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Original Research

Relationship Between Platelet Parameters and Eosinophils with Disease Severity, CRP and Treatment in Stable COPD

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Abstract

Objectives: Chronic obstructive pulmonary disease (COPD) is a complex inflammatory condition that primarily impairs respiration but can also affect hemostasis. This study aimed to determine differences in platelet-related parameters and eosinophil between COPD patients and healthy controls.

Methods: We included 149 patients with stable COPD and 30 healthy controls who were recruited from the outpatient department of Chest Diseases. Complete blood count, including platelet count (Plt), and C-reactive protein were measured. Other platelet-related parameters were determined, including mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (Pct), their ratios (MPV/Plt, MPV/Pct, PDW/Plt, PDW/Pct), and platelet to lymphocyte ratio (PLR).

Results: COPD patients and controls did not show significant differences in platelet parameters (Plt, Pct, PDW, MPV, PDW/Pct, MPV/Pct). PLR was significantly higher in the patient groups than in the control group (p=0.009). Correlation between platelet count and PLR (p=0.047; p=0.05) showed borderline significance. However, we found no correlation between the patients' CRP levels, Pct, PDW, PDW/Pct, MPV/Pct and MPV values. There were no significant differences in platelet parameters in patients using and not using long-acting muscarinic antagonists (LAMA). We did not find differences in eosinophil levels among COPD severity grades.

Conclusion: In our study, we found that PLR is elevated in COPD. PLR could be a useful and easily accessible parameter to evaluate ongoing inflammation in stable COPD. Large-scale studies are warranted to further investigate the role of platelet and eosinophil parameters in COPD.

Keywords: COPD, eosinophil, inflammation, platelet related parameters

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Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammatory response in the airway that results in airflow limitation.[1,2] Although preventable and treatable, COPD is very common and poses a huge social and economic burden. Exacerbations and comorbidities increase the risk of severe disease.[3] Treatment with short-acting β2-agonists (SABAs) or short-acting muscarinic antagonists is recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) to improve forced expiratory volume in the first second (FEV1) and reduce COPD symptoms. Long-acting β2-agonists (LABAs), long-acting muscarinic antagonists

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(LAMAs), or inhaled corticosteroids (ICS) can be combined with SABAs and LABAs to improve lung function through long-term bronchodilation.[1]

Platelets can induce the inflammatory response by secreting various cytokines, interacting with leukocytes, and facilitating the interaction between the endothelium and immune cells.[4] Inflammatory parameters, such as neutrophil–lymphocyte ratio and platelet–lymphocyte ratio (PLR), are widely used in the diagnosis of various inflammatory diseases and treatment responses.[5,6] Since platelets are an important feature of the inflammatory process in COPD, changes in peripheral platelet indices are expected during the disease.[7] Indeed, a previous study showed that mean platelet volume levels were reduced in patients with stable COPD.[8] In a different study, MPV was not correlated with any indicator of COPD severity.[9] CRP, another inflammatory molecule in COPD, can remain high in the stable disease as well as during exacerbations.[10]

Growing evidence suggests that blood eosinophil counts can be used for treatment prognosis in patients with COPD.[11] Previous studies suggest that patients in exacerbation and with low blood eosinophil levels may benefit less from glucocorticoids. Screening using eosinophils could be a useful marker to guide corticosteroid use.[12] The use of eosinophil count to predict COPD exacerbation is controversial, as it varies considerably throughout the course of the disease.[9] Very few studies have investigated the relationship between disease severity and blood eosinophils.

In this study, we aimed to evaluate the relationship of platelet parameters and eosinophil levels with disease severity (GOLD stages) in stable COPD. We also aimed to investigate the potential role of platelet parameters as markers of treatment response and inflammation.

Methods

This cross-sectional study was conducted in a tertiary care center in accordance with the Declaration of Helsinki (as revised in 2013). Our research plan was approved by our institutional ethics board (date: 02.03.2021, number: 3181). Participants were recruited from the outpatient clinic of Chest Diseases between February 2021 and July 2021. Written informed consent was obtained from all participants. Clinical information including sex, age, smoking history, concomitant diseases, and treatments received, were recorded.

Patients who were not diagnosed with and treated for COPD exacerbation in the last three weeks were considered stable and included in the study. Exclusion criteria were below 18 years of age, lung disease other than COPD, transplantations, severe liver disease, severe renal failure, malignant disease, diabetes with serious complications, systemic inflammatory disease, other specific or non-specific acute inflammation, and use of anticoagulant or antiplatelet drugs. Patients were classified using the GOLD criteria by performing spirometry and the CAT score was applied.

Laboratory

Venous blood samples were extracted from participants after 12 hours of overnight fasting. Whole blood samples were placed in K2 EDTA tubes (Sarsted AG & Co. Nümbrecht, Germany). Samples were analyzed for complete blood count using Mindray BC6800 (Shenzhen, China) on the day of collection. Serum samples were placed in gel vacuum tubes (Sarsted AG&Co. Nümbrecht, Germany) and underwent C-reactive protein analysis on a Roche Cobas 8000 analyzer (Roche Diagnostics, Manheim, Germany).

Statistics

Statistical analyses were performed using SPSS version 23.0 program (IBM, New York, USA). Normality of data was examined by histogram graphs and evaluated using Kolmogorov–Smirnov/Shapiro–Wilk tests. Quantitative variables are presented as mean, standard deviation, median, minimum, maximum, and interquartile range (IQR). To compare groups, independent sample t-test with Bonferroni correction was performed for normally-distributed variables (parametric) and Mann–Whitney U Test with Bonferroni correction for non-normally-distributed (nonparametric) variables. Categorical variables are presented as frequency and percentages and were analyzed using Chi-square of Fisher's exact test. Spearman correlation test was used to evaluate the relationships between quantitative variables. Statistical test results with p-values below 0.05 were considered statistically significant.

Results

A total of 149 individuals were included, which was composed of 124 stable COPD patients (29 female and 95 male) and 25 healthy volunteers. The mean age of the participants was 61.71±11.57 years. Patients were classified using the GOLD criteria: GOLD A–B (n=55) and GOLD C–D (n=69); GOLD 1–2 (n=68) and GOLD 3–4 (n=56).

The distribution of patients with GOLD A–B and GOLD C–D COPD according to age, sex, smoking history, medication, and comorbidities is given in Table 1. Groups did not differ in age (p=0.6) and sex distribution (p=0.63). Long-acting respiratory beta-agonists (LABA) and inhaled corticosteroid (ICS) did not differ between patient groups (p>0.99, p=0.70). However, long-acting muscarinic antagonist (LAMA) use was significantly higher in the GOLD C–D group (p=0.002). Frequency of hypertension (HT) and diabetes mellitus (DM) (p=0.14, p=0.3) were similar.

Table 1. Comparisons of parameters evaluated in GOLD A–B, GOLD C–D and all patient groups

	Patients (n=124)	GOLD A–B (n=55)	GOLD C–D (n=69)	p
Age, year				0.60[a]
Mean±SD	64±10.5	63.4±11.4	64.5±9.8	
Median (min–max)	64 (37–87)	65 (37–83)	64 (39–87)	
Gender, n (%)				0.63[b]
Female	29 (23.4)	14 (25.5)	15 (21.7)	
Male	95 (76.6)	41 (74.5)	54 (78.3)	
LABA, n (%)	121 (97.6)	54 (98.2)	67 (97.1)	>0.99[d]
LAMA, n (%)	101 (81.5)	38 (69.1)	63 (91.3)	**0.002**[b]
IKS, n (%)	117 (94.4)	51 (92,7)	66 (95.7)	0.70[d]
HT, n (%)	41 (33.1)	22 (40)	19 (27.5)	0.14[b]
DM, n (%)	18 (14.5)	10 (18.2)	8 (11.6)	0.30[b]
WBC				**0.017**[a]
Mean±SD	8.35±2.43	7.78±2.18	8.81±2.53	
Median (min–max)	8.05 (3.32–17.05)	7.83 (3.81–15.86)	8.91 (3.32–17.05)	
PLT				0.24[c]
Mean±SD	264.5±78.8	252.6±66.5	274±86,8	
Median (min–max)	257 (129–729)	251 (129–406)	263 (154–729)	
Pct				0.20[c]
Mean±SD	0.26±0.07	0.25±0.06	0.26±0.07	
Median (min–max)	0.25 (0.11–0.6)	0.24 (0.11–0.4)	0.26 (0.12–0.6)	
PDW				0.14[a]
Mean±SD	16.1±0.4	16±0,4	16.1±0.4	
Median (min–max)	16.1 (14.7–17.1)	16 (14.7–17.1)	16.1 (15.2–17.1)	
PDW/pct				0.10[a]
Mean±SD	67±18.7	70±21.1	64.5±16.3	
Median (min–max)	64 (25–145)	65 (39–145)	63 (25–128)	
MPV/pct				0.28[c]
Mean±SD	40.9±12.5	42.4±12.4	39.7±12.5	
Median (min–max)	38.5 (13–104)	40 (24–77)	38 (13–104)	
PLR				0.74[c]
Mean±SD	139.5±97	128.6±44.3	148.2±123.7	
Median (min–max)	130 (23–950)	123 (23–247)	132 (52–950)	
CRP				**0.001**[c]
Mean±SD	8.8±14.7	5.3±7.4	11.6±18.2	
Median (min–max)	4.9 (0.3–136.2)	3.5 (0.3–51.3)	6.6 (0.5–136.2)	
MPV				0.88[c]
Mean±SD	9.8±1.1	9.8±1	9.8±1.2	
Median (min–max)	9.7 (7.3–12.8)	9.7 (7.5–12.6)	9.7 (7.3–12.8)	
Lenfosit				0.34[c]
Mean±SD	2.21±0.91	2.15±0.92	2.25±0.91	
Median (min–max)	2.09 (0.51–6.72)	2.01 (1.02–6.72)	2.18 (0.51–5.15)	
Mean±SD (%)	58.9±14	67.1±10.6	52.3±12.9	
Median (min–max)	59 (22–93)	66 (45–90)	53 (22–93)	

[a]: Independent-Samples T-Test, [b]: Chi-Square, [c]: Mann–Whitney U, [d]: Fisher's Exact Test, p<0.05. GOLD: Chronic Obstructive Lung Disease, SD: Standard deviation, PLT: Platelet count, Pct: Plateletcrit, PDW: Latelet distribution width, MPV: Mean platelet volume, PLR: Platelet–lymphocyte ratio, CRP: C-reactive protein.

Mean white blood cells (WBC) showed significant differences between groups, with lower levels in the GOLD A–B group (p=0.017). There were no significant differences between the groups in the platelet parameters Plt, Pct, PDW, MPV, PDW/Pct, MPV/Pct, and PLR (p=0.24; p=0.20; p=0.14; p=0.10; p=0.28; p=0.74, respectively). While CRP was lowest in the GOLD A–B group, there was a significant difference between all groups (p=0.001).

Table 2. Comparison of the parameters evaluated in GOLD 1–2, GOLD 3–4 and control groups

	Control (n=25)	GOLD 1–2 (n=68)	GOLD 3–4 (n=56)	p
Age, year				**<0.001**[a]
Mean±SD	50.4±10*	64.2±11	63.8±10	
Median (min–max)	52 (35–68)	65.5 (37–83)	64 (39–87)	
Gender, n (%)				**0.005**[b]
Female	14 (56) *	16 (23.5)	13 (23.2)	
Male	11 (44) *	52 (76.5)	43 (76.8)	
WBC				**0.039**[c]
Mean±SD	7.65±2.04	8.03±2.51	8.74±2.27	
Median (min–max)	7.72 (4.6–13.23)+	7.74 (3.81–17.05)	9.2 (3.32–14.83)+	
PLT				0.82[c]
Mean±SD	260.1±67.8	262.3±86.6	267.1±68.9	
Median (min–max)	255 (130–391)	251 (129–729)	259 (154–580)	
Pct				0.84[c]
Mean±SD	0.31±0.3	0.26±0.08	0.26±0.05	
Median (min–max)	0.24 (0.15–1.7)	0.25 (0.11–0.6)	0.26 (0.12–0.42)	
PDW				0.77[c]
Mean±SD	16.1±0.4	16±0.5	16.1±0.4	
Median (min–max)	16 (15.6–16.8)	16.1 (14.7–17.1)	16.1 (15.4–17.1)	
PDW/pct				0.88[c]
Mean±SD	64.5±20.8	68±20.9	65.7±15.7	
Median (min–max)	67.5 (9.2–110)	65 (25–145)	63.5 (36–128)	
MPV/pct				0.72[c]
Mean±SD	38.8±13.6	41.3±12.3	40.3±12.7	
Median (min–max)	38 (5–76)	39.5 (13–77)	38 (17–104)	
PLR				**0.009**[c]
Mean±SD	105.5±38.5	125.8±44.6	156.1±134.6	
Median (min–max)	102 (56–244)*	125.5 (23–247)	131.5 (59–950)	
CRP				**0.001**[c]
Mean±SD	8.4±13.2	5.7±7.6	12.6±19.7	
Median (min–max)	3.4 (0.3–50.4)	3.8 (0.3–51.3)	6.9 (1.2–136.2)*	
MPV				0.60[c]
Mean±SD	9.7±1.1	9.8±1.1	9.8±1.2	
Median (min–max)	9.5 (8.2–12.2)	9.8 (7.5–12.6)	9.6 (7.3–12.8)	
Lenfosit				**0.034**[c]
Mean±SD	2.58±0.65	2.31±1.03	2.09±0.73	
Median (min–max)	2.35 (1.36–3.66)+	2.06 (1.02–6.72)	2.15 (0.51–3.85)+	

[a]: One-Way ANOVA, [b]: Chi-Square, [c]: Kruskal–Wallis H, *: The group from which the statistically significant difference originates, +: Statistically significant difference was found between the groups. p<0.05. GOLD: Chronic Obstructive Lung Disease, SD: Standard deviation, WBC: White blood cell, PLT: Platelet count, Pct: Plateletcrit, PDW: Latelet distribution width, MPV: Mean platelet volume, PLR: Platelet–lymphocyte ratio, CRP: C-reactive protein.

The comparison of platelet and lymphocyte parameters between GOLD 1–2 and GOLD 3–4 groups are shown in Table 2. WBC was significantly higher in the GOLD 3–4 group compared to the control group (p=0.039). Platelet parameters (Plt, Pct, PDW, MPV, PDW/Pct, MPV/Pct) were similar across groups (p=0.82; p=0.84; p=0.77; p=0.6; p=0.88; p=0.72, respectively). PLR values were observed to be significantly higher in COPD patients than in the control group (p=0.009). Moreover, CRP values were significantly higher in the GOLD 3–4 group compared to the GOLD 1–2 and control groups (p=0.001). Lymphocyte values in the GOLD 3–4 and control groups were significantly different (p=0.034).

The correlation between platelet parameters and CRP in the patients is shown in Table 3. While there were no correlations in the Pct, PDW, PDW/Pct, MPV/Pct and MPV with CRP levels, borderline significance was found in the correlation between platelet count and PLR (p=0.047; p=0.05).

Table 3. Correlation evaluation of CRP and platelet parameters

Patient (n=124)	CRP	
	r_s	p
PLT	0.179	**0.047**
Pct	0.174	0.053
PDW	0.063	0.49
PDW/Pct	−0.166	0.065
MPV/Pct	−0.163	0.070
PLR	0.177	**0.050**
MPV	−0.075	0.41

p<0.05. CRP: C-reactive protein, PLT: Platelet count, Pct: Plateletcrit, PDW: Latelet distribution width, MPV: Mean platelet volume, PLR: Platelet–lymphocyte ratio.

Platelet parameters stratified according to LAMA use are given in Table 4. There was no significant difference in platelet parameters between patients using LAMA and patients not using LAMA. While patient severity groups did not differ in current use of cigarettes (p=0.26), the amount of cigarettes smoked (number of pack-years) in the GOLD C–D group (p=0.007) was significantly higher. Lastly, there were no significant differences in eosinophil counts between GOLD 1–2 and 3–4 groups and between GOLD A–B and GOLD C–D groups (Table 5). We also found no relationship between CRP and eosinophil variables (p>0.05).

Discussion

In our study, platelet parameters did not significantly differ between groups (Plt, Pct, PDW, MPV, PDW/Pct, and MPV/Pct). PLR and WBC were values elevated in COPD patients compared to healthy controls. WBC was significantly higher in all patient groups compared to the control. Borderline significance was found only in the correlation between platelet count and PLR. Lymphocyte count also differed between the GOLD 3–4 and control groups. Platelet parameters were similar regardless of LAMA use. Eosinophils did not vary between controls and patients, across COPD severity grades, and with CRP levels.

In a large study on patients with COPD, WBC and CRP were found to be significantly higher in COPD patients compared to healthy controls.[12] We found similar WBC elevations in COPD patients (p=0.017). These suggest that despite having stable disease, inflammation can persist in patients with COPD.

PDW directly measures variability in platelet size, activation, and morphology.[13,14] Under physiological conditions, MPV and PDW are positively correlated.[14] In our study, we

Table 4. Evaluation of platelet parameters according to LAMA use

	LAMA – (n=23)	LAMA + (n=101)	p
PLT			0.98
Mean±SD	258.7±58	265.8±83.1	
Median (min–max)	257 (159–354)	257 (129–729)	
Pct			0.75
Mean±SD	0.25±0.07	0.26±0.07	
Median (min–max)	0.26 (0.15–0.44)	0.25 (0.11–0.6)	
PDW			0.43
Mean±SD	15.9±0.5	16.1±0.4	
Median (min–max)	16 (14.7–16.7)	16.1 (15.2–17.1)	
PDW/Pct			0.84
Mean±SD	66.6±16.6	67.1±19.2	
Median (min–max)	62 (36–99)	64 (25–145)	
MPV_Pct			0.92
Mean±SD	40.2±9.6	41±13.1	
Median (min–max)	39 (27–61)	38 (13–104)	
PLR			0.72
Mean±SD	124.2±40.5	143±105.6	
Median (min–max)	117 (23–247)	131 (52–950)	
MPV			0.84
Mean±SD	9.8±1.2	9.8±1.1	
Median (min–max)	9.6 (7.5–12.6)	9.7 (7.3–12.8)	

p<0.05. LAMA: Long-acting muscarinic antagonist, PLT: Platelet count, Pct: Plateletcrit, PDW: Latelet distribution width, MPV: Mean platelet volume, PLR: Platelet–lymphocyte ratio.

Table 5. Comparison of smoking and eosinophil levels between GOLD A–B and GOLD C–D, GOLD 1–2 and GOLD 3–4 groups

	GOLD A–B		GOLD C–D		p
	Mean±SD	Median (IQR)	Mean±SD	Median(IQR)	
Eozinofil	0.22±0.23	0.17 (0.1–0.24)	0.25±0.17	0.23 (0.14–0.33)	0.054
Eo%	2.92±3.04	2.2 (1.2–3.8)	2.91±1.90	2.3 (1.5–4)	0.443
Smoke	40.26±19.59	33 (30–45)	51.69±25.70	40 (35–60)	**0.007**
	GOLD 1–2		GOLD 3–4		p
	Mean±SD	Median(IQR)	Mean±SD	Median(IQR)	
Eozinofil	0.23±0.22	0.19 (0.12–0.32)	0.25±0.18	0.22 (0.13–0.29)	0.466
Eo%	2.94±2.79	2.3 (1.4–3.75)	2.88±2.01	2.25 (1.5–4.1)	0.837
Smoke	41.7±19.26	35.5 (30–52)	53.07±27.59	40 (35–80)	**0.032**

p<0.05. GOLD: Chronic Obstructive Lung Disease, SD: Standard deviation, IQR: Interquartile range

did not detect differences in the platelet parameters Plt, Pct, PDW, MPV, PDW/Pct, and MPV/Pct. In conditions of increased thrombopoiesis, MPV can elevate due to an increase in new platelets in the circulation.[15] Lifestyle modifications, pharmacological agents (antihypertensive, lipid-lowering) and dietary approaches may affect MPV values.[16] One-third of our patients had hypertension and 14% had diabetes and were taking medications. In our study, we did not detect a significant change in MPV levels in patients with stable COPD (p=0.88). Comorbidities and polypharmacy could have contributed to this negative finding. Although there are studies showing that MPV, an indicator of platelet production and stimulation, increases during the stable phase in COPD, other studies have observed that it can act as an acute phase reactant during exacerbation.[17,18]

PLR, a surrogate measure of inflammation, was higher in patients with COPD (p=0.009). Its clinical utility lies in the easy access of measuring PLR. Furthermore, Liu et al.[19] showed that PLR combined with other indices can predict exacerbation in patients with stable COPD.

CRP, another inflammatory marker in COPD, can be high in both stable and exacerbated COPD.[10] In a study evaluating 35 patients with stable COPD, CRP was higher in patients than in controls, consistent with continuous low-grade systemic inflammation in stable COPD.[20] In another study with 6574 COPD patients, CRP, leukocyte, and fibrinogen levels were elevated in the stable period and predicted a 4-fold higher risk of an exacerbation within a year than patients with normal levels.[21] Patients in our study consumed an average of 46.57±23.76 packs-years. We found that CRP and smoking levels differed between GOLD 1–2 and 3–4 groups and between GOLD A–B and C–D groups (p<0.05).

LABA and ICS use did not differ in COPD groups (p>0.99), while LAMA use was higher in the GOLD C–D group (p=0.002). Studies show that 4%–60% of ICS reaches the lungs, which produces its intended pharmacological effect. A small portion reaches the pulmonary vessels while most of the inhaled drug enters the gastrointestinal tract, both of which introduce the drug into the systemic circulation. The drug can undergo hepatic inactivation and possibly exert extrapulmonary side effects.[22] In the patients in our study, 51 patients in the GOLD A–B group and 66 patients in the GOLD C–D group were using ICS. Only 7 patients were not using ICS, which is a limitation of our study. Therefore, our outcome measures may have been affected by ICS in the systemic circulation.

Eosinophils play an important role in regulating and modulating immune responses. Although the role of eosinophilic inflammation in COPD remains controversial, an increase in eosinophilic cationic protein and eosinophilic peroxidase (EPO) levels was previously reported in sputum samples from patients with stable COPD. Most studies show that eosinophils are elevated in the airways during a COPD attack.[23] In our study, eosinophil count did not differ across groups and was not correlated with CRP levels (p>0.05). Corticosteroids are known to suppress the activation and movement of eosinophils and other inflammatory cells. We think that ICS may have contributed to this lack of effect on eosinophils. Although eosinophils are typically found in circulating blood, some reside in various tissues.[24] Eosinophils in induced sputum have been extensively studied as a valid biomarker for COPD. However, measuring sputum eosinophils has been limited to research applications, is not available in all centers, and is costly. Schumann et al.[25] found that blood eosinophil levels vary throughout the course of COPD and should be measured across different timepoints for long-term monitoring. Eltboli et al.[26] evaluated the number of bronchial submucosal eosinophils and reticular basement membrane thickening in 20 COPD patients and 21 controls. They found positive correlations

between these measures and differential blood eosinophil count. This suggests that peripheral blood eosinophil level is a good biomarker for submucosal eosinophils and airway remodeling in COPD.

According to the GOLD 2021 strategy report, for patients with blood eosinophil levels above 300 cells/μL, ICS is indicated in the treatment plan. Some studies suggest that eosinophil levels can be used for ICS response prognosis. In our study, we found no correlation between the number and percentage of blood eosinophils and the severity of COPD. Moreover, eosinophil and CRP levels were not correlated. Because pre-ICS treatment baseline eosinophil levels were not available, we could not rule out the occurrence of drug-induced immunocyte suppression.

The limitations of our study are the small sample size and a single center site, which may not be generalizable to COPD patients across the country. Moreover, we were not able to achieve our target sample size due to the COVID-19 pandemic, which resulted in a curfew for individuals over 65 years and reduced hospital admissions for non-COVID-19 patients. The duration of the treatment was extended to reduce hospital admissions for patients diagnosed with GOLD C–D.

Conclusion

Patients with stable COPD showed high levels of inflammatory markers, such as WBC and CRP, indicating ongoing systemic inflammation despite controlled disease. We found that PLR, another measure of inflammation, was elevated in patients with stable COPD. PLR could be a clinically useful and easily accessible parameter to evaluate ongoing inflammation during the stable phase of the disease. Other platelet parameters and eosinophil counts were apparently not useful as functional biomarkers of disease severity or inflammatory burden, which could have been confounded by the presence of comorbidities and polypharmacy.

Disclosures

Ethics Committee Approval: The study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (date: 02.03.2021, no: 3181).

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