Current Journal Of Medical Research 2023;3(2) 43-52 Araştırma Makalesi

The Prognostic Importance of the Systemic Immune Inflammation Index (SII) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Kronik Obstruktif Akciğer Hastalığı (KOAH) Tanılı Hastalarda Sistemik İmmün İnflamasyon İndeksinin (SII) Prognostik Önemi

Abstract

Aim: The aim of this study was to evaluate the prognostic significance of the Systemic Immune Inflammation Index (SII) in patients with a diagnosis of Chronic Obstructive Pulmonary Disease (COPD). We will evaluate whether SII is a simple and effective index that can be used to predict emergency department outcomes in patients with COPD.

Materials and Methods: This study was planned as a single-center retrospective observational study. Patients older than 18 years of age who were diagnosed with COPD exacerbation in the emergency department were included, and complaints, laboratory characteristics, and background information of the patients were accessed and recorded in the data registration form. SII=Platelet count x Neutrophil count/Lymphocyte count was calculated and its power in predicting outcome was analyzed.

Results: A total of 177 patients were included in the study, and the mean age was calculated as 72.11±9.96 years. Dyspnea was found to be the most common complaint in 159(89.8) patients. While 123 of the patients were discharged from the emergency department; 22 of them were admitted to the service and 32 of them were admitted to the intensive care unit. It was observed that 68 of 177 patients resulted in exitus. In the analysis of the area under the curve for the outcome, it was statistically determined that the SII value is a differential diagnosis($p<0.001$). The significant differential diagnosis value for SII in the outcome is over 2282.54. However, SII is not a differential diagnosis for survivors in COPD patients ($p=0.572$).

Conclusion: Our results show that SII can be used as an indicator of outcomes in COPD patients and a potential tool in the evaluation of the prognosis of the disease.

Keywords: COPD, SII, Prognosis, Inflammation, Emergency department

Özet

Amaç: Bu çalışmanın amacı, Kronik Obstruktif Akciğer Hastalığı (KOAH) tanılı hastalarda Sistemik İmmün İnflamasyon İndeksi'nin (SII) prognostik önemini değerlendirmektir. SII'nin KOAH hastalarının acil serviste sonlanımını öngörmek için kullanılabilecek basit ve etkili bir indeks olup olmadığını değerlendireceğiz.

Gereç ve Yöntem: Bu çalışma tek merkezli retrospektif gözlemsel bir çalışma olarak planlanmıştır. 18 yaşından büyük olan ve acil serviste KOAH alevlenme tanısı konulan hastalar dahil edilmiş olup hastaların sistem üzerinden başvuru şikayeti, laboratuvar özellikleri ve özgeçmiş bilgilerine ulaşılıp veri kayıt formuna not edilmiştir. SII = Trombosit sayısı x Nötrofil sayısı/Lenfosit sayısı formulü ile hesaplanıp sonlanımı öngörmedeki gücü analiz edilmiştir.

Bulgular: Çalışmaya toplam 177 hasta dahil edişmiş olup ortalama yaş 72,11±9,96 olarak hesaplandı. En sık başvuru şikayetinin 159 (89,8) hastada görülen dispne olduğu bulundu. Hastaların 123 tanesi acil servisten taburcu olurken; 22 tanesi servise, 32 tanesi yoğun bakım ünitesine yatırıldı. 177 hastadan 68 tanesinin exitus ile sonuçlandığı görüldü. Sonlanım için yaptığımız eğri altında kalan alan analizinde SII değerinin ayırıcı bir tanı olduğu istatistik olarak belirlenmiştir ($p<0,001$). Sonlanımda SII için anlamlı ayırıcı tanı değeri 2282,54 üzerinde olmasıdır. Fakat SII, KOAH hastalarında survivor için ayırıcı bir tanı değildir ($p=0,572$).

Sonuç: Sonuçlarımız, SII'nin KOAH hastalarında sonlanımın bir göstergesi olarak kullanılabileceğini ve hastalığın prognozunun değerlendirilmesinde potansiyel bir araç olabileceğini göstermektedir.

Anahtar Kelimeler: KOAH, SII, Prognoz, Inflamasyon, Acil servis

Received/Geliş : 05.08.2023

Accepted/Kabul: 16.08.2023

Publication date:31.08.2023

Efe KANTER
(Corresponding Author)

Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Emergency Medicine, Izmir, Turkey.
efekanter@hotmail.com,
https://orcid.org/0000-0002-0208-950X

Umut PAYZA

Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Emergency Medicine, Izmir, Turkey.
umutpayza@hotmail.com,
https://orcid.org/0000-0002-5297-1066

Semih Musa COSKUN

Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Emergency Medicine, Izmir, Turkey.
semihmusacosgun@gmail.com,
https://orcid.org/0009-0005-6495-1205

Elif KAYMAZ

İzmir Katip Celebi University, Faculty of Medicine, Department of Biostatistics, Izmir, Turkey.
kaymaz.elif@yahoo.com,
https://orcid.org/0000-0003-2631-3067

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease in which airflow is constantly obstructed, primarily caused by factors such as smoking and air pollution (1). The disease is an increasing health problem worldwide and tends to be seen especially in the elderly population (1,2). COPD patients usually present to the emergency department with symptoms such as shortness of breath, cough, and sputum production (3). Admissions to the emergency department are usually the result of an exacerbation of the disease, which may negatively affect the quality of life and prognosis of patients with COPD (3,4). Several parameters, such as the general condition of the patient, severity of COPD, respiratory and heart rate, oxygen saturation, and comorbid diseases can be used to predict the outcome of COPD patients in the emergency department (5).

Systemic Immune Inflammation Index (SII) is a parameter calculated from neutrophil, platelet, and lymphocyte counts (6). SII is calculated using the formula of neutrophil count times platelet count divided by lymphocyte count (6). SII has been used as a prognostic tool in several studies, especially in the field of oncology (7,8,9). SII has been associated with the ability to predict the prognosis of patients in several cancer types, including hepatocellular carcinoma, gastric cancer, bladder cancer, and esophageal cancer (7,8,9). There are limited studies on the ability of SII to predict prognosis in patients with COPD. However, some studies have shown that SII has potential value in predicting the risk of exacerbation of the disease in COPD patients (10).

In COPD, the effects of many different indices such as BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index on prognosis, as well as markers such as C-reactive protein (CRP) and procalcitonin, which are indicators of inflammation, were investigated (11,12). However, there is no clear biomarker or classification recommended by the guidelines as a prognostic indicator. This study aims to predict the prognosis in COPD patients using SII, which can be easily calculated from laboratory parameters. Learning more about the potential role of SII in determining the prognosis of COPD is an important step toward personalizing patients' treatment and improving outcomes.

MATERIALS AND METHODS

Study design

This study was planned as a single-center retrospective observational study. It was started after the patients between 1.1.2023 and 1.6.2023 were included in the tertiary training and research hospital emergency department and after the approval of our hospital's non-interventional research ethics committee before starting the study.

Study population

Adults (over 18 years of age) and patients who presented to the emergency department with COPD exacerbation symptoms, such as shortness of breath, cough, and increased sputum and diagnosed with COPD exacerbation were included in this study. Patients under the age of 18, trauma patients, patients with missing data, and patients whose outcomes could not be followed up (referred or refused treatment) were excluded from the study. Some diseases may cause differences in hemogram parameters, but patients who have these diseases were not excluded from the study.

Study protocol and data collection

Complaints at presentation, laboratory characteristics, and background information of the patients included in the study were accessed through the system and recorded in the data registration form. Laboratory characteristics were sorted and categorized. Through the hemogram parameters, Platelet count, Neutrophil count, and Lymphocyte count were used to calculate the SII index. The “SII = Platelet count x Neutrophil count/Lymphocyte count” formula was calculated and its power in predicting outcome was investigated. Background information and application complaints of the patients with other laboratory parameters were examined whether there is a relationship with the SII index. The recorded data was used for statistical analysis.

Statistical Analysis

Number and percentage were calculated for categorical variables, and mean and standard deviation for numerical variables. Histogram curves, kurtosis, skewness, and the Shapiro-Wilk test were employed to determine whether continuous variables were normally distributed. Student-t-test was used to compare the means of the two groups. All statistical calculations were carried out on SPSS 22.0 software and at a 95% confidence interval.

RESULTS

A total of 177 patients were included in the study and 62 of them were women. The mean age was calculated as 72.11±9.96 years. Dyspnea was found to be the most common complaint in 159 (89.8) patients. While 123 of the patients were discharged from the emergency department; 22 of them were admitted to the service and 32 of them were admitted to the intensive care unit. It was observed that 68 of 177 patients resulted in exitus. The descriptive characteristics of the patients are presented in Table 1.

Table 1: Descriptive Characteristics of the Patients (n=177)

Variables	Statistics
Age	
$\bar{x}$±sd	72,11±9,96
M (min-max)	72 (41-92)
Sex, n (%)	
Female	62 (35,0)
Male	115 (65,0)
Complaint, n (%)	
Dyspnea	159 (89,8)
Cough	5 (2,8)
Increase in sputum	3 (1,7)
Chest pain	10 (5,6)
Outcome, n (%)	
Discharge	123 (69,5)
Service Admission	22 (12,4)
ICU	32 (18,1)
Survivor, n (%)	
Survivor	109 (61,6)
Ex	68 (38,4)

$\bar{x}$: Mean, sd: Standart deviation, M: Median
ICU: Intensive care unit

When the measurement parameters including vital signs and laboratory data of the patients were examined, respiratory rate was higher than normal with an average of 20.27±3.60, WBC value was higher than normal, sat o2 value was lower than normal with 87.93±14.28, PaO2 value was average 76 It was found that it was lower than normal with .26±32.44, and the CRP value was found to be higher than normal with an average of 64.09±80.40. The mean SII value of all patients was calculated as 2573.47±4191.99. Measurement Parameters of the Patients are presented in Table 2.

Table 2: Measurement Parameters of Patients

Variables	Statistics	
	$\bar{x}$±*sd*	*M* (*min-max*)
Sistolic BP	141,75±31,55	135 (78-251)
Diastolic BP	76,58±14,81	78 (33-120)
Heart rate	91,80±19,71	90 (52-190)
Respiratory rate	20,27±3,60	20 (12-40)
Fever	36,35±0,26	36,3 (34,5-38)
WBC	10,9±4,93	9,35 (3-29,34)
Neutrophil	9,19±9,24	7,06 (1,7-85,8)
Eosinophil	0,32±1,37	0,1 (0-14)
Lymphocyte	1,69±1,51	1,39 (0,1-11,7)
Platelets	262,88±111,72	251 (2,4-989)
SII	2573,47±4191,99	1247,75 (5,42-35919,66)
Hgb	13,81±15,18	12,4 (5,6-195)
SpO2	87,93±14,28	93,9 (27-100)
PaO2	76,26±32,44	70 (24-207)
PaCO2	43,90±14,01	40,1 (7,4-95,7)
pH	7,33±0,51	7,4 (0,7-7,72)
Lactate	1,60±1,23	1,2 (0,3-8,9)
Creatinine	4,83±45,06	1,12 (0,06-599)
BUN	27,45±19,73	21 (5-124)
AST	45,52±187,44	22 (1-2468)
ALT	28,87±89,25	15 (3-1037)
Total bilirubin	0,58±0,45	0,5 (0,04-4,40)
Direct bilirubin	0,20±0,23	0,16 (0-2,4)
Indirect bilirubin	0,37±0,28	0,31 (0-2)
CRP	64,09±80,40	26,7 (0,4-394)
Sodium	137,26±10,40	138 (13,6-156)
Potassium	4,74±0,73	4,68 (3,37-9,7)
Calsium	8,89±0,88	9 (1,04-10,3)
INR	1,35±1,50	1,13 (0,31-19,45)
PT	14,71±5,20	13,6 (10,6-56)
APTT	31,87±6,41	31 (12,1-59)

$\bar{x}$: Mean, sd: Standart deviation, M: Median

BP: Blood Pressure, WBC: White Blood Cells, SII: Systemic Immune Inflammation Index, BUN: Blood Urea Nitrogen, AST: Aspartate Transaminase, ALT: Alanine Transaminase, CRP: C-Reactive Protein, INR: International Normalized Ratio, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time

The area under the curve for the SII value is statistically significant p<0.001 (0.705 (0.632-0.771)). The differential diagnosis value for SII is over 2282.54. In the analysis of the area under the curve for the outcome, it was statistically determined that the SII value is a differential diagnosis. In addition, the fact that this value is above 2282.54 is an important indicator in the selection of patients.

Table 3: SII ROC Analysis by Outcome (outcome: discharged and others)

	Area under the curve (*AUC*)	*se*	*p*	Area under the curve (*AUC*) %95 Confidence limits		Sensitivity	Selectivity	Limits
				Lower limit	Upper limit			
SII	0,705	0,045	<0,001	0,632	0,771	59,26	82,93	>2282,54

SII: Systemic Immune Inflammation Index

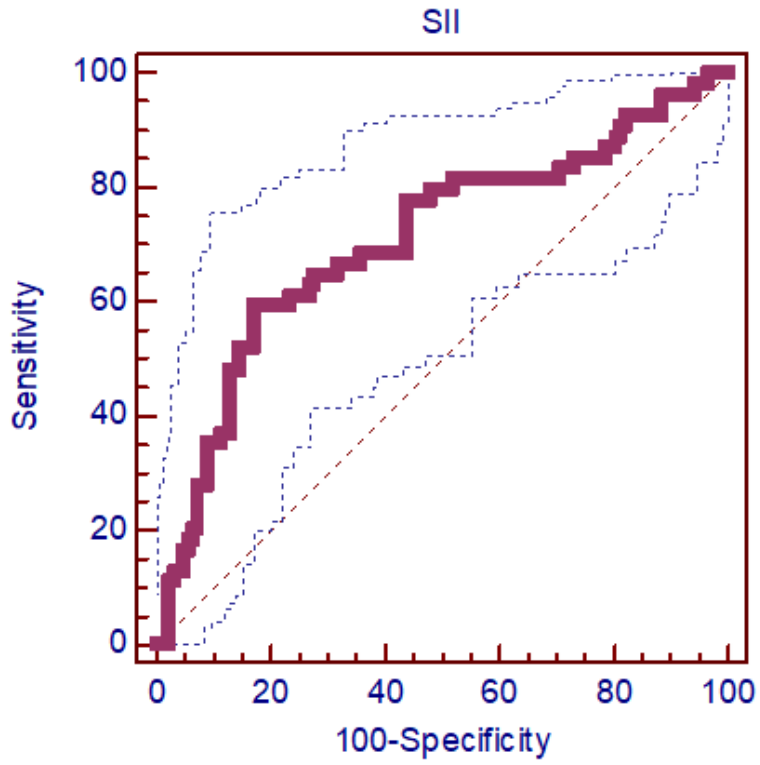

Figure 1. SII ROC Analysis by Outcome

The area under the curve according to the SII value of the survivors is not statistically significant (p=0.572). Level II is not a differential diagnosis for survivor in COPD patients.

Table 4: SII ROC Analysis by Survivor Status

	Area under the curve (*AUC*)	*se*	*p*	Area under the curve(*AUC*) %95 Confidence limits		Sensitivity	Selectivity	Limits
				Lower limits	Upper limits			
SII	0,525	0,044	0,572	0,449	0,631	61,76	48,62	-

SII: Systemic Immune Inflammation Index

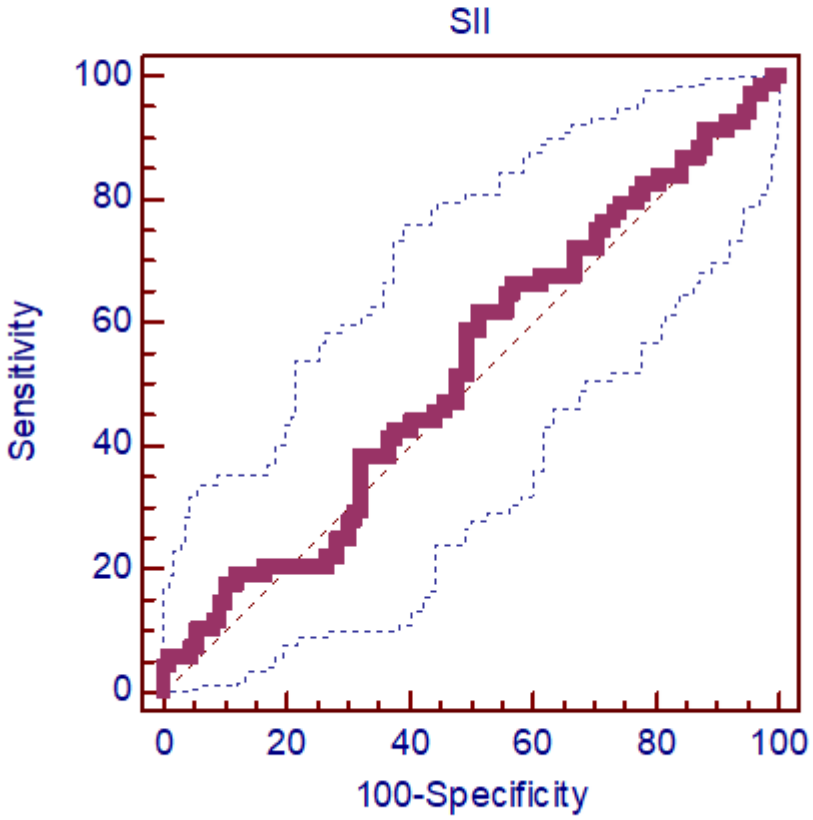

Figure 2. SII ROC Analysis by Survivor Status

Higher PaCO2 values were found to be 1.048 (1.010-1.086) times (p=0.012) in patients whose outcome was ward and intensive care unit compared to those who were discharged (odds ratio (OR)). A high CRP value was 1.011 (1.003-1.018) times higher (p=0.005) in patients who were hospitalized and in intensive care units compared to those who were discharged (odds ratio (OR)). Other variables do not indicate risk according to outcome (p>0.05).

Table 5: Logistic Regression Analysis by Outcome (outcome: discharged and others)

	β	*se*	Wald	df	*p*	Exp (*β*)	95% C.I.for EXP(*β*)	
							Lower	Upper
Constant	-45,398	37,206	1,489	1	0,222	0,000		
Sistolic BP	0,008	0,010	0,622	1	0,430	1,008	0,989	1,027
Diastolic BP	-0,026	0,020	1,726	1	0,189	0,975	0,938	1,013
Heart rate	0,000	0,012	0,000	1	0,995	1,000	0,976	1,024
Respiratory Rate	0,081	0,059	1,865	1	0,172	1,084	0,965	1,218
Fever	1,449	0,934	2,406	1	0,121	4,259	0,683	26,578
WBC	0,109	0,177	0,375	1	0,540	1,115	0,787	1,578
Neutrophil	-0,192	0,215	0,799	1	0,372	0,825	0,541	1,258
Eosinophil	-2,800	1,801	2,417	1	0,120	0,061	0,002	2,075
Lymphocyte	0,106	0,170	0,388	1	0,533	1,112	0,797	1,552
Platelets	0,000	0,003	0,007	1	0,934	1,000	0,995	1,005
SII	0,000	0,000	1,756	1	0,185	1,000	1,000	1,000
Hgb	-0,124	0,104	1,406	1	0,236	0,883	0,720	1,084
SpO2	-0,009	0,020	0,227	1	0,634	0,991	0,953	1,030
PaO2	0,009	0,009	1,087	1	0,297	1,009	0,992	1,027
PaCO2	0,046	0,018	6,386	1	**0,012**	1,048	1,010	1,086
pH	-1,743	1,353	1,661	1	0,197	0,175	0,012	2,479
Lactate	0,141	0,208	0,458	1	0,498	1,151	0,766	1,732
Creatinine	-0,005	0,037	0,021	1	0,886	0,995	0,926	1,069
BUN	0,021	0,014	2,332	1	0,127	1,021	0,994	1,048
AST	0,000	0,005	0,003	1	0,960	1,000	0,989	1,010
ALT	0,001	0,009	0,022	1	0,881	1,001	0,984	1,018
Total Bilirubin	-1,042	3,490	0,089	1	0,765	0,353	0,000	329,904
Direct Bilirubin	1,434	3,397	0,178	1	0,673	4,194	0,005	3270,096
Indirect Bilirubin	0,571	3,995	0,020	1	0,886	1,770	0,001	4449,237
CRP	0,011	0,004	8,024	1	**0,005**	1,011	1,003	1,018
Sodium	0,050	0,052	0,943	1	0,331	1,052	0,950	1,164
Potassium	-0,039	0,325	0,015	1	0,904	0,961	0,508	1,819
Calsium	-0,622	0,371	2,806	1	0,094	0,537	0,259	1,111
INR	-0,048	0,209	0,052	1	0,819	0,953	0,632	1,437
PT	0,008	0,050	0,028	1	0,866	1,008	0,914	1,112
APTT	0,029	0,038	0,577	1	0,448	1,029	0,956	1,108

BP: Blood Pressure, WBC: White Blood Cells, SII: Systemic Immune Inflammation Index, BUN: Blood Urea Nitrogen, AST: Aspartate Transaminase, ALT: Alanine Transaminase, CRP: C-Reactive Protein, INR: International Normalized Ratio, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time

High PaCO2 value is 1.079 (1.027-1.135) times higher (p=0.003) than those who survive (odds ratio (OR)). A high total bilirubin value is 1.045 (0.0-0.811) times more risky (odds ratio (OR)) in patients with ex (p=0.045). Other variables do not indicate risk according to survivor status (p>0.05).

Table 6: Logistic Regression Analysis by Survivor Status

	β	*se*	Wald	df	*p*	Exp (*β*)	95% C.I.for EXP(*β*)	
							Lower	Upper
Constant	-117,939	44,568	7,003	1	**0,008**	0,000		
Sistolic BP	0,003	0,008	0,096	1	0,756	1,003	0,986	1,019
Diastolic BP	0,011	0,017	0,419	1	0,518	1,011	0,978	1,045
Heart rate	-0,005	0,011	0,187	1	0,666	0,995	0,975	1,017
Respiratory Rate	-0,079	0,061	1,684	1	0,194	0,924	0,819	1,041
Fever	-0,145	0,738	0,039	1	0,844	0,865	0,203	3,676
WBC	-0,039	0,075	0,281	1	0,596	0,961	0,831	1,113
Neutrophil	-0,009	0,056	0,028	1	0,867	0,991	0,887	1,106
Eosinophil	-0,249	0,165	2,283	1	0,131	0,780	0,565	1,077
Lymphocyte	0,252	0,168	2,248	1	0,134	1,287	0,925	1,789
Platelets	0,003	0,002	1,340	1	0,247	1,003	0,998	1,007
SII	0,000	0,000	0,539	1	0,463	1,000	1,000	1,000
Hgb	0,074	0,108	0,477	1	0,490	1,077	0,872	1,330
SpO2	0,025	0,020	1,446	1	0,229	1,025	0,985	1,067
PaO2	-0,010	0,009	1,391	1	0,238	0,990	0,973	1,007
PaCO2	0,076	0,025	8,981	1	**0,003**	1,079	1,027	1,135
Lactate	0,056	0,257	0,047	1	0,828	1,058	0,639	1,752
Creatinine	0,012	0,043	0,076	1	0,783	1,012	0,930	1,101
BUN	0,027	0,015	3,157	1	0,076	1,027	0,997	1,058
AST	0,009	0,008	1,271	1	0,260	1,009	0,994	1,024
ALT	-0,012	0,017	0,466	1	0,495	0,988	0,956	1,022
Total Bilirubin	-9,584	4,783	4,015	1	**0,045**	0,000	0,000	0,811
Direct Bilirubin	6,067	4,495	1,822	1	0,177	431,360	0,064	-
CRP	0,001	0,003	0,037	1	0,848	1,001	0,994	1,007
Sodium	0,001	0,026	0,003	1	0,956	1,001	0,951	1,055
Potassium	-0,370	0,276	1,796	1	0,180	0,691	0,402	1,186
Calsium	-0,581	0,332	3,051	1	0,081	0,559	0,292	1,074
INR	-0,305	0,466	0,429	1	0,513	0,737	0,296	1,837
PT	-0,012	0,060	0,041	1	0,840	0,988	0,879	1,111
APTT	0,025	0,032	0,597	1	0,440	1,025	0,963	1,091
pH	16,542	4,320	14,660	1	<0,001	-	3209,829	-
Indirect Bilirubin	12,989	5,262	6,092	1	0,014	-	14,512	-

BP: Blood Pressure, WBC: White Blood Cells, SII: Systemic Immune Inflammation Index, BUN: Blood Urea Nitrogen, AST: Aspartate Transaminase, ALT: Alanine Transaminase, CRP: C-Reactive Protein, INR: International Normalized Ratio, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time

DISCUSSION

It is increasingly widely recognized that systemic inflammation initiates and aggravates the pathological process of chronic diseases. Numerous inflammatory markers associated with prognosis and mortality in COPD patients have been discovered and targeted therapies have been recommended. We found that a high SII index among COPD patients was closely associated with increased mortality and all-cause mortality in the general population. In short, SII can be considered an effective predictor for the assessment of COPD patients. The screening tool can be used to quickly and at a relatively low cost identify high-risk patients with adverse health problems and risks of death.

Although the SII value was not a sufficient parameter to show survival among COPD patients in this study, it was found to be statistically significant when correlated in terms of outcome (admission/ discharge). In addition, an SII value above 2282.54 is an important indicator in the selection of patients.

In line with the studies conducted by Abete et al. and Lassale et al., it has been suggested that SII is the first predictor of poor prognosis in cancer and may reflect the body's system inflammatory response (13, 14). Recently, in both large-scale general population studies conducted by Jin et al. and Li et al., it was reported that high SII levels were associated with an increased risk of all-cause mortality in the general population (15, 16). In the study of Benz et al. in which they investigated the usability of SII in predicting mortality in patients with COPD and Asthma, middle-aged and elderly people with COPD (with and without sarcopenia) and middle-aged and elderly people with sarcopenia were only less likely to have an all-cause mortality risk compared to people without COPD, asthma or sarcopenia. Additionally, they observed that subjects with higher SII levels had an increased risk of death compared to those with lower SII levels. With these findings, they concluded that sarcopenia and high SII levels are important risk factors for mortality risk in individuals with and without COPD (17). Again, according to this study, the results showed that high SII levels increase the risk of death even in people without sarcopenia, COPD, or asthma (17). However, in our study, no statistically significant relationship was found between SII and mortality. This may be due to our limited patient population, as well as the high number of additional comorbidities and thus mortality due to our high mean age.

In our study, it was concluded that SII is an easily calculated parameter that can be used to predict hospitalization. There is no parameter recommended by the guidelines that can be used in deciding hospitalization and discharge in patients with a diagnosis of COPD presenting to the emergency department. This decision is made depending on the general condition of the patient and the clinician's decision. As a result of our study, it was concluded that an SII value of 2282.54 and above may be an effective parameter in making the hospitalization decision and can be used for this purpose. This situation is seen as a result that can be effective in the operation of the emergency department, where the number of difficult patients is high and the hospitalization decisions need to be acted quickly.

LIMITATIONS

Our study has several limitations. Initially, initial measurements of hemogram values were used, and the concentrations of these blood cells may change during follow-up. In addition, blood cell counts may be affected by other factors, such as the measuring device, transport conditions, and special drugs, and this may have affected our results. Also, some parameters to measure the SII index we seek in the hemogram can be affected by some diseases, like anemia, leukemia, lymphoma, or some infectious diseases. However, this group of patients was not excluded from the study, so that could be a dominant limitation. In addition, the design of the study in the form of a retrospective file scan, its single-center design, and the limited number of patients stand out as other limitations.

CONCLUSION

This study investigated the prognostic significance of the Systemic Immune Inflammation Index (SII) in patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD). Our results suggest that SII can be used as an indicator of inflammation in COPD patients and may be a potential tool for assessing the prognosis of the disease.

Our data suggest that high SII values are associated with poorer outcomes in COPD patients. High-Level SII is associated with increased frequency of exacerbations and hospitalizations and negatively impacts long-term survival rates. Therefore, SII can be used as a simple and effective index to determine the prognosis of COPD patients.

REFERENCES

1. GBD 2015 Chronic Respiratory Disease Collaborators. (2017). Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Respiratory Medicine, 5(9), 691-706.

2. Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., ... & Abraham, J. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The lancet, 380(9859), 2095-2128.

3. Donaldson, G. C., Seemungal, T. A., Bhowmik, A., & Wedzicha, J. A. (2002). Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax, 57 (10), 847-852.

4. Seemungal, T. A., Donaldson, G. C., Paul, E. A., Bestall, J. C., Jeffries, D. J., & Wedzicha, J. A. (1998). Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine, 157(5), 1418-1422.

5. Emerman, C. L., Cydulka, R. K., & Effron, D. (1991). Use of peak expiratory flow rate in emergency department evaluation of acute exacerbation of chronic obstructive pulmonary disease. Annals of Emergency Medicine, 20(7), 755-758.

6. Hu, B., Yang, X. R., Xu, Y., Sun, Y. F., Sun, C., Guo, W., ... & Zhou, J. (2014). Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clinical Cancer Research, 20(23), 6212-6222.

7. Zhang, W., Wang, R., Ma, W., Wu, Y., Maskey, N., Guo, Y., ... & Wang, L. (2019). Systemic immune-inflammation index predicts prognosis of bladder cancer patients after radical cystectomy. Annals of translational medicine, 7(18).

8. Geng, Y., Shao, Y., Zhu, D., Zheng, X., Zhou, Q., Zhou, W., ... & Shao, J. (2016). Systemic immune-inflammation index predicts prognosis of patients with esophageal squamous cell carcinoma: a propensity score-matched analysis. Scientific Reports, 6, 39482.

9. Hong, X., Cui, B., Wang, M., Yang, Z., Wang, L., & Xu, Q. (2015). Systemic Immune-inflammation Index, Based on Platelet Counts and Neutrophil-Lymphocyte Ratio, Is Useful for Predicting Prognosis in Small Cell Lung Cancer. Tohoku Journal of Experimental Medicine, 236(4), 297-304.

10. Garcia-Rio, F., Miravitlles, M., Soriano, J. B., Muñoz, L., Duran-Tauleria, E., Sánchez, G., ... & Ancochea, J. (2010). Systemic inflammation in chronic obstructive pulmonary disease: a population-based study. Respiratory Research, 11(1), 1-8.

11. Bafadhel, M., Umar, I., Gupta, S., Raj, J. V., Vara, D. D., Entwisle, J. J., ... & Brightling, C. E. (2011). The role of CT scanning in multidimensional phenotyping of COPD. Chest, 140(3), 634-642.

12. Celli, B. R., Cote, C. G., Marin, J. M., Casanova, C., Montes de Oca, M., Mendez, R. A., ... & Cabral, H. J. (2004). The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. New England Journal of Medicine, 350(10), 1005-1012.

13. Abete, I., Lu, Y., Lassale, C., Verschuren, M., van der Schouw, Y., & Bueno-de-Mesquita, B. (2019). White cell counts in relation to mortality in a general population of cohort study in the Netherlands: a mediating effect or not?. *BMJ open*, *9*(10), e030949.

14. Lassale, C., Curtis, A., Abete, I., van der Schouw, Y. T., Verschuren, W. M. M., Lu, Y., & Bueno-de-Mesquita, H. B. A. (2018). Elements of the complete blood count associated with cardiovascular disease incidence: Findings from the EPIC-NL cohort study. *Scientific reports*, *8*(1), 3290.

15. Jin, Z., Wu, Q., Chen, S., Gao, J., Li, X., Zhang, X., Zhou, Y., He, D., Cheng, Z., Zhu, Y., & Wu, S. (2021). The Associations of Two Novel Inflammation Indexes, SII and SIRI with the Risks for Cardiovascular Diseases and All-Cause Mortality: A Ten-Year Follow-Up Study in 85,154 Individuals. *Journal of inflammation research*, *14*, 131–140.

16. Li, H., Wu, X., Bai, Y., Wei, W., Li, G., Fu, M., Jie, J., Wang, C., Guan, X., Feng, Y., Meng, H., Li, M., He, M., Zhang, X., & Guo, H. (2021). Physical activity attenuates the associations of systemic immune-inflammation index with total and cause-specific mortality among middle-aged and older populations. *Scientific reports*, *11*(1), 12532.

17.Benz, E., Wijnant, S. R. A., Trajanoska, K., Arinze, J. T., de Roos, E. W., de Ridder, M., Williams, R., van Rooij, F., Verhamme, K. M. C., Ikram, M. A., Stricker, B. H., Rivadeneira, F., Lahousse, L., & Brusselle, G. G. (2022). Sarcopenia, systemic immune-inflammation index and all-cause mortality in middle-aged and older people with COPD and asthma: a population-based study. *ERJ open research*, *8*(1), 00628-2021.