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Immature platelet fraction as a systemic inflammation marker in patients with chronic obstructive pulmonary disease

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Abstract

Introduction: Recently, there has been an increasing interest to find a simple, low cost, widely available biomarker for outcome predictors in chronic obstructive pulmonary disease (COPD).

Methods: Absolute immature platelet count (AIPC), the percentage of AIPC to the total platelet count (immature platelet fraction [IPF%]), symptoms, spirometry results, age-dyspne-airflow obstruction index, and C-reactive protein tests of COPD patients and control group were recorded. Neutrophil/lymphocyte, monocyte/lymphocyte, and platelet/lymphocyte ratios and Charlson comorbidity index scores were calculated.

Results: One hundred and thirty-four COPD patients and 30 healthy control subjects were included in the study. Eighty-nine patients were in exacerbation (AECOPD) and 45 of them were in stable COPD period. There was a difference between IPF% values and AIPC of COPD group and control group (3.45 ± 2.41 vs. 2.04 ± 1.12, $p = 0.01$; 5.87 ± 2.45 vs. 5.20 ± 3.02, $p = 0.01$). A positive correlation was observed between IPF% with white blood cell count and neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, monocyte/lymphocyte ratio in all patients ($r = 0.352$, $p < 0.001$; $r = 0.399$, $p < 0.001$; $r = 0.186$, $p = 0.032$; $r = 0.200$, $p = 0.021$) and AECOPD ($r = 0.356$, $p < 0.001$; $r = 0.414$, $p < 0.001$; $r = 0.239$, $p = 0.025$; $r = 0.273$, $p = 0.010$). At a cut-off of 3.4, IPF% showed the highest accuracy in identifying COPD (sensitivity: 80.3%, specificity: 82.5%) using receiver-operating characteristic analysis.

Conclusion: This is the first study to examine the relationship between AIPC, IPF%, and COPD. The higher IPF% values in COPD and the positive correlation between IPF% and other inflammatory markers are suggested that IPF may be an indicator of systemic inflammation in COPD.

KEYWORDS

absolute immature platelet count, COPD, immature platelet fraction, monocyte/lymphocyte ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

This study was presented at International European Respiratory Society Congress Barcelona in 2022.

1 | INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by frequent exacerbations and chronic inflammation. It is known that there is an increase in the number of acute phase reactant proteins and inflammatory cells in the circulation during exacerbations. However, it is known that some patients with COPD have an increase in inflammatory markers and low-grade systemic inflammation even in stable period. This chronic inflammatory period seen in patients with COPD has an important role in the pathogenesis of the disease. In addition, these high inflammation markers were found to be associated with poor prognosis of the disease and increased comorbidity rates.[1]

Although the role of leukocytes and its subtypes in inflammation in COPD is well known, the relationship of thrombocyte with COPD inflammation is less known. Platelets have an important role in maintaining hemostasis. However, they also secrete some inflammatory mediators other than hemostasis. These mediators cause changes in leukocyte and endothelial responses to various inflammatory stimuli. Platelets have an important role in inflammation and immune responses because they interact with neutrophils, lymphocytes, monocytes, and endothelial cells.[2] The platelet count was found to be higher in COPD patients than in healthy individuals. In addition, it has been observed that it increases in direct proportion to the stage of COPD.[3]

Immature platelet fraction (IPF%) is a hematologic parameter of automated hematologic analyzer and is related to platelet size and cytoplasmic RNA contents. Immature platelets with high RNA content are the initial form of platelet formation. Absolute immature platelet count (AIPC) and IPF% reflect thrombopoiesis and also are often used as the marker of platelet activity. IPF% reference ranges are not clear.[4–6] However, the high results obtained in different inflammatory pathologies suggest that it is promising as a systemic inflammation marker.

The importance of systemic inflammation in COPD and its relationship with disease severity were demonstrated.[7,8] In this study, we aimed to investigate the importance of AIPC and IPF% in COPD and its relationship with systemic inflammation.

2 | MATERIALS AND METHODS

One hundred and thirty-four COPD patients and 30 healthy control subjects with smoking history followed in the outpatient clinic between May 2021 and January 2023 were enrolled to the single center prospective case control study. Among the 134 COPD patients included in this study, 89 were in COPD exacerbation period (AECOPD) and 45 patients were in stable period. Demographics, clinical symptoms, spirometry test results within the last year, hemogram, AIPC, IPF%, and C-reactive protein (CRP) tests performed in the laboratory were recorded. White blood cell (WBC) count, neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and platelet/lymphocyte ratio (PLR) were calculated. In addition, the comorbidities of the patients were questioned and the age-dyspne-airflow obstruction (ADO) index and Charlson comorbidity index (CCI) scores were calculated accordingly.[9,10] The Modified Medical Research Council (mMRC) dyspnea score was determined for the cases.[1,11] Written informed consent obtained from all subjects. Ethics Committee approval was obtained from the Human Research Ethics Committee with no. İ5-332-21.

2.1 | Subjects

Patients under the age of 40 years old, with a history of smoking less than 20 pack-years, with active infection other than the respiratory system, hematological disease, or active malignancy were excluded from the study. A written informed consent was obtained from each subject. All subjects underwent detailed clinical evaluation. The mMRC scale serves as a self-assessment dyspnea scale to gauge the impact of breathlessness on day-to-day activities, rated on a scale from 0 to 4 as follows: 0, absence of breathlessness except during heavy exercise; 1, experiencing shortness of breath while hurrying on the level or walking up a slight hill; 2, walking more slowly than individuals of the same age on the level due to dyspnea or needing to stop to catch breath when walking at their own pace on the level; 3, taking a break for breath after walking approximately 100 m or after a few minutes on the level; and 4, too breathless to leave the house, or experiencing dyspnea when dressing.[11] Thirty healthy, nonsmokers over 40 years of age without respiratory, inflammatory, malignant, and chronic diseases were included in the control group. COPD diagnosed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[1] Cases of COPD with confirmed airflow obstruction, as proven by spirometry, were categorized into GOLD A, B, and E groups based on symptom severity and the number of exacerbations in the past year. Those with low symptom severity and a low number of exacerbations were placed in Group A, those with high symptom severity and a low number of exacerbations were assigned to Group B, and individuals with high symptom severity and a high number of exacerbations were included in Group E.[1] The COPD patients who admitted to the outpatient were divided into two groups according to their clinical presentations: AECOPD and stable COPD. Patients who had no significant change in respiratory symptoms in the last 3 months did not need any additional treatment and did not admitted to the emergency department or hospitalized due to respiratory symptoms were defined as stable COPD. Patients with acute worsening of symptoms requiring additional treatment were classified as AECOPD and included in the study.[1,2]

2.2 | Measurement of IPF%

K2EDTA whole blood was used for measurement of IPF%. It was tested within 2 h after collection. The IPF% were measured using Sysmex XN 9000 (Kobe, Japan). The IPF% value is the ratio of absolute immature platelet count (AIPC) to the total platelet count (t-PLT). The

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formula is IPF% = AIPC/(t-PLT × 100). Test was performed according to the standardized protocols recommended by the manufacturers.

2.3 | Statistical analysis

Continuous variables were tested for normality of distribution by the Kolmogorov–Smirnov test. For normally distributed values, descriptive results are presented as mean (standard deviation) and median (minimum-maximum). In the comparison of continuous data with two-group independent variables, *t*-test was used for normally distributed data and Mann Whitney *U* test was used for data not normally distributed. Chi-square and Fisher's Exact tests were used for group comparisons of nominal variables.

The relationship between IPF%, AIPC, and continuous data was analyzed with Spearman's correlation coefficient. A receiver-operating characteristic (ROC) analysis was conducted to calculate the optimal cut-off value for the level of IPF% in COPD patients. IBM SPSS Statistics 20 program was used in the evaluations and $p < 0.05$ was accepted as the statistical significance limit.

3 | RESULTS

One hundred and thirty-four COPD patients (89 exacerbation and 45 stable COPD) and 30 control subjects were included in the study. The mean overall age was 68.42 ± 10.05 years and 69.4% of the subjects were male. When the stable, AECOPD and control groups were compared, no age difference was observed (69.42 ± 14.15, 64.34 ± 9.13, 61.24 ± 11.31, $p > 0.05$, respectively). The ratio of male subjects was higher in the stable, AECOPD, and control groups, and groups did not show any sex difference (male ratio was 68%, 71%, and 70%, $p > 0.05$, respectively).

The mMRC score of the AECOPD was higher than the stable COPD group ($p = 0.01$). GOLD stages of AECOPD were more severe than stable group of COPD patients. ($p = 0.01$). The rate of patients included in Group E, characterized by high severity of COPD, was found to be higher in the COPD exacerbation group. 37% of the AECOPD were in the GOLD E group, while 22% of the stable COPD group were in the E group. When pulmonary function tests were evaluated, the ratios of FVC, FEV1, and FEV1/FVC in the exacerbation group were found to be significantly lower than the stable group (71.04 ± 22.53 vs. 78.51 ± 11.44 [$p = 0.03$], 44.36 ± 27.15 vs. 69.73 ± 22.27 [$p = 0.01$], 45.61 ± 17.43 vs. 66.52 ± 4.27 [$p = 0.01$], respectively). The pulmonary function tests of the control group characterized by FVC, FEV1, and FEV1/FVC were within normal limits (>80% predicted), and they were found to be statistically significantly higher compared with the stable COPD group (94 ± 10.26, 92 ± 10.35, 87 ± 5.34, $p = 0.01$) The number of exacerbations and hospitalizations in the last year was higher in the AECOPD (0.73 ± 1.34, 0.68 ± 0.29) then stable group (0.11 ± 0.17, 0.14 ± 0.36) ($p = 0.01$, $p = 0.02$, respectively). The CCI score and ADO index of the AECOPD (6.18 ± 1.34, 7.83 ± 1.42) were higher than the stable COPD (2.26 ± 1.44, 2.74 ± 1.46) ($p = 0.01$) (Table 1).

While there was no significant difference between the IPF% values of the AECOPD (3.52 ± 2.47) and stable group (3.31 ± 2.30, $p > 0.05$), the IPF% values of the total COPD group (3.45 ± 2.41) were significantly higher than the control group (2.04 ± 1.12, $p = 0.01$) (Table 2).

The AIPC in the AECOPD group was found to be higher than in the stable COPD group (6.08 ± 2.43 vs. 5.75 ± 2.54, $p = 0.02$), while the AIPC in the total COPD group was found to be higher than in the control group (5.87 ± 2.45 vs. 5.20 ± 3.02, $p = 0.01$) (Table 2).

When compared with stable COPD, the AECOPD group exhibited higher WBC counts (9.4 ± 3.7 vs. 7.3 ± 1.9, $p = 0.01$), a higher NLR (4.18 ± 3.22 vs. 2.70 ± 1.54, $p = 0.01$), and a higher CRP level (16.71 ± 29.55 vs. 5.85 ± 5.88, $p = 0.001$).

In comparison with the control group, the whole COPD group showed higher WBC counts (8.8 ± 2.8 vs. 5.7 ± 1.2, $p = 0.001$), a higher NLR (4.00 ± 1.85 vs. 1.98 ± 1.04, $p = 0.003$), and a higher CRP level (12.65 ± 17.34 vs. 3.45 ± 3.71, $p < 0.001$) (Table 2).

The cut-off value for IPF% level in COPD was determined using the area under the ROC curve analysis, with an area under the curve of 0.72. At a cut-off point of 3.4, IPF% exhibited the best discriminatory power for COPD (sensitivity: 80.3%, specificity: 82.5%) (Figure S1).

IPF% was correlated with NLR ($r = 0.199$, $p = 0.041$) and PLR ($r = 0.206$, $p = 0.032$) in stable COPD group, and IPF% was correlated with WBC ($r = 0.356$, $p < 0.001$), NLR ($r = 0.414$, $p < 0.001$), PLR ($r = 0.239$, $p = 0.025$), and MLR ($r = 0.273$, $p = 0.01$) in exacerbation group (Table 3).

AIPC was correlated with WBC ($r = 0.447$ $p < 0.001$), NLR ($r = 0.465$ $p < 0.001$), PLR ($r = 0.301$, $p = 0.01$), and MLR ($r = 386$, $p = 0.01$) in AECOPD group (Table 3).

There was correlation between IPF% and number of exacerbation in the last year in stable COPD ($r = 0.265$, $p = 0.005$) and AECOPD ($r = 0.329$, $p = 0.002$). There was no correlation between IPF% and mMRC, spirometric grade, GOLD, CCI, and ADO index in COPD and control group (Table 4).

AIPC was correlated with exacerbation number in stable COPD ($r = 0.258$, $p = 0.041$) and AECOPD groups ($r = 0.286$, $p = 0.036$) (Table 4).

There was no difference between the IPF% values of patients with and without additional comorbidities (coronary artery disease ($n = 25$), hypertension ($n = 66$), diabetes melitus ($n = 40$), atrial fibrillation ($n = 16$), and chronic kidney disease ($n = 10$)) (Table 5).

4 | DISCUSSION

Systemic inflammation in COPD is associated with disease severity, number of exacerbations, and degree of respiratory function loss.[7] Different biomarkers are used to determine the degree of systemic inflammation.[12] Platelets are cells that play a role in the immune system and inflammation. It has been shown that the level of IPF%

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TABLE 1 Baseline demographics, clinical and laboratory features of stable and acute exacerbation of COPD groups.

Variables	AECOPD $n = 89$	Stable COPD $n = 45$	p
Age (years)	69.42 ± 14.15	64.34 ± 9.13	NS
Sex, male	61 (68)	32 (71)	NS
mMRC, 0, 1, 2, 3, 4	0, 9 (10), 30 (34), 27 (30), 23 (26)	15 (33), 17 (38), 10 (22), 3 (7)	0.01
mMRC	2.8 ± 2.1	1.7 ± 1.5	0.01
GOLD, A, B, E	6 (7), 50 (56), 33 (37)	20 (44), 15 (33), 10 (22)	0.01
FVC, %	71.04 ± 22.53	78.51 ± 11.44	0.03
FEV1, %	44.36 ± 27.15	69.73 ± 22.27	0.01
FEV1/FVC, %	45.61 ± 17.43	66.52 ± 4.27	0.01
No. of exacerbations in the last year	0.73 ± 1.34	0.11 ± 0.17	0.01
No. of hospitalizations in the last year	0.68 ± 0.29	0.14 ± 0.36	0.02
CCI	6.18 ± 1.34	2.26 ± 1.44	0.01
ADO	7.83 ± 1.42	2.74 ± 1.46	0.01

Abbreviations: ADO, age-dyspne-airflow obstruction; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, Modified Medical Research Council; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

TABLE 2 Comparison of blood cell counts and inflammatory biomarkers between stable COPD and COPD exacerbation groups, as well as between the total COPD group and the control group.

Lab	AECOPD $n = 89$	Stable COPD $n = 45$	p	Total COPD group $n = 134$	Control $n = 30$	p
WBC, 10^9/L	9.4 ± 3.7	7.3 ± 1.9	0.01	8.8 ± 2.8	5.7 ± 1.2	0.001
PLT, 10^9/L	272 ± 114	257 ± 342	NS	261 ± 115	225 ± 131	NS
MPV, fl	10.29 ± 1.71	10.50 ± 1.02	NS	10.42 ± 1.4	10.70 ± 1.33	NS
NLR	4.18 ± 3.22	2.70 ± 1.54	0.01	4.00 ± 1.85	1.98 ± 1.04	0.003
PLR	180 ± 127	165 ± 99	NS	168 ± 130	160 ± 74	NS
MLR	0.82 ± 1.26	0.41 ± 0.15	NS	0.55 ± 1.1	0.37 ± 0.11	NS
AIPC, 10^9/L	6.08 ± 2.43	5.75 ± 2.54	0.02	5.87 ± 2.45	5.20 ± 3.02	0.01
IPF, %	3.52 ± 2.47	3.31 ± 2.30	NS	3.45 ± 2.41	2.04 ± 1.12	0.01
CRP, mg/dl	16.71 ± 29.55	5.85 ± 5.88	0.001	12.65 ± 17.34	3.45 ± 3.71	<0.001

Abbreviations: AIPC, absolute immature platelet count; CRP, C-reactive protein; IPF, immature platelet fraction; MLR, monocyte lymphocyte ratio; MPV, mean platelet volume; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PLT, platelet; WBC, white blood cell.

increases in inflammatory diseases.[13-15] In this study, the IPF% value of the patients in the AECOPD and stable period had a higher value than the healthy control group.

A positive correlation was found between IPF% values with WBC, PLR, MLR, and NLR values in COPD exacerbation subjects. Di Mario et al. based on the fact that neutrophilia in hemogram indicates bacterial infection, IPF% values were found to be higher in those with gram positive blood culture compared with negative blood culture group (4.86 vs. 1.79). They also found a positive correlation between WBC and IPF% values.[13]

Georgakopoulou et al. compared the IPF% value between patients with community-acquired pneumonia (CAP), aspiration pneumonia (AP), and a healthy control (C) group. The IPF% value was found (2.55, 3.07, 1.70, respectively). While a statistically significant difference was found between the C group and AP, there was no statistically significant difference between the C group and CAP group, and between AP and CAP groups. Compared with this study our study results demonstrated that COPD patients in both exacerbation and stable period had a higher IPF% value than CAP and AP patients.[14] This result emphasized that IPF% may be an indicator of increased systemic inflammation during the exacerbation period, which is also present in the stable period of COPD.

De Blasi et al. examined the IPF% value in patients treated in intensive care unit, with diagnosis of sepsis or not and there was no correlation between IPF% and WBC values.[15] Contrasting results regarding infection in various studies, it can be deduced that there are some unexplained points in the use of this parameter as an indicator of infection. For example, there may be changes according to the factor such as bacterial, viral infection, the severity and duration of inflammation.

In the study by Enz Hubert et al., it was demonstrated that among the 41 sepsis patients, 12 of whom had severe sepsis-septic shock,

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TABLE 3 Correlation between IPF%, AIPC and WBC, NLR, PLR, MLR in COPD and control group.

		IPF%		AIPC	
	Lab	*r*	*p*	*r*	*p*
Stable COPD $n = 45$	WBC, 10^9/L	0.092	0.201	0.074	0.440
	PLT, 10^9/L	0.142	0.134	0.120	0.105
	MPV, fl	−0.101	0.249	−0.165	0.150
	NLR	0.199	0.041*	0.220	0.085
	PLR	0.206	0.032*	0.197	0.066
	MLR	0.150	0.061	0.230	0.124
	CRP, mg/dl	0.093	0.284	0.175	0.130
AECOPD $n = 89$	WBC, 10^9/L	0.356	<0.001*	0.447	<0.001*
	PLT, 10^9/L	0.187	0.079	0.222	0.064
	MPV, fl	−0.173	0.107	−0.264	0.189
	NLR	0.414	<0.001*	0.465	<0.001*
	PLR	0.239	0.025*	0.301	0.01*
	MLR	0.273	0.010*	0.386	0.01*
	CRP, mg/dl	0.168	0.117	0.125	0.197
Control $n = 30$	WBC, 10^9/L	0.190	0.199	0.232	0.097
	PLT, 10^9/μl	0.043	0.778	0.104	0.540
	MPV, fl	−0.005	0.972	−0.017	0.641
	NLR	0.174	0.252	0.155	0.221
	PLR	0.069	0.653	0.133	0.354
	MLR	0.092	0.550	0.152	0.360
	CRP, mg/dl	0.057	0.709	0.098	0.514

Abbreviations: AIPC, absolute immature platelet count; CRP, C-reactive protein; IPF, immature platelet fraction; MLR, monocyte lymphocyte ratio; MPV, mean platelet volume; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PLT, platelet; WBC, white blood cell.
*Statistically significant correlation.

TABLE 4 Correlation between IPF%, AIPC, and mMRC, number of exacerbations in the last year, GOLD stages, CCI, and ADO scores in COPD patients.

		IPF%		AIPC	
		r	*p*	*r*	*p*
Stable COPD $n = 45$	mMRC	−0.041	0.636	−0.103	0.417
	Exacerbation no	0.265	0.005*	0.258	0.041*
	GOLD group	0.043	0.624	0.079	0.320
	CCI index	0.073	0.402	0.085	0.614
	ADO index	−0.121	0.272	−0.040	0.355
AECOPD $n = 89$	mMRC	−0.102	0.341	−0.235	0.081
	Exacerbation no	0.329	0.002*	0.286	0.036*
	GOLD group	−0.003	0.976	−0.095	0.247
	CCI index	0.112	0.296	0.154	0.318
	ADO index	−0.079	0.569	−0.037	0.712

Abbreviations: ADO, age-dyspne-airflow Obstruction; AIPC, absolute immature platelet count; CCI, Charlson comorbidity index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IPF%, immature platelet fraction; mMRC, Modified Medical Research Council.
*Statistically significant correlation.

there was a significant increase in IPF% values. This increase was found to be associated with scores indicating the severity of sepsis and laboratory values.[16]

The increased values IPF% have been demonstrated in patients with primary immune thrombocytopenia.[17] Additionally, it was found to be higher in patients responding to steroids compared to

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TABLE 5 IPF% values of COPD patients with and without additional comorbidities.

		IPF%	
Comorbidity	***n***	**Mean ± SD**	**Median (min.–max.)**
CAD			
With	25	3.36 ± 2.30	2.70 (0.70–10.8)
Without	109	3.47 ± 2.44	2.70 (0.53–13.70)
HT			
With	66	3.37 ± 1.96	2.85 (0.70–9.20)
Without	68	3.53 ± 2.79	2.50 (0.53–13.70)
DM			
With	40	3.33 ± 1.80	3.20 (0.80–9.0)
Without	94	3.50 ± 2.63	2.60 (0.53–13.70)
AF			
With	16	3.58 ± 2.55	3.20 (0.70–10.80)
Without	118	3.43 ± 2.40	2.70 (0.53–13.70)
CKD			
With	10	3.48 ± 2.20	3.13 (0.75–9.60)
Without	124	3.14 ± 1.40	2.40 (0.64–10.40)

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes melitus; HT, hypertension.

nonresponders.[18] In light of these studies, the correlation of IPF% values with clinical parameters in cases of systemic lupus erythematosus (SLE) with autoimmune features was investigated. Furthermore, the utility of IPF% in predicting the improvement of platelet counts with treatment was assessed in thrombocytopenic patients.[19] As a result, it was reported that IPF% indicates the rate of platelet production in the bone marrow and reflects the severity of the disease, while the AIPC was suggested to predict a rapid response to steroids in the treatment of thrombocytopenia in SLE patients.

In this study, IPF% and AIP were found to have similar prognostic value in COPD patients. In SARS-COV2 infection manifests as COVID-19, characterized by increased inflammatory response and platelet activation, AIPC and IPF% serve as biomarkers associated with disease severity and mortality.[20] There are studies showing that AIPC is a better prognostic factor in thrombotic thrombocytopenic purpura patients than IPF%.[21] In patients with immune thrombocytopenia, IPF% is a more important parameter than the total platelet count in monitoring the recovery process of platelet function.[22]

According to our results, there was no statistically significant difference in mean IPF% value between patients with AECOPD and stable period, but it was significantly higher than the healthy control subjects. This result led us to the conclusion that IPF% may be a biomarker associated with systemic inflammation, which is not much affected by acute infection in COPD. This raises the question of whether it can be used to evaluate the severity of inflammation independent of exacerbation in COPD. It is clear that more extensive research needs to be done to answer this question.

NLR has now been recognized as a valuable biomarker in systemic inflammation. IPF% has been found to be associated with disease stage, severity, hospitalization, morbidity, relapses, and mortality in many chronic diseases such as metabolic, cardiovascular, liver and kidney diseases.[23] In this study, there was a positive correlation between IPF% values and NLR values in stable and AECOPD. Although there is no study on the correlation of IPF% with NLR, reviews demonstrated that there are many studies investigating the relationship between NLR and COPD. In line with the results of our study, İn et al. showed that NLR values of patients with COPD were found to be significantly higher in both acute exacerbation and stable periods compared with the healthy control group. However, the significance was higher in the exacerbation period. In addition, in the same study, when the threshold value of NLR was taken as 3.34, the sensitivity of detecting COPD exacerbation was 78.7% and the specificity was 73.2% (AUC 0.863, $p < 0.001$).[24]

Although the CRP value was significantly higher in exacerbation patients than in stable patients, there was no linear correlation between CRP and IPF% values. Similar to our study, Georgakopoulou et al. could not show a linear correlation between IPF% and CRP in the study with pneumonia cases.[14]

Liu et al. used together IPF% 5.50 cutoff and CRP for the diagnosis of infection concluded that the sensitivity and specificity were 91.78 and 93.18%, respectively.[25]

It is an expected result in COPD that systemic inflammation plays a role in the pathogenesis, with infection being the most significant risk factor for exacerbations. An increase in WBC count in the complete blood count is an important biomarker for the onset, classification, and exacerbation of COPD. Particularly, COPD exacerbation is mostly associated with infection, and during this period, we observe an increase in leukocyte count, especially in the number of neutrophils. It is known that COPD patients with a high eosinophil count have a higher risk of exacerbation, and the severity of the disease is more pronounced.[1,2]

PLR may be a valuable inflammatory marker in cancer cases. However, heterogeneous results are obtained in rheumatological and immunological diseases, providing more meaningful results when used in conjunction with NLR.[26]

Research findings indicate that the MLR could serve as a biomarker demonstrating the short-term prognosis associated with inflammatory response in sepsis, cancer, and cardiovascular diseases.[27,28] Furthermore, it has been demonstrated to have the potential to be an independent indicator of acute kidney injury in the critically ill patient population with organ failure.[29] In our study, the absence of significant differences among stable COPD patients, COPD exacerbation groups, and the control group suggests that MLR may not be a meaningful indicator for systemic inflammation in COPD.

The frequency of exacerbation in COPD is related to disease severity and is an indicator of systemic inflammation. In our study, IPF % was found to be associated with the number of COPD exacerbations in the last year. This relationship suggests that IPF% may be a different indicator of systemic inflammation.

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5 | CONCLUSIONS

This is the first study to examine the relationship between AIPC, IPF% value, and COPD. The higher IPF% values in patients with exacerbation and stable COPD compared with the healthy group and the positive correlation between WBC, NLR with IPF% values are the parameters showing that IPF% can be used as an inflammation marker in COPD patients. The lack of difference between IPF% values in patients with exacerbation and stable patients indicates that patients in the stable period are also characterized by low-grade systemic inflammation.

AUTHOR CONTRIBUTIONS

N. A. performed the literature search and data collection, and reviewed the manuscript. F. A. designed the study, performed the literature search and data collection, and reviewed and submitted the manuscript. Ö. D. designed the study, performed tests, and reviewed the manuscript. A. G. K. designed the study, performed data collection, and prepared and reviewed the manuscript. M. Ö. designed the study, performed data collection, and prepared and reviewed the manuscript. S. E. performed data collection and prepared and reviewed the manuscript. A. Ç. performed data collection and prepared and reviewed the manuscript. A. K. designed the study, prepared and reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in http://www.medicine.ankara.edu.tr/en/academic-faculty at http://www.medicine.ankara.edu.tr/en/academic-faculty.

PATIENT CONSENT STATEMENT

The written consent of the participants has been obtained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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