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ORIGINAL ARTICLE

Prognostic importance of systemic immune inflammation index in chronic obstructive pulmonary disease

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ABSTRACT

Objective: Chronic obstructive pulmonary disease (COPD) is associated with various immunopathophysiological pathways. Therefore, several inflammatory, hematological and immunological biomarkers are essential for diagnosis, prognosis, and survival of COPD. Among these inflammatory markers, such as C-reactive protein (CRP), neutrophil, lymphocyte and platelet counts were shown to have strong correlations with prognosis, survival and mortality. Recently, a novel inflammatory marker stated as systemic immune-inflammation index (SII) were presented as the most accurate in predicting inflammatory status and prognosis in various clinical settings. We aimed to investigate whether SII can be a useful tool for predicting prognosis and survival in COPD patients.

Material and Methods: We aimed to evaluate retrospectively the effect of SII (the ratio of platelet and lymphocyte multiplication to neutrophil count) on the course of the COPD in 270 patients. The effect of hemogram values, spirometric measurements, such as FEV1, and CRP on the number of attacks in COPD patients seen in the outpatient clinic and the effect of SII on clinical or intensive care hospitalization in COPD patients were evaluated. Whether the SII correlates with symptoms and one-month survival in COPD patients were evaluated. FEV1 and CRP values, duration of hospitalization, smoking and modified Medical Research Council (mMRC) scales were correlated among each other.

Results: mMRC was significantly correlated with FEV1(%) and FEV1(lt) levels, and CRP. The effects of mMRC, FEV1/FVC and smoking on survival in COPD patients were also significantly shown. CRP values were significantly correlated with WBC, neutrophil and lymphocyte counts, and SII values. Unfortunately, SII values were non-significantly correlated with FEV1 values, duration of hospitalization, smoking and mMRC, due to earlier stage and small number of cases.

Conclusion: We investigated the clinical significance of SII on prognosis of COPD patients. SII might assist the identification of high-risk patients with low FEV1 and high CRP values. This study sheds light on future research on SII as a prognostic marker.

Keywords: Systemic immune inflammation index, COPD, prognosis.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the world, with a prevalence of 5-20% in the world, with a prevalence of 19.2% in Turkey [1]. COPD patients constitute the majority of applications to the pulmonary outpatient clinic [2]. COPD is a disease with chronic inflammation in the airways and has a high mortality and morbidity rate [3].

COPD is a common, preventable and treatable condition that has a complex pathophysiology and an even more complex immunopathological process [4]. In this process, there are both immune and non-immune inflammatory changes with oxidative stress imbalance and alterations in the protease/anti-protease ratio caused by genetic, epigenetic and environmental defects. COPD produces irreversible tissue damage and chronic inflammation with tissue repair alteration, which induces chronic obstruction of the airway, bronchitis and systemic damage [5, 6].

Most common resulting comorbidities include cardiovascular disease, metabolic syndrome, osteoporosis, depression, musculoskeletal dysfunction, increased biological age, lung cancer and other types of malignancies [7]. In the conception of COPD, recognizing that it is a non-transmittable and preventable disease is indispensable.

The systemic immune-inflammation index (SII), is calculated by multiplying neutrophil and platelet counts and then dividing the result by the lymphocyte count, is a recently introduced inflammation parameter and a prognostic indicator of adverse outcomes and survival in various cancer types. The clinicopathological features and follow-up data were evaluated to compare SII with other systemic inflammation-based prognostic indices such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to lymphocyte ratio (PLR) in patients with colorectal cancer [8]. Higher SII levels was associated with poor prognosis in cervical cancer patients [9], bladder cancer patients [10], hepatocellular carcinoma patients [11], endometrial cancer patients [12], breast [13] and NSCLC [14] patients. The SII was an independent predictor of survival in multivariate analysis. Moreover, recent studies have demonstrated that the SII can also be used as a prognostic indicator in different cardiovascular diseases (CVD) [15]. Individuals with higher SII had an increased risk of CVD and SII at the onset of CVD was significantly higher than that in the general population [15].

In addition, SII is a predictor of Contrast-Induced Nephropathy in patients with ST-segment elevation Myocardial Infarction [16]. Last, but not the least, NLR, PLR, and SII values of the COPD patients with pulmonary hypertension were significantly higher in the group of COPD patients with the acute exacerbation, so NLR, PLR, and SII values could be early indicators of pulmonary hypertension in patients with acute exacerbation of COPD [17]. Higher SII levels were associated with worse clinical outcome in pneumonia [18]. The hemogram indexes PLR, SII, and SIRI (monocyte × neutrophil/lymphocyte ratio; systemic inflammation response index) were associated with COPD exacerbation in 275 stable COPD patients [18]. SII and NLR is a potential new diagnosed biomarker in severe-patients with COVID-19 pneumonia [19]. Sarcopenia and a higher SII levels are significantly linked with morbidity and mortality in patients with COPD [20].

Finally, a recent study on 16,636 COPD patients showed a significant positive correlation among SII and different age groups, gender, Body Mass Index, smoking status, and those with a history of hypertension [21]. Higher SII levels are significantly linked to higher prevalence of COPD. COPD patients with a higher SII levels have a higher risk of all-cause mortality [21]. Additional long-term studies in different stages of COPD with different comorbidities and treatments are necessary to confirm these results.

Therefore, we aimed to investigate the clinical significance of SII on prognosis of patients with COPD. We correlated SII levels with one-month survival in 270 COPD patients in order to understand whether SII can be a useful tool for predicting prognosis and survival in patients with COPD, among other inflammatory markers.

MATERIAL AND METHODS

This study is a retrospective study. Patients over the age of 18 who applied to Lokman Hekim Chest Diseases outpatient clinic between January 2018

and May 2023 and followed up with the diagnosis of chronic obstructive pulmonary disease (COPD) were included in the study with an ethical approval of Lokman Hekim University Ethical Committee Approval No: 2023120. Patients under the age of 18 and pregnant, who have a history of malignancy, active systemic disease, collagen tissue disease, interstitial lung disease and those who use drugs that could affect the hemogram level were excluded from the study.

Patients over 18 years old and retrospective analysis of the files of patients admitted to the outpatient clinic with the diagnosis of COPD. The files of these patients were examined. Pulmonary function tests were recorded from their files for COPD disease. Platelet, lymphocyte and neutrophil count rates were examined from the patients' admission hemogram results.

We evaluated retrospectively the effect of SII (the ratio of platelet and lymphocyte multiplication to neutrophil count) on the course of the disease in 270 COPD patients.

The effect of hemogram values, spirometric measurements, such as FEV1, and CRP on the number of attacks in COPD patients seen in the outpatient clinic and the effect of SII on clinical or intensive care hospitalization in COPD patients were evaluated. Whether the SII correlates with symptoms and one-month survival in COPD patients were evaluated. All parameters were correlated among each other, by using correlation analysis.

The one-month survival of the patients from the day of admission to the hospital were recorded. The patients were divided into two groups, according to their survival or death status.

FEV1 (lt), FVC (lt) and FEV1/FVC levels were measured by spirometry.

The mMRC scale is a self-rating tool to measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 to 4: 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking ~100 m or after few minutes on the level; and 4, too breathless to leave the house, or breathless when dressing or undressing [22].

In their initial blood tests which were obtained at admission, following parameters were studied: White Blood Cells (WBC) numeric value (normal range 4.6-10.2 $x10^3$/μL), neutrophil numeric value (normal range 1800-7700/μL), lymphocyte numeric value (normal range 1500-4000/μL), platelet numeric value (normal range 142-450x10 3/μL), CRP value (normal range 0-0.5 mg/dL) and creatinine value (normal range 0.5-1.2 mg/dL).

WBC, neutrophil and lymphocyte counts were measured by fluorescent flow scatter. Platelet counts were measured by electric impedance.

Serum CRP levels were measured by nephelometric/turbidometric method (Beckman). Serum creatinine levels were measured by alkaline picrate based assay (Beckman).

In order to determine the number of samples, a power analysis (α =0.05, β =0.80) was performed by taking a study with similar methodology and a sample size of n=275 was obtained [18], but because of their missing data, the number of people were excluded from the analysis, and a total sample of 270 people was obtained.

Analysis was performed with the SPSS v.25 software. Significance was set at $p < 0.05$ for all comparisons/analyses. Continuous data were summarized with mean ± standard deviation values, categorical data were summarized with frequency (n) and relative frequency (%). Univariate comparisons for continuous data were performed with the Mann-Whitney U test due to the fact that parametric assumptions were not met for any of the comparisons or variable sets. Categorical data distributions were compared with the Pearson Chi-square or the Fisher's exact test depending on assumptions. The binary logistic regression model to identify factors that were independently associated with mortality (odds ratio (OR) for one-month survival) was created by including all variables that demonstrated significant differences in univariate analysis. The model included age, hypertension, diabetes mellitus, smoking package-years, FEV1 (lt), FVC (lt), FEV1/FVC levels, and mMRC scales. The forward conditional parameter selection method was used.

RESULTS

41 female and 229 male COPD patients were included in our study. Median age were 65 years old. We found older age, comorbities such as hypertension and diabetes mellitus; smoking, lower FEV1(%), FEV1(lt), FVC(%), FVC(lt), FEV1/FVC levels and mMRC scales were significantly associated with one-month survival by univariate analysis in these 270 COPD patients (Table 1).

Low mMRC scales and low FEV1(%) and FEV1(lt) levels were significantly correlated (Table 2). Additionally, low mMRC scales and high CRP levels were significantly correlated (Table 2). SII values were non-significantly correlated with FEV1, duration of hospitalization, smoking and mMRC scales (Table 2). CRP values were significantly correlated with WBC, neutrophil and lymphocyte counts, and SII values (Table 2b).

By regression analysis of these COPD patients, mortality risk increases 1.043 fold, if smoking package/year increases one level (OR=1.043) (Table 3). If FEV1/FVC level increases one level, mortality risk increases 0.945 fold (OR=0.945) (Table 3). If mMRC scale increases one level, mortality risk increases 4.138 fold (OR=4.138) (Table 3).

Table 1. Comparison of patients based on one-month survival by using univariate analysis of possible risk factors in 270 COPD patients

		Survivors	Deceased	p
Gender	female	34 (15%)	7 (16.3%)	0.827
	male	193 (85%)	36 (83.7%)	
Age (years)		62.6 ± 8.2	67.3 ± 9	**0.001**
Rheumatologic diseases	-	227 (100%)	43 (100%)	N/A
	+	0 (0%)	0 (0%)	
Coronary artery diseases	-	206 (90.7%)	37 (86%)	0.403
	+	21 (9.3%)	6 (14%)	
Hypertension	-	168 (74%)	25 (58.1%)	**0.035**
	+	59 (26%)	18 (41.9%)	
Diabetes Mellitus	-	199 (87.7%)	32 (74.4%)	**0.023**
	+	28 (12.3%)	11 (25.6%)	
Smoking (package/year)		28.6 ± 14.2	44.7 ± 22.6	**<0.001**
Smoking habit	none	0 (0%)	0 (0%)	0.868
	Still smoking	182 (80.2%)	34 (79.1%)	
	Quitted	45 (19.8%)	9 (20.9%)	
BMI	30 and less	118 (52%)	24 (55.8%)	0.645
	30 and more	109 (48%)	19 (44.2%)	
FEV1(%)		51.1 ± 12.4	43.9 ± 15.7	**0.002**
FEV1(lt)		1.3 ± 0.5	1.1 ± 0.5	**0.001**
FVC		66.1 ± 13.5	60.2 ± 19.2	**0.045**
FVC(lt)		2.3 ± 0.7	2 ± 0.7	**0.028**
FEV1/FVC		59 ± 8.4	53.3 ± 11.5	**0.003**
mMRC scales		2 ± 0.5	2.7 ± 0.8	**<0.001**
WBC (mm^3)		12.9 ± 4.9	12.5 ± 5.9	0.642
Platelet count (mm^3)		235.6 ± 83.1	227.9 ± 135	0.616
Neutrophil count (mm^3)		10.5 ± 4.8	10.1 ± 5.4	0.667
Lymphocyte count (mm^3)		1.6 ± 1.3	1.46 ± 1.3	0.602
CRP (mg/L)		38 ± 72.1	40.2 ± 70.8	0.853
Creatinine (mg/dL)		1.1 ± 0.6	1.1 ± 0.8	0.552
SII		2462 ± 2778	2449 ± 2163	0.978

DISCUSSION

COPD is a major cause of death and morbidity worldwide. The pathogenesis of disease is briefly characterized by irreversible expiratory airflow limitation, uncontrolled chronic inflammation with acute exacerbations, and emphysematous pulmonary damage. Even though this disease is an increasing unmet global healthcare problem; unfortunately, the conventional therapies are still symptomatic, and regenerative therapies are undergoing clinical trials [5, 6]. Sub-optimal COPD patient phenotyping, an incomplete understanding of COPD pathogenesis and a shortage of sensitive tools, such as effective diagnostic, prognostic and predictive biomarkers, that provide patient-relevant intermediate endpoints likely all result in the lack of novel and effective COPD interventions [23]. Therefore, COPD patients are still diagnosed based on the presence of persistent airflow limitation, which is measured by spirometry. These measurements reflect the global sum of all the different possible COPD pathologies, so we cannot differentiate different effects of airway and parenchymal defects on the disease pathogenesis. Imaging techniques are helpful to diagnose pulmonary structural and functional pathologies, but COPD pathogenesis covering deregulated inflammation, proteolysis/anti-proteolysis imbalance, and destroyed repair mechanisms, dysbiosis, smoking-related damage,

Table 2a. Correlations among continuous variables (Smoking, FEV1(%), FEV1(lt), FVC, FVC (lt) FEV1/FVC and mMRC scales) , CRP and creatinine examined by using correlation analysis in 270 COPD patients

		Smoking Package/year	FEV1(%)	FEV1(lt)	FVC	FVC(lt)	FEV1/FVC	mMRC scales	crp	Creatinine
Smoking Package/year	r	1								
	p									
FEV1(%)	r	-0.035	1							
	p	0.570								
FEV1(lt)	r	-0.032	**0.694**	1						
	p	0.600	**<0.001**							
FVC	r	-0.123	**0.722**	**0.597**	1					
	p	0.045	**<0.001**	**<0.001**						
FVC(lt)	r	-0.038	**0.506**	**0.843**	**0.644**	1				
	p	0.540	**<0.001**	**<0.001**	**<0.001**					
FEV1/FVC	r	-0.053	**0.715**	**0.412**	**0.310**	**0.073**	1			
	p	0.388	**<0.001**	**<0.001**	**<0.001**	**0.235**				
mMRC scales	r	**0.242**	**-0.232**	**-0.298**	**-0.246**	**-0.211**	**-0.221**	1		
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**			
WBC	r	-0.019	0.103	0.028	0.048	-0.021	0.111	0.038		
	p	0.762	0.092	0.644	0.440	0.730	0.070	0.538		
Platelet count	r	-0.004	-0.008	-0.009	-0.022	-0.009	0.032	0.010		
	p	0.949	0.900	0.883	0.723	0.881	0.607	0.875		
Neutrophil count	r	-0.010	0.068	0.004	0.034	-0.032	0.080	0.039		
	p	0.868	0.268	0.953	0.581	0.598	0.193	0.528		
Lymphocyte count	r	-0.014	0.026	-0.026	0.006	-0.045	0.021	0.062		
	p	0.818	0.678	0.676	0.926	0.463	0.732	0.310		
CRP	r	-0.063	-0.082	-0.082	-0.054	-0.048	-0.051	-0.046	1	
	p	0.306	0.178	0.182	0.380	0.432	0.404	0.451		
Creatinine	r	0.017	0.043	0.007	-0.010	-0.001	-0.001	-0.041	-0.006	1
	p	0.786	0.484	0.907	0.876	0.984	0.991	0.507	0.918	
SII	r	-0.009	0.025	0.001	0.016	0.002	0.032	0.016	**0.134**	0.034
	p	0.882	0.680	0.981	0.790	0.976	0.609	0.794	**0.029**	0.575

Table 2b. Correlations among continuous variables (WBC, platelet, neutrophil and lymphocyte count, CRP and Creatinine) examined by using correlation analysis in 270 COPD patients

		WBC	Platelet count	Neutrophil count	Lymphocyte count	CRP	Creatinine
Smoking Package/year	r						
	p						
FEV1(%)	r						
	p						
FEV1(lt)	r						
	p						
FVC	r						
	p						
FVC(lt)	r						
	p						
FEV1/FVC	r						
	p						
mMRC scales	r						
	p						
WBC	r	1					
	p						
Platelet count	r	**0.151**	1				
	p	**0.014**					
Neutrophil count	r	**0.965**	**0.126**	1			
	p	**<0.001**	**0.040**				
Lymphocyte count	r	0.101	0.064	-0.092	1		
	p	0.100	0.294	0.134			
CRP	r	**0.165**	-0.068	**0.187**	**-0.122**	1	
	p	**0.007**	0.266	**0.002**	**0.045**		
Creatinine	r	0.033	0.172	0.017	0.015	-0.006	1
	p	0.587	**0.005**	0.788	0.802	0.918	
SII	r	**0.510**	**0.257**	**0.618**	**-0.386**	**0.134**	0.034
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.029**	0.575

Table 2c. Summary table of significant correlations among FEV1(%), FEV1(lt), Smoking (package/year), CRP and mMRC scales

		FEV1(%)	FEV1(lt)	Smoking Package/year	CRP
FEV1(%)	r	1.000			
	p	-			
FEV1(lt)	r	0.687	1.000		
	p	**<0.001**	-		
Smoking Package/year	r	-0.043	-0.041	1.000	
	p	0.483	0.508	-	
CRP	r	-0.010	-0.071	-0.033	1.000
	p	0.868	0.249	0.592	-
mMRC scales	r	-0.275	-0.330	0.224	-0.053
	p	**<0.001**	**<0.001**	**<0.001**	0.386

Table 3. Forward-conditional logistic regression model, final step (Step 3)

	Beta Coefficient	Std. Error	Wald	Df	**P value**	**Exp. Beta (OR)**	95% CI for OR	
							Lower	Upper
Smoking package/year	0.043	0.011	15.913	1	**<0.001**	**1.043**	1.022	1.065
FEV1/FVC	-0.057	0.020	7.797	1	**0.005**	**0.945**	0.908	0.983
mMRC scales	1.420	0.302	22.060	1	**<0.001**	**4.138**	2.288	7.484
Constant	-3.318	1.339	6.142	1	**0.013**	0.036		

OR: odds ratio.

CI: confidence interval

Nagelkerke R2: 0.367

and autoimmune pulmonary defects have to be evaluated, regarding the complex pathologic process of the disease [24]. Therefore, several inflammatory, hematological and immunological biomarkers are essential for diagnosis, prognosis, and survival of COPD. These can be useful for better phenotyping of these patients, in addition to the support of imaging. Among these inflammatory markers, such as CRP, CRP-to albumin ratio, fibrinogen-to-albumin ratio, neutrophil, lymphocyte, platelet counts, NLR and PLR have been shown to have strong correlations with prognosis, clinical outcomes and survival/mortality. Recently, a novel inflammatory marker SII were suggested to be more powerful than either NLR or PLR alone in predicting inflammatory process and prognosis in various clinical settings, such as cancer, cardiovascular diseases, nephropathy, pneumonia and COPD. Inflammatory markers will be helpful in order to reveal COPD phenotypes and what COPD really 'looks' like, beyond spirometric and imaging measurements [24].

Similar to the findings in the recent literature [17-20], we found older age, COPD comorbities such as hypertension and diabetes mellitus; smoking, lower FEV1 (%), FEV1(lt), FVC(%), FVC(lt), FEV1/FVC levels and mMRC scales were significantly associated with one-month survival in 270 COPD patients. Additionally, low FEV1(%) and FEV1(lt) and high CRP levels were significantly correlated with low mMRC scales. By regression analysis of these COPD patients, mortality risks increase 1.043, 0.945 and 4.138 fold, respectively: if smoking package/year, FEV1/FVC levels and mMRC scales increase one level.

We investigated the clinical significance of SII on prognosis of COPD patients. SII has a potential to be a beneficial tool for predicting prognosis and survival outcome in patients with COPD in several studies in the literature. It might assist COPD patient phenotyping and importantly, the identification of high-risk patients with low FEV1 and high CRP values.

Recently, Ye et al. showed that higher SII levels are significantly linked to higher prevalence of COPD and their patients with a higher SII levels have a higher risk of all-cause mortality [21]. In this study, logistic regression analysis was performed to assess the correlation between COPD, lung function, chronic respiratory symptoms and SII. They used Cox proportional hazards model to analyze the relationship between SII and mortality in COPD patients and healthy individuals. They used propensity score matching method to match the COPD population with similar baseline levels with the normal population for further analyzing the correlation between SII and COPD [21] .

SII values were non-significantly correlated with FEV1 values, duration of hospitalization, smoking and mMRC. CRP values were correlated with WBC, neutrophil and lymphocyte counts, and SII values. Therefore, further comprehensive studies in larger groups are necessary to assess whether SII is a powerful tool to predict prognosis and survival in COPD patients. In addition, considering the various stages, different pathogenesis, and overall complex process of the COPD disease, patients were in earlier stages of COPD in our study, so this may affect the non-significant SII differences among our patients, since SII is an inflammatory marker. Designing a study with additional advanced stage patients in larger groups will overcome this significancy problem. In addition, even though we chose patients in the earlier stage to be consistent, choosing patients in various stages, especially acute exacerbations, of COPD, categorizing according to

their various treatments and co-morbidities, and comparing every group of COPD patients with healthy controls will be more powerful to evaluate SII as a prognostic marker. Last, but not the least Cox proportional hazards analysis will be helpful in order to analyze the correlation between SII and mortality in COPD patients and healthy controls, and propensity score matching analysis will be useful to match the COPD population with similar baseline levels with the normal population.

Author contribution

Study conception and design: ESG and BC; data collection: ESG and BC; analysis and interpretation of results: ESG and BC; draft manuscript preparation: BC. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Lokman Hekim University Ethical Committee (Approval No: 2023120/17.07.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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