. The hazard ratio (95% confidence interval) for the high-SII group compared with the low-SII group for 30-day all-cause mortality was 2.61 (1.33-4.79), and 1.23 (0.71-2.61) respectively.

Conclusion: In ICU patients, a high SII was linked to higher mortality. Consequently, SII is a predictive biomarker of patients that may be valuable. Additional research should be conducted to assess our findings using prospective trials with longer follow-ups.

Keywords: Systemic immune inflammation index, intensive care, predictivity

ÖZ

Amaç: Periferik kanda, trombosit, nötrofil ve lenfosit sayılarına dayanan sistemik immün-enflamasyon indeksinin (SII) farklı hastalıklarda etkili bir öngörücü aracı olduğu gösterilmiştir. Bu çalışmanın amacı, yoğun bakım ünitesinde (YBÜ) yatan hastalarda kısa dönem sonuçları tahmin etmede başlangıç SII'nin rolünü araştırmaktır.

Gereç ve Yöntem: 01 Ocak ile 31 Aralık 2019 tarihleri arasında YBÜ'de izlenen hastaların verileri çalışmaya dahil edildi. Demografik veriler, YBÜ'de kalış süresi, ek hastalıklar, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II skoru, komorbidite ve mortalite varlığı ve tam kan sayımı test sonuçları elektronik dosyalardan kaydedildi. SII, trombosit \times nötrofil/lenfosit sayıları olarak hesaplandı. SII'nin klinik sonuçlar (kalış süresi ve 30 günlük mortalite) üzerindeki prediktif değeri geriye dönük olarak araştırıldı.

Bulgular: Dahil etme ve hariç tutma kriterlerine göre, dahil edilmek üzere toplam 201 hasta (104 kadın ve 97 erkek) seçildi. Medyan yaş 73 [çeyrekler açıklığı (IQR): 61-82] bulundu. Hastanede ortalama kalış süresi 19 gündü (IQR: 8-32). Elli dokuz (n=59) hasta (%29,3) öldü, 142 hasta (%70,64) sağ olarak taburcu edildi. Ölen hastalar, hayatta kalanlara kıyasla önemli ölçüde daha yüksek SII değerlerine sahipti (medyan; 1.566; IQR: 812-3.455 ve 1.019; IQR 599-1771, p=0,037). Otuz günlük tüm nedenlere bağlı ölüm için düşük SII grubuna kıyasla yüksek SII grubu için risk oranı (%95 güven aralığı) sırasıyla 2,61 (1,33-4,79) ve 1,23 (0,71-2,61) idi.

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Sonuç: YBÜ hastalarında yüksek SII, daha yüksek mortalite ile bağlantılıydı. Sonuç olarak, SII, yoğun bakım hastalarının sonuçları için öngörücü bir biyobelirteç olabilir. Ancak, bulgularımızı doğrulamak için daha uzun takip süreli, prospektif ek araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Sistemik immün enflamasyon indeksi, yoğun bakım, prediktivite

INTRODUCTION

In systemic inflammation, changes in peripheral blood such as neutrophilia, lymphopenia and thrombocytosis are observed (1). In the last decade, new biomarkers that can be easily calculated using complete blood count (CBC) parameters have been used in the determination of systemic inflammation. The indices obtained with the ratios of hematological parameters in the CBC test are accepted as a good indicator of the systemic inflammatory response, and are suggested as biomarkers to support in the identification, monitoring, and risk assessment of many diseases (2-5). The severity and mortality of various inflammatory conditions especially cancer have been predicted using hematological inflammation indices, such as the neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio, platelet/lymphocyte ratio (PLR) (6-8). Systemic inflammation index (SII) was first described as a promising tool for determining hepatocellular carcinoma (HCC) treatment strategy and a powerful prognostic indicator of poor outcome in patients with HCC (9). It has been proposed as a potent predictive tool of poor outcomes in individuals with many types of malignancies and other disorders (10-16). Much research revealed that a higher SII is preferable to NLR and PLR for reflecting the balance of the host's inflammatory and immune condition.

Intensive care scoring systems are used to standardize patient participation in clinical trials and compare the effectiveness of intensive care units (ICU) by predicting recovery from illness, assessing the severity of the disorders and the degree of organ dysfunction, and evaluating treatments (17,18). In scoring, patient records from regular analyses are utilized and many clinical rating systems are defined. These systems consist of two parts: "prognostic" for predicting mortality, and "organ failure" scoring systems to assess morbidity. One of the many in ICU scoring systems is Acute Physiology and Chronic Health Evaluation-II (APACHE-II), which classifies disease severity (19). APACHE-II assess acute physiology, age, and chronic health and outcomes from these three segments collected and patient mortality was calculated. Data used in APACHE-II are the values that differ most from average in the first 24 h in the ICU. The chronological age reveals the decline in physical backup and is a significant feature in determining the possibility of death in acute illness, irrespective of illness severity. For this reason, it has been

added as a weighted score. In APACHE-II, when the total score is 25, estimated mortality is 25% and, when the score is above 35, this prediction value rises above 80% (20,21). This recording method has some shortcomings. Aging patients can receive a score greater than needed. There are no regulated measurements for mechanical ventilation or the medications for hemodynamic care treatment in the acute physiology score. Additional studies of predicting mortality among these elder critical patients should be undertaken (22,23). This study was designed to retrospectively explore the association among APACHE-II score and mortality in patients hospitalized in the anesthesia and reanimation ICU of a tertiary hospital.

METHODS

This study included data on patients who go through ICU in the anesthesia and reanimation department of a third hospital between January-December 2019. The hospital information system (HIS) was used to obtain information on the clinical features, lab test findings, and clinical outcomes of the patients who were enrolled. The HIS was used to obtain information on the clinical features, lab test findings, and clinical outcomes of the patients who were enrolled. Adult patients and a diagnosis-requiring ICU hospitalization were the inclusion criteria. Exclusion criteria were attendance of malignancies and coexisting chemotherapy and immunosuppressive usage, patients using drugs or blood products that affect the CBC, under 18, pregnancy, and lack of necessary data. Consequently, data of 201 patients were involved in the final study.

In accordance with the Declaration of Helsinki, data were obtained from hospital records after the patients gave their consent to share their data and the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approved the collection (decision no: 2022-160, date: 07.09.2022). Age, gender, previous medical history, ICU risk factors, APACHE-II score, therapeutic care, and laboratory assessment were recorded. After being admitted to the ICU, all parameters were measured within 24 h. In the laboratory, Sysmex XE-5000 was used for CBC measurement. In the presence of preanalytical factors such as holding, clotting, and transfer conditions that adversely affect the platelet count, the sample was rejected and not analyzed. No technical abnormalities or flags were noted on resulting screening of Sysmex XE-5000. All patients were

then monitored for 30 days. Retrospective records of the clinical outcomes were analysed as related to SII.

The SII was calculated from the platelet (reference range: $150\text{--}400 \times 10^3/\mu\text{L}$), neutrophil (reference range: $1.8\text{--}6.98 \times 10^3/\mu\text{L}$), and lymphocyte (reference range: $1.26\text{--}3.35 \times 10^3/\mu\text{L}$), counts using the formulation: $\text{SII} = \text{platelet} \times \text{neutrophil} / \text{lymphocyte}$ counts as defined previously (9). The SII was expressed as $\times 10^3/\mu\text{L}$. The relationship between the SII and the APACHE-II score at the time of admission to the ICU and 30-day mortality was examined. The efficacy of SII and other hemogram parameters in determining ICU mortality was investigated using the "receiver operating characteristic (ROC) curve." Sensitivity and specificity were calculated according to standard formulas (24). In comparing the results, the area under the curve (AUC) in the ROC analysis was calculated (the value must be between 0.5-1.0 for it to be significant; 1.0 indicates the most significant relationship).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). Categorical variables were expressed as numbers and percentages. Mann-Whitney U test was used to compare the numerical variables with non-normally distributed between the two groups. Non-normally distributed numerical variables are expressed as medians [minimum-maximum (max)]. In a comparison of categorical data, chi-square and Fisher's Exact chi-square tests were used. The relationship between numerical variables was evaluated with Spearman correlation analysis. In statistical analysis, $p < 0.05$ (*) value was set as significant. The relationship between SII and 30-day mortality was also estimated with Cox proportional hazard regressions, and the consequences were shown as hazard ratios (HR) and 95% confidence intervals (CIs).

RESULTS

The study population consisted of 201 patients, 104 females (51.7%) and 97 males (48.3%). The median age was 73 [interquartile range (IQR): 61-82] years old. Comorbid disease was present in 95.5% ($n=179$) of the study population. The max shared comorbidities are hypertension (50.7%; $n=102$), diabetes mellitus (40.1%; $n=81$), chronic kidney disease (28.8%; $n=58$), coronary artery disease (24.3%; $n=49$). Pneumonia ($n=67$, 33.3%) was the most common cause for admission to the ICU, and sepsis developed in 35.2% ($n=71$) of the patients. The median length of stay in the ICU was 19 days (IQR: 8-32). It was determined that 29.32% of the patients ($n=59$) died from various reasons in the 30-day survival. Survivors had significantly longer hospital stays

than non-survivors (median: 24 days, IQR: 14-36 days vs. 15 days, IQR 12-19 days). The baseline characteristics and related information between survivors and non-survivors are presented in Table 1. Also, the distribution of APACHE-II scores and laboratory findings of the patients on admission to the ICU according to survival are shown in Table 1. SII was significantly higher in the non-survivor cohort (median; 1,566; IQR: 812-3,455 vs. 1,019; IQR 599-1,771, $p=0.001$). The HR (95% CI) for the high-SII group compared with the low-SII group for 30-day all-cause mortality was 2.61 (1.33, 4.79), and 1.23 (0.71, 2.61) respectively (Table 2). The sensitivity of SII over 1635 in determining mortality was 78.6%, and the specificity was 71.8%. The AUC in ROC analysis for SII was calculated as 0.823 (95% CI: 0.789-0.856).

DISCUSSION

Ratios derived from hemogram, which have been frequently used recently, can be an efficient implement in enabling the initial classification of patients in the ICU. We conducted a retrospective observational data study to investigate the capability of a SII to predict in-ICU mortality. Using Cox regression models, we observed a positive correlation between SII and all-cause mortality in ICU patients. Recently, SII, that involves three important immune cells, including neutrophil, lymphocyte, and platelet, is regarded as a good predictor of both local immunological response and systemic inflammation. This ratio can also be predictive in intensive care patients in terms of feasibility, ease of use and usability. Prognostic scoring systems are analyses of illness severity implemented to anticipate outcomes, usually mortality, of patient populations in the ICU (23). APACHE-II is one of the "prognostic scoring systems" that is widely used in ICUs and estimate mortality by evaluating the severity of the disease. The most important deficiency of APACHE-II is the lack of evaluation criteria for haemodynamic support therapy and mechanical ventilation. In addition to clinical scoring systems, the predictive contribution of indices obtained from the CBC can enable appropriate analyses and treatment to be occupied initially during the clinical progression.

Leukocytes create a physiological response to stress, and this response is manifested by a proliferation of neutrophils and a decline of lymphocytes. Although the main task of platelets is on the hemostasis and coagulation system, an increase in the proliferation of the megakaryocytic lineage and a consequent increase in the number of platelets are observed in chronic inflammatory processes. The lymphocyte count tends to decrease due to increased apoptosis. All these values are a single collection under

Table 1. Comparisons of baseline characteristics and lab findings between the survive and the non-survive group

Parameter	All cohort (n=201)	Survivors (n=142)	Non-survivors (n=59)	p-value
Demographics				
Age, years (median, IQR)	73 (61-82)	69 (61-78)	79 (74-82)	0.001
Gender, n (%)				
Male	97 (48.3%)	66 (68.1%)	31 (31.9%)	0.211
Female	104 (51.7%)	76 (73%)	28 (27%)	-
Comorbidities, n (%)				
Hypertension	102 (50.7%)	69 (48.6%)	33 (55.9%)	0.117
Diabetes mellitus	81 (40.1%)	54 (38%)	27 (45.7%)	0.322
Chronic kidney disease	58 (28.8%)	38 (26.7%)	20 (33.8%)	0.172
Coronary artery disease	49 (24.3%)	33 (23.2%)	16 (27.1%)	0.205
ICU admission reasons n (%)				
Pneumonia	67 (33.3%)	39 (27.4%)	28 (47.45%)	0.012
Acute kidney disease	25 (12.1%)	17 (11.9%)	8 (13.55%)	0.125
Gastrointestinal event	31 (25.4%)	24 (16.9%)	7 (11.8%)	0.119
Others	78 (38.8%)	-	-	-
Sepsis	71 (35.2%)	-	-	-
Length of ICU stay, days (IQR)	19 (8-32)	24 (14-36)	15 (12-19)	0.021
APACHE-II	19 (5-43)	18 (6-41)	20 (7-43)	0.204
Lab findings on admission				
Hemoglobin, g/dL	10.90 (9.80-12.20)	11.20 (9.60-12.40)	10.60 (9.30-11.70)	0.023
WBC (×10 ³ μL)	10.75 (5.00-15.32)	11.05 (5.20-14.30)	9.640 (4,80-19.60)	0.014
Neutrophils (×10 ³ μL)	8.14 (9.20-10.48)	8.10 (6.66-9.40)	8.90 (6.60-12.20)	0.12
Lymphocytes (×10 ³ μL)	1.10 (0.65-1.25)	1.15 (0.80-1.20)	0.80 (0.70-1.00)	0.033
Monocytes (×10 ³ μL)	0.45 (0.30-0.60)	0.50 (0.35-0.65)	0.35 (0.25-0.55)	0.62
Platelets (×10 ³ μL)	214 (172-275)	225 (179-267)	194 (165-255)	0.45
SII (median, IQR)	1,148 (756-2,483)	1,019 (599-1,771)	1,566 (812-3,455)	0.037

All continuous variables are reported as medians and IQRs. Statistical significance set at 0.05.

ICU: Intensive care unit, WBC: White blood cells, SII: Systemic immune inflammation index, IQR: Interquartile range, APACHE-II: Acute Physiology and Chronic Health Evaluation-II

the parameter-formed SII. It has been suggested in recent publications that this value, which is formed from whole blood parameters involved in the inflammation process, should be used as an indicator of inflammation. In a study by Dey et al. (25), assumed the collective impact of pro-inflammatory and pro-thrombotic corpuscular lines in

calculating the new indices, SII represents a modest and reproducible factor representing the possible of describing the patients susceptible to poor results later off-pump coronary artery bypass grafting (26). It has been reported that SII, which is one the inflammatory parameters, cheap and easily available, can be a good predictor in predicting

Table 2. Cox regression analysis for the risk factors associated with 30-day mortality

Variables	30-day mortality		p-value
	HR	95% CI	
Age (per 1 year increase)	1.03	1.01-1.12	0.014
APACHE-II			
<18	1	-	-
>20	1.49	0.31-4.73	0.151
SII			
<1,019	1	-	-
1,019-1,566	1.21	0.73-2.67	0.013
>1,566	2.61	1.33-4.79	0.011

All statistically significant values are reported in bold.

HR: Hazard ratio, CI: Confidence interval, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SII: Systemic immune-inflammation index

most important adverse cardiac and cerebral accidents later bypass surgery (26). In the other study intended to elucidate the possible prognostic meaning of SII, expressed it effectively predicts 30- and 90-day mortality and the great risk of the existence of main cardiac adverse actions (27). It was stated that in coronavirus disease-2019 patients, SII at admission independently predicted in-hospital mortality and helped with early risk stratification in this group (28,29). SII is also a possibly valuable predictive tool for acute pancreatitis that is an illness defined as acute inflammation of the pancreas (30). The index of SII may guess intravenous immunoglobulin resistance, myocarditis, valve regurgitation in Kawasaki disease as a specific factor (31). SII has also been recognized as a predictive marker in several cancers (10-13). In most of these studies, SII was preferable to other indices. The cause for the advantage of the SII can be explained in the following way: there is a lymphopenia, and this is due to augmented inflammatory response and high cortisol levels triggered by an enlarged sympathetic activity. The increased neutrophil count is thought to be subordinate to the increased inflammatory response. The inflammatory reaction may be tributary to increased oxygen radicals due to hypoxia-induced reperfusion injury or may be related with a thorough increase in interleukin (IL)-6, IL-8, P-selectin, tumor necrosis factor alpha in inflammatory cells because of endothelial damage (32). Enlarged platelet in patients might be related to platelet activation. This is due to inflammation or associated with increased catecholamine secretion induced by comorbidity, high oxidative stress and endothelial damage. Therefore, SII is accepted as a parameter that shows both high neutrophil levels reflecting acute inflammation, low lymphocyte levels reflecting

physiological stress, and negative effects of thrombocytosis induced by endothelial damage.

CONCLUSION

In our study, the multivariate Cox regression models showed that the SII was significantly related to survival after correction for age, and APACHE score. This index has only three components, is easily calculated and inexpensive. The fact that our study was retrospective conducted at a single center and therefore only included few patients is its most significant limitation. Another limitation is due to the study's retrospective design, the effects of highly sensitive inflammatory parameters like IL-6, procalcitonin, and C-reactive protein could not be assessed. To understand the mechanism of SII's impact on poor results, prospective studies involving many patients are required.

ETHICS

Ethics Committee Approval: In accordance with the Declaration of Helsinki, data were obtained from hospital records after the patients gave their consent to share their data and the Bakirköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee approved the collection (decision no: 2022-160, date: 07.09.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: C.K., Concept: H.Y., C.K., A.G., Design: H.Y., C.K., A.G., Data Collection or Processing: H.Y., C.K., A.G., Analysis or Interpretation: H.Y., C.K., A.G., Literature Search: H.Y., A.G., Writing: H.Y., A.G.

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