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Evaluation of novel hematological indices in idiopathic pulmonary fibrosis: Impact of antifibrotic therapy

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Abstract:

BACKGROUND AND AIM: Idiopathic pulmonary fibrosis (IPF) is a lung disease of unknown etiology, characterized by inflammation. Ratios involving neutrophils, lymphocytes, monocytes, and platelets reflect chronic inflammation more accurately than individual cell counts. Biomarkers play a critical role in assessing disease risk, enabling early diagnosis, predicting prognosis, and monitoring treatment response. This study aimed to evaluate hematological indices as markers of inflammation in newly diagnosed IPF patients and to compare these indices with those in healthy controls and patients receiving antifibrotic therapy.

METHODS: We assessed the demographic characteristics and hematological parameters of 55 IPF patients undergoing antifibrotic treatment and 20 healthy controls. Novel hematological indices were evaluated at diagnosis and after one year of treatment.

RESULTS: There were no significant differences in age or gender between the IPF group and the healthy controls. Pre-treatment inflammatory markers were significantly elevated in IPF patients compared to healthy individuals. However, no significant changes in these markers were observed before and after antifibrotic therapy.

CONCLUSIONS: Neutrophil counts, neutrophil-to-lymphocyte ratio, systemic inflammatory index, systemic inflammation response index, and the aggregate index of systemic inflammation may serve as useful inflammatory and prognostic markers in IPF. Given that these parameters are part of routine laboratory investigations, their application is simple, cost-effective, and practical for clinical follow-up during antifibrotic treatment.

Keywords:

Antifibrotic treatment, hematological inflammatory indices, idiopathic pulmonary fibrosis, nintedanib, pirfenidone

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease of unknown cause, characterized by poor prognosis and advanced fibrosis.[1] It is the most common and severe form of idiopathic interstitial pneumonias, accounting for approximately 20% of all interstitial diseases.[1,2] Although incidence varies by country, it is estimated to be around 10 per 100,000 people per year,

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with a reported prevalence ranging from 10 to 494.5 per 100,000 per year.[2] IPF predominantly affects older adults, particularly males, and is rare before the age of 50. The median age at diagnosis is 66 years.[3] The disease is marked by dyspnea, progressive decline in lung function, and high mortality.[2,3]

Fibrosis in IPF results from repetitive microtrauma to the alveolar epithelium.[4] This process may be triggered by both genetic mutations and environmental exposures, such as tobacco smoke, infections, and occupational hazards. Several cytokines, including transforming growth factor-β (TGF-β), play a role in the pathogenesis of IPF.[5] Repeated micro-injuries to the alveolar epithelium and basement membrane activate immune cells and lead to the secretion of proinflammatory cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and monocyte chemotactic protein-1 (MCP-1). IPF is characterized by both acute and chronic inflammation.[5,6]

Biomarkers are crucial for identifying disease risk, facilitating early diagnosis, assessing prognosis, and monitoring treatment response. Ideally, biomarkers should be non-invasive, valid, reliable, and easy to obtain. Although numerous biomarkers have been studied in IPF, none have yet been established for routine clinical practice.[3]

Inflammation is mediated by direct interactions between inflamatory mediators and blood cells.[7,8] Over the past decade, accumulating evidence suggests that indices derived from ratios of blood cell counts correlate more strongly with chronic inflammatory states than individual cell populations.[7] For example, neutrophilia and lymphopenia are commonly observed in systemic inflammation. Additionally, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) have all been reported as markers of inflammation.[9] These indices are inexpensive and easily accessible markers derived from complete blood counts, though they have not previously been used to assess disease presence or disease activity in IPF.

In this study, we aimed to evaluate hematologic indices as indicators of systemic inflammation in newly diagnosed IPF patients. We also compared these parameters with those of healthy controls and patients who had completed one year of antifibrotic therapy.

Materials and Methods

This retrospective study included 55 patients diagnosed with idiopathic pulmonary fibrosis at the chest diseases clinic and treated with antifibrotic therapy (nintedanib or pirfenidone) for at least one year between October 1, 2022 and September 20, 2024, along with 20 healthy controls. The diagnosis of IPF was made in a multidisciplinary council by applying the 2022 guidelines of the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT), evaluating patients with suspected IPF based on anamnesis, clinical findings, respiratory examination, and thoracic high-resolution computed tomography showing probable or usual interstitial pneumonia patterns.[1] The control group consisted of individuals who had visited the chest diseases clinic for screening purposes over the past two years, had no known diseases, were over the age of 18, and were matched to the patient group in terms of age and gender based on their medical records. A simple random sampling method, aided by random number generator software, was used to select the sample from this population.

Patients diagnosed with IPF who had hemograms available at the initiation of treatment and after one year were included in the study. Patients who did not consent to participate, or who had cancer, systemic inflammatory or immunosuppressive diseases, or were taking immunosuppressive medications, were excluded. Demographic characteristics such as age, gender, and smoking history, along with hemogram parameters (neutrophils, lymphocytes, monocytes, and platelets), were retrieved from the hospital database for analysis. The study protocol was approved by Aydın Adnan Menderes University, Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (Approval Number: 2024/160, Date: 07.10.2024). This study was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki, its later amendments, and comparable ethical standards. Due to the retrospective nature of the study, informed consent was not obtained.

New hematological indices were calculated as indicators of systemic inflammation at the time of diagnosis and in patients who had completed the first year of treatment. These inflammation indices were derived from the hemogram data and calculated as follows:

NLR = Neutrophil-to-Lymphocyte Ratio,

MLR = Monocyte-to-Lymphocyte Ratio,

PLR = Platelet-to-Lymphocyte Ratio,

Systemic Inflammatory Index (SII) = Platelet x Neutrophil / Lymphocyte,

Systemic Inflammation Response Index (SIRI) = Neutrophil x Monocyte / Lymphocyte,

Aggregate Index of Systemic Inflammation (AISI) = Neutrophil x Platelet x Monocyte / Lymphocyte.

Statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences), version 25 (IBM Inc., Armonk, NY). Numerical data were expressed as median (25^{th}-75^{th} percentile) or mean±standard deviation (SD), while categorical variables were presented as frequency and percentage (%). The Kolmogorov-Smirnov test, histogram analysis, and skewness/kurtosis values were used to assess the conformity of numerical variables to normal distribution. The independent samples t-test was used to compare the means of two samples to determine whether the population means differed significantly for parameters with a normal distribution. The Mann-Whitney U test was used to compare two samples or groups for parameters that did not follow a normal distribution. Chi-square or Fisher's exact tests were used to analyze relationships between binary categorical variables and to compare categorical data. Comparisons within the IPF group at different time points were performed using the paired t-test for parametric data and the Wilcoxon signed-rank test for non-parametric data. Receiver operating characteristic (ROC) curve analysis was conducted to determine cut-off values, sensitivity, and specificity. A p value of <0.05 was considered statistically significant.

Results

The mean age of patients in the IPF group was 67.6±5.6 years, compared to 65.2±6.9 years in the healthy control group. In terms of gender, there were 44 male patients (80%) in the IPF group and 19 male participants (95.0%) in the healthy control group. There was no significant difference between the groups regarding age and gender. All patients with IPF had a history of smoking. Among them, 15 (27.3%) were current smokers and 40 (72.7%) were ex-smokers. In contrast, 13 individuals (65.0%) in the control group had never smoked. Regarding treatment, 25 IPF patients (45.5%) received nintedanib, and 30 (54.5%) received pirfenidone (Table 1).

The mean forced vital capacity (FVC) before treatment was 79.7±20.4, and the mean diffusing capacity for carbon monoxide (DLCO) was 57.1±16.1. After one year of treatment, mean FVC was 79.8±24.2, and the mean DLCO was 58.8±17.2. The changes in both FVC (p=0.91) and DLCO (p=0.19) during follow-up were not statistically significant. Before IPF treatment, no differences were found between the two groups, except for neutrophil count. The neutrophil count was 6691.6±2672.5 in the IPF group and 5158.5±1460.8 in the healthy control group (p=0.005). When inflammatory markers were evaluated before treatment, NLR, SII, SIRI, and AISI values in the IPF group were significantly higher than those in the healthy control group (p=0.002, p=0.002, p=0.01, and p=0.009, respectively) (Table 1).

When IPF patients were evaluated over time, no significant changes were observed in laboratory findings or composite inflammation indices, except for neutrophil count, when comparing values before treatment and after one year of antifibrotic treatment. The neutrophil count decreased from 6691.6±2672.5 in the newly diagnosed IPF group to 5905.6±2043.7 in the treated group (p=0.02). Overall, systemic inflammation markers and composite indices showed a decreasing trend during the first year of therapy. However, these changes were not statistically significant. Table 2 shows the distribution of changes in derived blood cell count-based inflammation indices in the patient group at the beginning of treatment and after antifibrotic therapy. A box plot illustrating SII, SIRI, and AISI values before and after antifibrotic treatment is presented in Figure 1. In Figure 1, the x-axis represents the Systemic Inflammatory Index, Systemic Inflammation Response Index, and Aggregate Index of Systemic Inflammation. The y-axis shows the corresponding index values, and the box plots represent the distribution of each index before and after antifibrotic treatment.

There was no statistically significant difference in hematological parameters between the pirfenidone and nintedanib groups before treatment. Similarly, no significant difference was observed between the two groups after treatment. Additionally, there were no statistically significant changes in any inflammatory marker before and after treatment within either the pirfenidone or nintedanib groups. Both within-subject and between-group differences were assessed simultaneously, and no statistically significant differences were found (p>0.05) (Table 3).

Table 1: Demographic characteristics, laboratory findings, and composite indices reflecting inflammation in the idiopathic pulmonary fibrosis and healthy control groups

	Idiopathic pulmonary fibrosis (n=55)		Healthy control group (n=20)		p
	n	%	n	%	
Age, years (mean±SD)	67.6±5.6		65.2±6.9		0.14
Gender					0.11
Male	44	80.0	19	95.0	
Female	11	20.0	1	5.0	
Treatment					–
Nintedanib	25	45.5	–	–	
Pirfenidone	30	54.5			
Smoking status					**<0.001**
Current smoker	15	27.3	5	25.0	
Ex-smoker	40	72.7	2	10.0	
Never smoked			13	65.0	
Blood cell counts (mean±SD)					
Neutrophil	6691.6±2672.5		5158.5±1460.8		**0.005**
Lymphocyte	2410.5±1012.7		2647.5±830.0		0.22
Monocyte	709.8±240.6		719.5±234.5		0.49
Platelet	316909.0±94381.8		285200.0±56808.6		0.25
Inflammation indices (mean±SD)					
NLR	3.64±3.53		2.05±0.76		**0.002**
MLR	0.34±0.23		0.27±0.08		0.30
PLR	164.2±131.2		117.8±47.5		0.10
SII*	782.7 (537.1–1184.9)		534.7 (437.0–626.5)		**0.002**
SIRI	2.39±2.22		1.39±0.46		**0.01**
AISI	736.7±556.8		397.5±162.1		**0.009**

*: Median [25th-75th percentile]. IPF: Idiopathic pulmonary fibrosis, SD: Standard deviation, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, SII: Systemic inflammatory index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

There was no statistically significant difference between the treatment groups in terms of male gender (pirfenidone: 76% vs. nintedanib: 83.3%, p=0.49), age (pirfenidone: 67.8±5.8 vs. nintedanib: 67.5±5.4, p=0.80), or smoking status (pirfenidone: 16% vs. nintedanib: 36.7%, p=0.08). The cut-off values for the inflammatory markers NLR, SII, SIRI, and AISI were 2.04, 600.5, 1.57, and 429.0, respectively. The sensitivity, specificity, area under the curve, and p-values for these markers are presented in Table 4. The ROC analysis is illustrated in Figure 2.

Discussion

In our study, inflammatory markers, including neutrophils, NLR, MLR, PLR, SII, SIRI, and AISI, were investigated in patients diagnosed with IPF who received antifibrotic treatment for at least one year, as well as in healthy controls. Neutrophil count, NLR, SII, SIRI, and AISI values were significantly higher in the IPF group compared to the control group. When IPF patients were compared before and after treatment, a significant decrease was observed in neutrophil count, while the other markers remained largely unchanged. When the treatment arms were evaluated separately, no significant changes in inflammatory markers were found in either the pirfenidone or nintedanib groups.

Table 2: Derived blood cell count inflammation indices in the idiopathic pulmonary fibrosis patient group before and after antifibrotic treatment

	Before treatment	After one year of treatment	p
Neutrophil	6691.6±2672.5	5905.6±2043.7	**0.02**
Lymphocyte	2410.5±1012.7	2370.1±964.5	0.53
Monocyte	709.8±240.6	715.2±268.2	0.58
Platelet	316909.0±94381.8	295400.0±92097.8	0.21
NLR	3.64±3.53	2.75±1.18	0.14
MLR	0.34±0.23	0.33±0.18	0.70
PLR	164.2±131.2	144.8±84.0	0.27
SII*	782.7 (537.1–1184.9)	712.2 (519.2–107.2)	0.12
SIRI	2.39±2.22	1.98±1.31	0.20
AISI	736.7±556.8	578.2±359.8	0.11

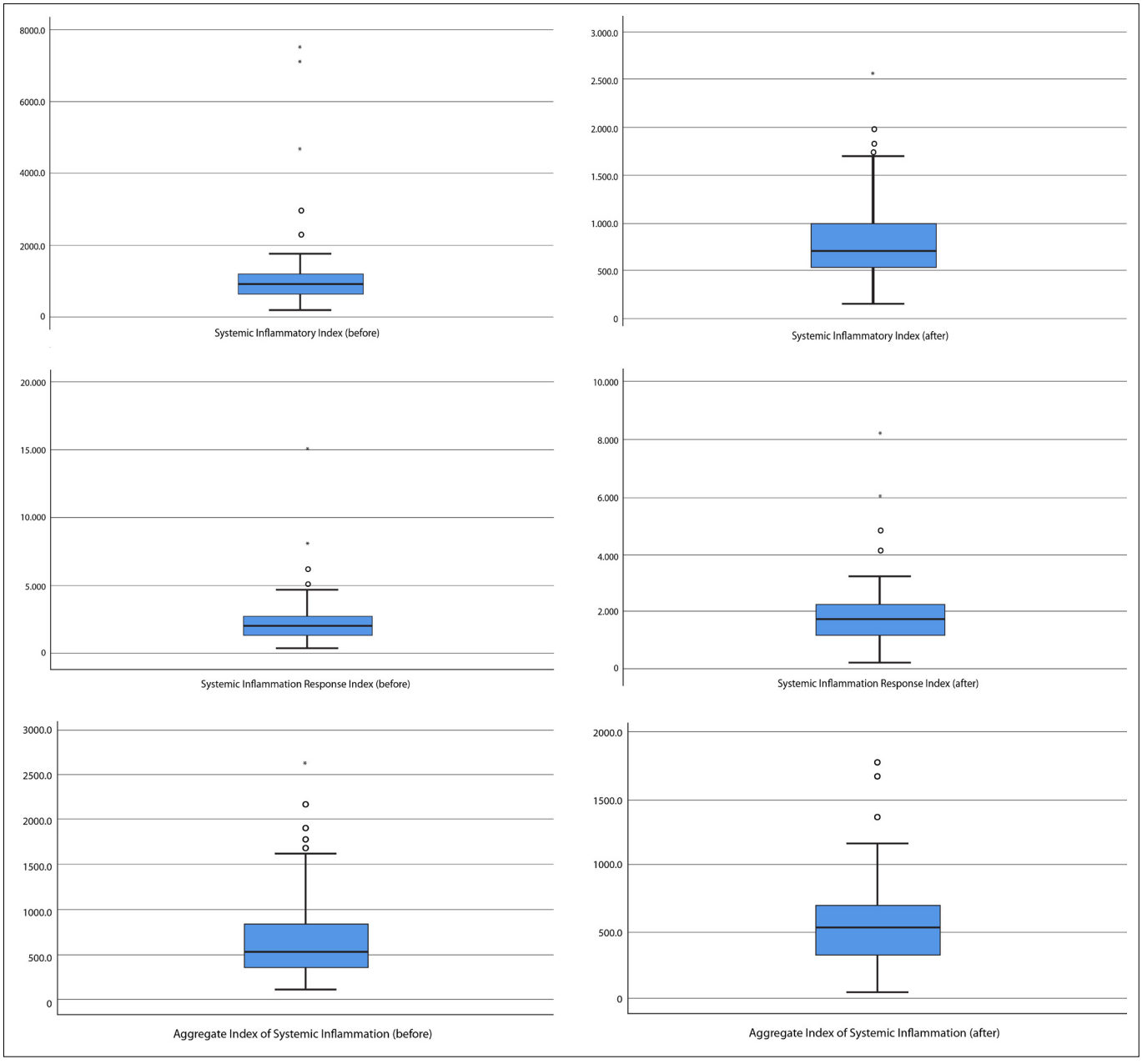

Figure 1: Box plot of systemic inflammatory index, systemic inflammation response index, and aggregate index of systemic inflammation before and after antifibrotic treatment

Early diagnosis of IPF is essential, as it is a chronic, progressive fibrotic disease with a poor prognosis.[10,11] Biomarkers play a crucial role in early diagnosis, prognosis determination, and monitoring response to treatment. An ideal biomarker should be easily obtainable using noninvasive, valid, and reliable methods.[12] IPF is a progressive condition characterized by acute or chronic inflammation.[5,6] Although matrix metalloproteinases (especially matrix metalloproteinase-7 [MMP-7] and MMP-1), surfactant proteins A and D, endothelin-1, and Krebs von den Lungen-6 (KL-6) antigen have recently been considered potential biomarkers, there is currently no established biomarker to monitor the severity of inflammation in IPF.[12,13] Recently, it has been shown that complete blood count parameters, including neutrophils, lymphocytes, monocytes, and platelets, play an important role in inflammatory diseases.[14,15] Hematological indices such as NLR, PLR, MLR, SII, SIRI, and AISI have been investigated as indicators of inflammation in various conditions, including connective tissue diseases, cardiovascular diseases, and gastric cancer, with studies exploring their relationship to disease activity.[16–20] These

Table 3: Derived blood cell count-based inflammation indices in the idiopathic pulmonary fibrosis patient group before and after antifibrotic treatment

	Before treatment		After one year of treatment	
	Pirfenidone (n=25)	Nintedanib (n=30)	Pirfenidone (n=25)	Nintedanib (n=30)
Neutrophil	6637.6±1799.4	6736.6±3258.0	5908.4±1635.5	5903.3±2358.7
Lymphocyte	2369.2±992.6	2445.0±1044.8	2340.8±735.9	2394.6±970.6
Monocyte	678.0±207.8	736.3±265.4	720.4±190.5	711.0±322.3
Platelet	307640.0±95168.6	324633.3±94635.5	308480.0±85221.3	284500.0±97535.7
NLR	3.45±2.39	3.81±4.29	2.70±0.85	2.79±1.41
MLR	0.31±0.10	0.36±0.30	0.32±0.10	0.33±0.23
PLR	164.5±128.2	163.9±135.9	147.7±75.1	142.3±91.9
SII*	1881.6 (1357.0–2769.7)	1829.1 (1150.8–2781.9)	1895.5 (1332.8–2174.5)	1565.8 (1188.9–2390.2)
SIRI	2.11±0.99	2.63±2.87	1.96±0.93	2.01±1.58
AISI	688.6±455.2	766.8±634.2	608.3±341.0	553.2±378.6

*: Median [25th-75th percentile]. IPF: Idiopathic pulmonary fibrosis, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, SII: Systemic inflammatory index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

Table 4: Cut-off values of blood cell count-derived indices for distinguishing idiopathic pulmonary fibrosis from the healthy control group

	Area under the curve (95% CI)	Cut-off value	Sensitivity (%)	Specificity (%)	p
NLR	0.736 (0.615–0.858)	2.04	70.9	70	0.002
SII	0.735 (0.612–0.857)	600.5	69.1	70	0.002
SIRI	0.684 (0.562–0.805)	1.57	60.0	60.0	0.016
AISI	0.699 (0.579–0.820)	429.0	60.0	60.0	0.009

CI: Confidence interval

inflammation-related hematological parameters have been found to be elevated not only in IPF but also in other conditions such as connective tissue diseases, cardiovascular diseases, and gastric cancer, when compared to healthy controls.[16–20] The relationship between systemic inflammation and disease activity has been evaluated in systemic lupus erythematosus (SLE), where all parameters were found to be significantly higher compared to healthy controls.[16] Moreover, a positive correlation was observed between disease activity and NLR, SII, SIRI, and AISI.[16] In another study investigating the role of hematological indices in assessing inflammation in IPF patients, NLR, MLR, PLR, SIRI, and AISI were all found to be significantly elevated in IPF patients compared to the healthy control group.[9]

However, there is still limited data on the sensitivity and specificity of these parameters in detecting inflammation. When the sensitivity of hematological parameters for predicting very high disease activity in SLE was evaluated using ROC curve analysis, the parameters with the highest sensitivity were SIRI, AISI, SII, and NLR. The area under

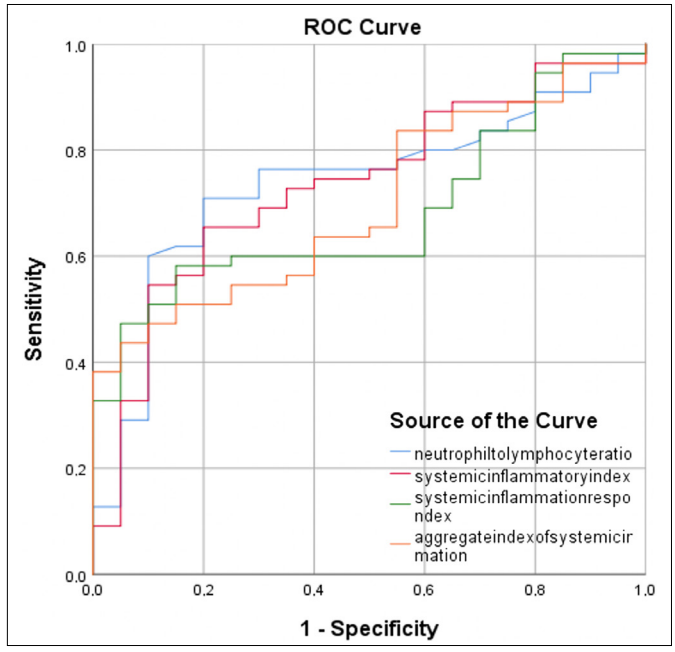

Figure 2: Receiver operating characteristic (ROC) curves for neutrophil/lymphocyte ratio, systemic inflammatory index, systemic inflammation response index, and aggregate index of systemic inflammation in distinguishing idiopathic pulmonary fibrosis patients from healthy controls

the curve (AUC) values were found to be 0.747 for SIRI, 0.734 for AISI, 0.701 for SII, and 0.664 for NLR.[16] In a study conducted on IPF patients, the AUC values for NLR, MLR, SIRI, and AISI were found to be statistically significant. Among them, NLR was identified as the best-performing index, with a cut-off value of 2.545 (AUC=0.735), showing 55% sensitivity and 85% specificity.[9] In our study, the cut-off values for NLR, SII, SIRI, and AISI were 2.04, 600.5, 1.57, and 429.0, respectively. In our study, NLR emerged as the most effective index, with a sensitivity of 70.9%, specificity of 70%, and a cut-off value of 2.04 (AUC=0.736).

In another study, AISI was reported to be a potential prognostic marker in IPF.[21] NLR, MLR, PLR, SII, SIRI, and AISI were measured at baseline in 82 IPF patients and followed up over time. AISI was found to be associated with mortality in that study.[21] However, evidence on whether these parameters are useful as markers for the follow-up of IPF patients and their response to treatment is limited. In our study, neutrophil count significantly decreased during the first year of antifibrotic treatment, while the other indices remained relatively unchanged. When patients were evaluated separately by treatment type, no significant changes were observed in inflammatory markers in either the pirfenidone or nintedanib groups. Although IPF is characterized by both acute and chronic inflammation, the inflammatory and immune responses in this fibrotic disease are not as severe and prominent as those seen in autoimmune conditions.[4,5] This may explain why the inflammatory parameters did not show significant changes. However, this finding is based on only one year of treatment. Changes in these parameters beyond the first year are currently unknown, as extended follow-up data are lacking. The main limitations of our study include its retrospective design, a small sample size, and limited data on long-term follow-up.

Conclusion

Idiopathic pulmonary fibrosis is a disease characterized by inflammation, and this study suggests that hematological parameters such as neutrophils, NLR, as well as indices like SII, SIRI, and AISI, may serve as useful markers of inflammation in IPF patients. Since these parameters are derived from routine laboratory tests, their use is simple, cost-effective, and practical. We believe that larger, prospective cohort studies are necessary to confirm whether these markers can also be used as prognostic indicators in patients undergoing antifibrotic treatment and during follow-up.

Ethics Committee Approval

The study was approved by the Aydın Adnan Menderes University, Faculty of Medicine, Non-interventional Clinical Research Ethics Committee (No: 2024/160, Date: 07/10/2024).

Informed Consent

Due to the retrospective nature of the study, informed consent was not obtained.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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No artificial intelligence (AI)-assisted technologies (such as large language models [LLMs], chatbots, or image generation tools) were used in the preparation of this manuscript.

Author Contributions

Concept – Ş.T.G., G.S.; Design – Ş.T.G., G.S.; Supervision – Ş.T.G., G.S.; Materials – Ş.T.G., G.S.; Data collection &/or processing – Ş.T.G., G.S.; Analysis and/or interpretation – Ş.T.G., G.S.; Literature search – Ş.T.G., G.S.; Writing – Ş.T.G., G.S.; Critical review – Ş.T.G., G.S.

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