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The prognostic value of peripheral hematological biomarkers in patients with hypersensitivity pneumonitis: A single-center retrospective study

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Abstract. *Background/aim:* Investigating inflammation-related biomarkers in hypersensitivity pneumonitis (HP) patients may provide valuable insights, particularly in determining their clinical course and prognosis. This study aimed to explore the potential role of peripheral hematological biomarkers in predicting the clinical course and prognosis of HP patients. *Materials and methods:* This retrospective study included 75 patients diagnosed with HP. Demographic data, symptoms, exposure history, pulmonary function tests, the systemic immune-inflammation index (SII), and the aggregate index of systemic inflammation (AISI) were analyzed. *Results:* Elevated SII (1353.6±915.15) and AISI (1001.1±695.38) values were significantly higher in patients with fibrotic HP compared to non-fibrotic HP (SII: 607.84±334.53, AISI: 375.01±235.18) ($p<0.001$). ROC analysis showed that SII (cut-off: 644.9, AUC: 0.788) and AISI (cut-off: 438.79, AUC: 0.767) had good predictive value for fibrotic HP. For mortality, SII ≥690.12 (AUC: 0.736) and AISI ≥490.35 (AUC: 0.753) were significant predictors. These elevated values were also associated with higher mortality (46.3% vs. 8.8%, $p=0.001$ for SII, and 42.5% vs. 14.3%, $p=0.004$ for AISI). In univariate analysis, older age, digital clubbing, low FVC%, and high SII/AISI were associated with fibrotic HP, while multivariate analysis identified only increased SII (OR: 1.45, $p = 0.021$) and reduced FVC% (OR: 0.999, $p = 0.043$) as independent predictors. *Conclusion:* SII and AISI appear as valuable prognostic tools in determining the clinical course and prognosis of HP patients. These biomarkers may be beneficial in the early diagnosis and management of HP, offering high sensitivity and specificity.

Key words: Hypersensitivity pneumonitis (HP), systemic immune-inflammation index, aggregate index of systemic inflammation, prognostic biomarkers, interstitial lung diseases

Introduction

Hypersensitivity pneumonitis (HP) is one of the interstitial lung diseases that occurs as a result of an excessive immune response to various environmental antigens (1). HP is typically associated with organic dust, mold, animal dander, and other environmental allergens and, if not diagnosed early and treated appropriately, it can progress to irreversible lung damage. In individuals with genetic predisposition, the disease may present as an asymptomatic sensitivity to a specific antigen or progress to pulmonary fibrosis, depending on the type of antigen and the duration of exposure (2). As a result, the clinical manifestations of HP can vary widely, exhibiting a range of imaging patterns, morphological appearances, and outcomes (1). Diagnosis of this disease is usually based on clinical findings, radiological evidence, and biological markers that support a definitive diagnosis. However, these markers may not be evident in all patients, and the diagnostic process can become complex. Moreover, a recent study conducted in Turkey emphasized

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that HP remains an underrecognized pulmonary disorder (3). Peripheral hematological biomarkers are important prognostic indicators in many diseases and may play a crucial role in predicting the clinical course of patients. Recent studies have demonstrated that various peripheral blood parameters, particularly the Systemic Immune-Inflammation Index (SII), are effective in the diagnosis and prognosis of different systemic diseases (4,5). Elevated SII values have been found to be significantly higher in patients with tuberculosis lymphadenitis compared to sarcoidosis and reactive lymphadenopathy, indicating its potential role as a biomarker in differentiating granulomatous and reactive lymphadenopathies (6), as well as in patients with hepatitis B virus-associated hepatocellular carcinoma following transcatheter arterial chemoembolization (7). The Aggregate index of systemic inflammation (AISI) is a new biomarker derived by calculating the ratio of four blood cells contributing to inflammation: neutrophils, monocytes, platelets, and lymphocytes. This index has been studied in conditions such as stroke, hypertension, and idiopathic pulmonary fibrosis (IPF), with findings suggesting a correlation between AISI and the prognosis of these diseases (8,9). Notably, Song (10) identified a strong association between SII, AISI, and an increased prevalence of peripheral arterial disease in Type 2 Diabetes Mellitus patients, highlighting a potential relationship with disease severity. C-reactive protein (CRP) is a positive acute-phase reactant synthesized by the liver, and its blood levels rise within hours in response to inflammation and infection. Elevated CRP levels are commonly associated with infections, tissue damage, inflammatory conditions such as psoriatic arthritis, venous thromboembolism (VTE), and cardiovascular events (11,12). However, there are limited studies on the prognostic value of peripheral hematological biomarkers in interstitial lung diseases such as HP. The aim of this study was to investigate the potential role of peripheral hematological biomarkers in predicting the clinical course and prognosis of patients with HP.

Materials and methods

Patients and study design

This study was conducted with the approval of the Clinical Research Ethics Committee of Gazi University (decision number 986, dated June 11, 2024). A total of 75 patients diagnosed with HP between February 2014 and December 2022 were retrospectively evaluated using clinical data obtained at the time of diagnosis. The diagnosis of HP (both fibrotic and non-fibrotic forms) was established based on patients' demographic characteristics, symptom duration, clinical and laboratory findings, radiological imaging, bronchoalveolar lavage (BAL) results, and histopathological assessments, in accordance with the 2020 ATS/JRS/ALAT guideline on the "Diagnosis of Hypersensitivity Pneumonitis in Adults" (2). The study included patients aged 18 years and older who had a confirmed diagnosis of HP supported by clinical, radiological, biological, and histopathological evidence, along with a complete blood count performed at the time of diagnosis. Patients with other pulmonary diseases (e.g., chronic obstructive pulmonary disease (COPD), asthma, IPF, or other interstitial lung diseases), active infections, malignancy, those undergoing immunosuppressive therapy, individuals with hematological disorders, or those with incomplete data were excluded.

Data collection and laboratory tests

This study was designed as a retrospective, single-center study. Patient data was obtained through the hospital system, and the following information was recorded for the patients included in the study: age, gender, comorbidities, symptoms, exposure history, HP phenotype, smoking status, medication history, results of pulmonary function tests (Forced Vital Capacity (FVC in mL, FVC%), Diffusing Capacity of the Lung for Carbon Monoxide (DLCO%), DLCO adjusted for alveolar volume (DLCO/VA), 6-minute walk test (6MWT), CRP, AISI, SII, treatment history, history of antifibrotic treatment, treatment duration, death, which were recorded on a patient follow-up form. Complete blood count (CBC) values obtained at the time of hospital admission were also documented. At the time of diagnosis, SII and AISI values were calculated based on the CBC results. CBC was analyzed using the spectrophotometric/impedance method (Beckman Coulter LH 780 Analyzer; Beckman Coulter, Inc., CA, USA). The SII value was calculated using the formula: (absolute platelet count × absolute neutrophil count) / absolute lymphocyte count. The AISI was calculated using the formula: (neutrophil × platelet × monocyte) / lymphocyte.

Pulmonary function test, carbon monoxide diffusion test, and 6-Minute Walk Test (6MWT)

Pulmonary function tests were conducted in a sitting position at our hospital's PFT unit. Spirometry was performed using the Carefusion Masterscreen device (Germany). At least three maneuvers with less than 5% variation were performed, and forced vital capacity (FVC) values were recorded. The carbon monoxide diffusion test (DLCO) was also performed at our PFT unit. Using the single-breath method performed at least twice, patients inhaled 0.3% CO and inert gas (1-5% helium) and then held their breath for 10 ± 2 seconds before exhaling rapidly. CO and helium concentrations were measured, and corrections were made based on hemoglobin levels. The results were then standardized according to age, gender, height, and race.

Statistical analysis

All statistical analyses were conducted using IBM SPSS (Statistical Package for the Social Sciences) 26.0 (SPSS Inc., Chicago, IL, USA) software. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Data exhibiting normal distribution were presented as mean ± standard deviation (SD), while categorical data were expressed as frequencies and percentages (%). For group comparisons, independent sample t-tests were employed for continuous variables with normal distribution, and chi-square tests were used for categorical variables. Receiver Operating Characteristic (ROC) curve analysis was utilized to assess the performance of SII and AISI in predicting fibrotic HP and mortality. The optimal cut-off values derived from the ROC analysis (SII: 644.9; AISI: 438.8) were used to stratify patients into high and low inflammatory index groups, followed by comparative analyses between these groups. Pearson correlation analysis was conducted to explore relationships between variables. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors associated with fibrotic HP. The model's goodness of fit was assessed using the Hosmer-Lemeshow test, with its explanatory power further supported by the Nagelkerke R^2 value. A significance level of $p<0.05$ was considered for all tests.

Results

A total of 75 patients with a mean age of 62±14.5 years were included in the study. Forty-eight (64%) of the patients were female (Table 1). The majority of patients were smokers (54.66%, n=41), while 45.3% (n=34) were non-smokers. When the exposures of the patients in the HP group were evaluated, 64 patients (85.3%) had a history of exposure to one or more of the specified environmental factors. The most frequently reported exposures were bird breeding (57.3%, n=43), farming (26.6%, n=20), poultry keeping (17.3%, n=13), agriculture and animal husbandry (14.6%, n=11), and trombone playing (1.33%, n=1). The most common symptom at presentation was dyspnea in 66 (88%) and cough in 57 (75%) of the patients included in the study. Of the 75 patients, 33 had non-fibrotic HP, while 42 had fibrotic HP. Treatment was started in 63 patients: 62 with corticosteroids, 18 with azathioprine, 9 with mycophenolate mofetil, and 4 with nintedanib. 22 of the patients died. Of the 75 patients, 33 had non-fibrotic HP, while 42 had fibrotic HP. Fibrotic HP patients demonstrated significantly reduced pulmonary function, with lower FVC values both in absolute terms (1447.74 ± 984.86 ml vs. 2288.97 ± 1085.49 ml, $p = 0.003$) and as a percentage of predicted values (62.18 ± 27.56% vs. 76.23 ± 22.41%, $p = 0.029$), compared to non-fibrotic HP patients. Velcro crackles are more commonly heard in fibrotic HP compared to non-fibrotic HP ($p<0.001$). The mean SII of the patients included in the study was found to be 934.75±749.39, and the mean AISI was 649.46±580.32. The mean SII and AISI were significantly higher in the fibrotic HP group (1353.6±915.15; 1001.1±695.38, respectively) compared to the non-fibrotic HP group (607.84±334.53; 375.01±235.18, respectively) ($p<0.001$; $p<0.001$). There was no statistically significant difference in CRP levels between patients with fibrotic HP (16.83 ± 23.03) and those with non-fibrotic HP (15.56 ± 18.15) ($p = 0.628$). Twenty-two of the cases died. The average SII and AISI values were significantly higher in the deceased patients compared to those who survived. In the deceased patients, the mean SII was 1604.13±926.89 and the mean AISI was 1166.44±724.7, whereas in the living patients, these values were 606.89±311.37 and 396.24±233.27, respectively ($p<0.001$; $p<0.001$).

Table 1. Demographic, clinical, and laboratory characteristics of patients with hypersensitivity pneumonitis

Variables	n (%) / Mean ± SD
Demographic Data	
Mean age (years)	62±14.5
Sex (female)	48(64%)
Smoking history (pack-years)	10.8±16.3
Symptoms	
Dyspnea Cough Chest pain Fatigue Sputum	66(88%) 57(75%) 56(74.6%) 50(66.6%) 28(37.3%)
Physical Examination Findings	
Digital clubbing	18(24%)
Velcro crackles	32(42.7%)
Pulmonary Function Test Parameters	
FVC, ml	1931.6±1103.7
FVC, %	70.8±24.1
DLCO, %	28.3±31.7
DLCO/VA	31.1±41.2
6MWT, m	291.4±138.6
Laboratory Findings	
Hemoglobin (g/dL)	13.6±1.7
WBC (10^9 /L)	10.8±2.7
Neutrophils (10^9 /L)	7.7±3.5
Platelets (10^9 /L)	387.1±96.3
Lymphocytes (10^9 /L)	2.4±0.8
Monocytes (10^9 /L)	0.7±0.25
SII	934.75±749.39
AISI	649.46±580.32

Abbreviations: SD: Standard deviation; FVC: Forced vital capacity; DLCO: Diffusing capacity of the lung for carbon monoxide; DLCO/VA: DLCO adjusted for alveolar volume;6MWT: 6-minute walk test;WBC: White blood cell count; SII: Systemic immune-inflammation index; AISI: Aggregate index of systemic inflammation.

ROC Curve analysis and optimal cut-off determination for SII and AISI

ROC analysis was performed to determine the prognostic value of SII and AISI in differentiating between fibrotic and non-fibrotic HP. For SII, the cut-off value was determined to be 644.9, with a sensitivity of 80.6%, specificity of 61%, and an AUC of 0.788 (p<0.001) (Figure 1&Table 2). For deceased patients, the cut-off value for SII was found to be 690.12, with a sensitivity of 86.4%, specificity of 62%, and an AUC of 0.736. Similarly, for AISI, the cut-off value was determined to be 438.79, with a sensitivity of 80.6% and specificity of 70.7% (p<0.001) (Figure 2 & Table 2). For deceased patients, the cut-off value for AISI was 490.35, with a sensitivity of 68.2%, specificity of 66%, and an AUC of 0.753 (Figure 2 & Table 2).

Subgroup comparisons based on ROC-derived cut-off values

Based on the optimal cut-off values derived from the ROC analysis (SII: 644.9; AISI: 438.8), patients were stratified into two subgroups for each index: high and low inflammatory index groups. Comparative analyses between these subgroups are presented in Table 3. Patients in the high SII (>644.9) and AISI (>438.8) groups demonstrated significantly higher mortality rates (46.3% vs. 8.8%, p=0.001 and 42.5% vs. 14.3%, p=0.004, respectively), lower FVC and FVC% values, and a greater prevalence of velcro crackles. Additionally, CRP and neutrophil levels were significantly elevated, whereas albumin levels were lower in the high-index groups.

Correlation between inflammatory indices and pulmonary function parameters

In correlation analysis, significant positive correlations were found between SII and age (r=0.234, p=0.047), AISI (r=0.890, p=0.001), neutrophils (r=0.712, p=0.001), and deceased patients (r=0.534, p=0.001). Conversely, significant negative correlations were observed between SII and DLCO (r=-0.234, p=0.017), lymphocytes (r=-0.434, p=0.001), and FVC% (r=-0.345, p=0.005).Similarly, for AISI, significant positive correlations were found with age (r=0.312, p=0.008), CRP (r=0.281, p=0.018), and deceased patients (r=0.520, p=0.001). Negative correlations were observed between AISI and FVC (ml) (r=-0.291, p=0.015), albumin (r=-0.400, p=0.001), FVC% (r=-0.254, p=0.020), and DLCO (r=-0.224, p=0.012).

Logistic regression analysis

Logistic regression analysis was conducted to identify predictors of fibrotic hypersensitivity pneumonitis. As shown in Table 4, older age, digital

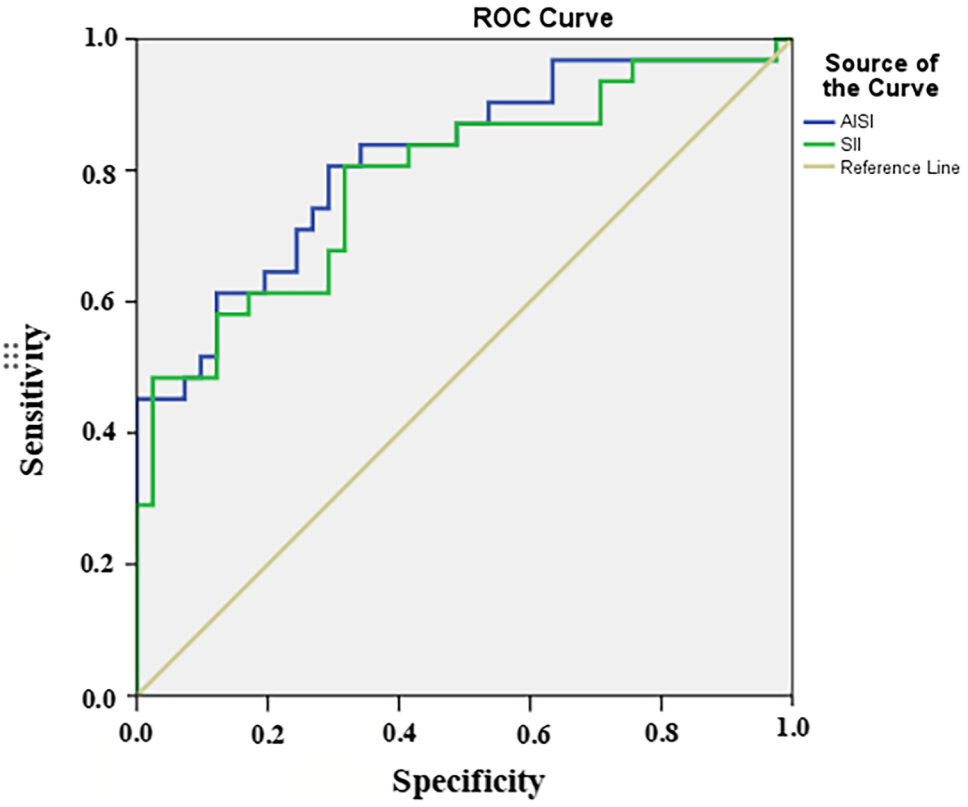

Figure 1. ROC analysis of AISI, SII for differentiating between fibrotic HP and nonfibrotic HP.

Table 2. ROC Analysis Results of SII and AISI Values

	Cut-off value	Sensitivity %	Specificity %	AUC	P value
Fibrotic/Non-Fibrotic HP Patients					
SII	644.9	80.6	61	0.788(0.678-0.897)	0.001
AISI	438.8	80.6	70.7	0.817(0.716-0.918)	0.001
Surviving/Deceased Patients					
SII	690.12	86.4	62	0.736(0.606-0.866)	0.001
AISI	490.35	68.2	66	0.753(0.627-0.879)	0.001

Abbreviations: SII:Systemic immune inflammation index; AISI:Aggregate index of systemic inflammation

clubbing, reduced FVC%, and elevated inflammatory indices (SII, AISI) were significantly associated with fibrotic HP in univariate analysis. In multivariate analysis, only increased SII (OR: 1.45, 95% CI: 1.11–1.68, p=0.021) and reduced FVC% (OR: 0.999, 95% CI: 0.997–1.000, p=0.043) remained independently associated with fibrotic HP. Mortality was also significantly higher in the fibrotic group (OR: 41.49, 95% CI: 2.27–60.17, p=0.012).

Discussion

In this retrospective study, we evaluated the prognostic significance of peripheral hematological biomarkers—specifically SII and AISI—in patients with HP. Our findings indicate that elevated SII and AISI levels are significantly associated with the fibrotic form of HP, reduced pulmonary function, and increased mortality. These results underscore the

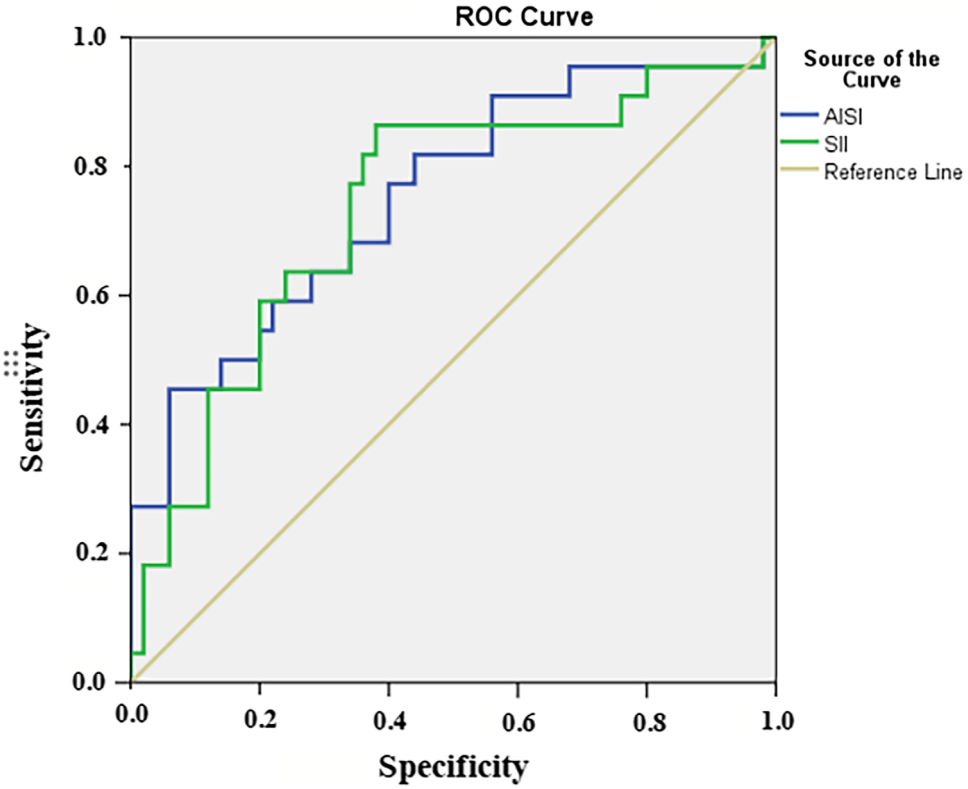

Figure 2. ROC analysis of AISI, SII for differentiating between deceased patients and survivors.

Table 3. Comparison of Demographic, Clinical, and Laboratory Characteristics of HP Patients Stratified by SII and AISI Cut-off Values

	SII			**AISI**		
	>644.9 (n=41)	**<644.9 (n=34)**	**P-value**	**>438.8 (n=40)**	**<438.8 (n=35)**	**P-value**
Mean age (years)	58.8±14.2	55.5±9.1	0.104	59.4±12.2	54.9±12.1	0.068
Smoking history (pack-years)	15.8±24.1	6.9±9.2	0.126	11.24±21.2	10.7±19.7	0.919
Dyspnea	37(90.2%)	29(85.3%)	0.646	34(85%)	33(94.3%)	0.564
Cough	34(82.9%)	23(67.6%)	0.265	32(80%)	24(68.6%)	0.069
Chest pain	10(24.4%)	8(23.5%)	0.612	11(27.5%)	7(20%)	0.614
Exitus	19(46.3%)	3(8.8%)	**0.001**	17(42.5%)	5(14.3%)	**0.004**
Digital clubbing	11(26.8%)	7(20.6%)	0.626	10(25%)	8(22.9%)	0.683
Velcro crackles	21(52.2%)	11(32.4)	**0.048**	22(55%)	10(28.6%)	**0.041**
Ongoing Antigen Exposure, n (%)	13 (31.7%)	9 (26.5%)	0.615	12 (30%)	10 (28.6%)	0.882
FVC, ml	1674.6±679.7	2551.5±1397.6	**0.006**	1546.2±1026.8	2280±1111.4	**0.002**
FVC, %	61.6±20.1	75.2±25.8	**0.028**	60.2±25.3	72.5±25.5	**0.023**
DLCO, %	23.6±20.8	39.5±25.4	**0.042**	29.5±40.1	33.5±22.8	**0.031**
6MWT, m	308.4±143.9	269±143.5	0.363	242.5±135.9	326.7±133.1	0.095
HGB	13.3±1.6	14.6±1.5	**0.011**	13.26±1.73	13.92±1.59	0.159
Neutrophils(10^9/L)	8.2±4.4	4.5±1.4	**0.001**	8.6±3.87	4.68±1.47	**0.001**

Platelets (10^9 /L)	329.5±89.66	202.36±85.1	**0.001**	325.6±81.97	248.9±95.91	**0.001**
Lymphocytes(10^9/L)	2.2±0.9	2.4±0.7	0.126	2.25±0.83	2.58±0.83	0.127
Monocytes (10^9 /L)	0.7±0.3	0.6±0.2	**0.085**	0.76±0.26	0.59±0.21	**0.007**
CRP	20.7±23.8	10.4±13.8	**0.024**	17.6±16.3	14.9±24.2	**0.048**
Albumin	3.8±0.46	4.12±0.45	**0.011**	4.1±0.44	3.8±0.5	**0.022**

Abbreviations: SII: Systemic Immune-Inflammation Index, AISI: Aggregate Index of Systemic Inflammation, FVC: Forced Vital Capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, 6MWT: 6-Minute Walk Test, HGB: Hemoglobin, CRP: C-Reactive Protein. P-values were calculated using independent t-test or chi-square test as appropriate

Table 4. Univariate and multivariate logistic regression analyses of factors associated with fibrotic hypersensitivity pneumonitis

	Univariate			**Multivariate**		
Variable	**OR 95% CI**		**p-value**	**OR 95% CI**		**p-value**
Age (years)	1.053	1.008-1.100	0.021	1.000	0.913-1.095	0.999
Smoking history (pack-years)	1.001	0.980-1.022	0.289	-	-	-
Digital clubbing	7.194	2.070-25.06	0.002	11.83	0.852-64.24	0.660
Velcro crackles	2.547	0.968-6.701	0.058	-	-	-
FVC, %	0.977	0.956-0.997	0.028	0.999	0.997-1.000	0.043
DLCO, %	0.989	0.973-1.004	0.161	-	-	-
6MWT, m	0.893	0.877-0.922	0.893	-	-	-
SII	1.002	1.002-1.004	0.001	1.450	1.112-1.678	0.021
AISI	1.003	1.002-1.006	0.001	1.006	0.998-1.009	0.178
Exitus	76.36	9.220-93.48	0.001	41.49	2.265-60.17	0.012

Abbreviations: OR, odds ratio; CI, confidence interval; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; 6MWT, 6-minute walk test; SII, systemic immune-inflammation index; AISI, aggregate index of systemic inflammation.

potential utility of these indices as accessible and cost-effective tools for disease stratification and outcome prediction. SII, derived from platelet, neutrophil, and lymphocyte counts, has been recognized as a marker associated with disease severity and poor prognosis in a variety of pathological conditions, including malignancies and inflammatory diseases (11,12). Previous studies have demonstrated that both FIB-4 and SII are significantly correlated with increased mortality risk in patients with IPF, suggesting their potential utility in the early identification of high-risk individuals (13). In another study, elevated Platelet-to-Lymphocyte Ratio (PLR) and SII values reflecting a more prominent inflammatory profile were observed in patients with secondary pulmonary fibrosis compared to those with IPF (14). Consistent with these findings, our study also observed significantly higher SII values in patients with HP who experienced a fatal disease course. Numerous studies have highlighted the strong association between SII and conditions such as hyperlipidemia, heart failure, and mortality due to cardiogenic shock (15-17). These findings indicate that SII serves not only as a marker of systemic inflammation but also as a robust prognostic biomarker for cardiovascular diseases and other critical health conditions. In a study conducted by Kanter

et al., an SII value of 2282.54 or higher in patients presenting with COPD exacerbations was identified as a significant predictor for hospitalization decisions; elevated SII values were statistically associated with both hospital admission and discharge outcomes (18). In our study, SII values were found to be significantly higher in the non-fibrotic HP group compared to the fibrotic HP group ($p<0.001$). In the study evaluating COPD patients, a strong association was found between elevated SII levels and the development of COPD, as well as increased all-cause mortality. Furthermore, the results suggest that an increase in SII is correlated with a decline in FEV1, highlighting its potential as a biomarker for clinical assessments (19). Our study demonstrated that patients with elevated SII levels had significantly higher mortality rates and markedly lower FVC and FVC% values. According to the ROC analysis, SII levels above the determined cut-off value (>644.9) were significantly associated with increased mortality (46.3% vs. 8.8%, $p=0.001$). Moreover, multivariate logistic regression analysis identified elevated SII as an independent predictor of fibrotic HP (OR: 1.45, 95% CI: 1.11–1.68, $p=0.021$). Similarly, a retrospective cohort study conducted in patients with non-cystic fibrosis bronchiectasis found that elevated SII levels were significantly associated with decreased pulmonary function (FEV1 and FVC) and an increased risk of hospitalization due to exacerbations (20). AISI has been reported to demonstrate strong performance in predicting the severity of inflammation and disease prognosis in many studies. In a study involving patients with IPF, it was shown that AISI could better reflect the inflammatory status and allow for early identification of patients at risk of death (8). In this study, patients with AISI ≥ 434 had lower FEV1, FVC, and 6-MWT (8). In a study by Ay Damla and colleagues, it was found that DLCO, FVC, and 6-MWT had significant negative correlations with SII and AISI, respectively (21). Similarly, in our study, a significant negative correlation was observed between DLCO, FVC %, and AISI in HP patients. In our results, it was observed that patients with a fatal outcome had higher AISI values. The findings of our study align with research on cardiovascular diseases, where the prognostic value of AISI has also been well established. In patients with acute myocardial infarction, high AISI levels were significantly associated with cardiovascular mortality risk, new-onset atrial fibrillation, and contrast-induced nephropathy (22). Another study found that high AISI levels increased the risk of cardiovascular mortality in patients with hypertension (9). In COPD patients with COVID-19, AISI was identified as a reliable indicator of mortality (23). Additionally, in stroke patients, AISI levels were significantly higher compared to the control group, particularly in hemorrhagic stroke patients compared to ischemic stroke patients (24). This study provides significant findings by examining the prognostic value of peripheral hematological biomarkers, such as SII and AISI, in patients with HP. Our results demonstrate that both SII and AISI are associated with the clinical course and prognosis of HP. These findings suggest that these biomarkers could serve as valuable prognostic tools for monitoring patient status. In particular, SII and AISI emerge as important indicators that may help predict mortality risk and disease progression. Although statistically significant results were obtained for both SII and AISI in the ROC analyses conducted in our study, the relatively low specificity levels (61% and 70.7%, respectively) indicate that caution should be exercised when using these biomarkers alone. For instance, in a study by Ercan et al. involving COVID-19 patients with chronic renal failure, the AISI demonstrated an AUC of 0.820 for predicting hospital mortality, with a sensitivity of 81% and specificity of 69.1% (25). In another example, the ROC analysis of SII in squamous cell lung cancer demonstrated an AUC of 0.78, with a sensitivity of 75.3% and a specificity of 69.4% (26). These findings indicate that while SII and AISI are promising markers, they should be evaluated in conjunction with clinical, radiological, and functional parameters. One potential limitation of this study is the lack of detailed data regarding acute exacerbation episodes prior to blood sampling. Although samples were collected during clinically stable phases, the possibility that subclinical or recent exacerbations may have influenced systemic inflammation indices cannot be completely excluded. This could have partially confounded the observed association between elevated SII/AISI levels and increased mortality. Future studies should consider stratifying patients based on exacerbation history to more clearly delineate this relationship. Additionally, this study was conducted with a relatively small sample size, which may limit the generalizability of the findings. Therefore, larger, multi-center, prospective, randomized controlled trials are needed to validate the clinical applicability of these results.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangem ent etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: All authors have approved and take responsibility for the final version of the manuscript. AM: Conceptualization, data curation, methodology, writing-review Editing. ZY: formal analysis. NYD: Conceptualization, methodology, formal analysis, writing-review editing. HT:Conceptualization, methodology,writing-review editing.

Informed Consent: This study was approved by the Gazi University Clinical Research Ethics Committee (Decision No: 986, Date: 11.06.2024). As a retrospective study with no direct patient contact or intervention, individual informed consent was not required. The study was conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki.

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