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RESEARCH ARTICLE

Systemic Inflammatory Response Index (SIRI) in Hypersensitivity Pneumonitis: Association with Clinical Course and Mortality

Hipersensitivite Pnömonisinde Sistemik İnflamatuar Yanıt İndeksi (SIRI): Klinik Seyir ve Mortalite ile İlişkisi

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ABSTRACT

Objective: Hypersensitivity pneumonitis (HP) is an interstitial lung disease that can range in its course from reversible inflammation to progressive fibrosis. Identifying reliable biomarkers to predict disease phenotype and prognosis remains a major clinical challenge. This study aimed to evaluate the prognostic significance of the Systemic Inflammatory Response Index (SIRI) in patients with HP and to investigate its association with clinical parameters, pulmonary function, and mortality.

Materials and Methods: A retrospective analysis was conducted on 73 patients diagnosed with HP between 2014 and 2022. Patients were classified into fibrotic and non-fibrotic groups based on clinical, radiological, and histopathological criteria. Hematological indices including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and SIRI were calculated. Kaplan–Meier and Cox regression analyses assessed survival outcomes and independent predictors of mortality.

Results: SIRI levels were significantly higher in patients with fibrotic HP and those who died during follow-up. SIRI correlated positively with inflammatory markers, and negatively with pulmonary function (Forced Vital Capacity), carbon monoxide diffusion capacity (DLCO%)) and 6-minute walk distance. ROC analysis demonstrated high diagnostic accuracy for SIRI in differentiating fibrotic HP (AUC = 0.858) and predicting mortality (AUC = 0.932), with an optimal mortality cut-off of 1.92. Kaplan–Meier survival curves illustrated significantly shorter survival in patients with SIRI >1.92 compared to those with SIRI ≤1.92, with a Log-Rank test confirming this difference (mean survival time 74.6 ± 3.2 months vs. 127.7 ± 2.9 months; $p < 0.001$). In multivariable Cox analysis, fibrotic phenotype, reduced DLCO%, and SIRI >1.92 were independent predictors of mortality.

Conclusion: SIRI, as a quantitative indicator of systemic inflammation, may be regarded as a meaningful biomarker for predicting disease severity and mortality risk in patients with hypersensitivity pneumonitis. While more evidence is needed before integration into routine clinical use, it holds potential as a supportive tool for risk stratification, early detection of fibrotic progression, and long-term management strategy planning.

Keywords: Fibrosis, Hypersensitivity pneumonitis, Neutrophil-to-lymphocyte ratio, Systemic Inflammatory response index, Interstitial lung disease

ÖZET

Amaç: Hipersensitivite pnömonisi (HP), reversibl inflamasyondan ilerleyici fibrozise kadar değişen bir seyir gösterebilen intersitisyel akciğer hastalığıdır. Hastalık fenotipinin ve prognozunun öngörülmesine yönelik güvenilir biyobelirteçlerin tanımlanması günümüzde önemli bir klinik gereksinimdir. Bu çalışmada, Sistemik İnflamatuar Yanıt İndeksi'nin (SIRI) HP'deki prognostik değerinin değerlendirilmesi ve klinik parametreler, solunum fonksiyonları ile mortalite arasındaki ilişkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: 2014–2022 yılları arasında HP tanısı alan 73 hastanın retrospektif verileri analiz edilmiştir. Hastalar, klinik, radyolojik ve histopatolojik bulgulara göre fibrotik ve non-fibrotik olarak sınıflandırılmıştır. Hematolojik inflamatuar parametreler (Nötrofil/lenfosit oranı (NLR), monosit/lenfosit oranı (MLR) ve SIRI hesaplanmıştır. Kaplan–Meier ve Cox regresyon analizleri ile sağkalım ve mortaliteye etki eden bağımsız değişkenler değerlendirilmiştir.

Bulgular: SIRI düzeyleri, fibrotik HP fenotipinde hastalarında ve takip sürecinde hayatını kaybedenlerde anlamlı şekilde daha yüksekti. SIRI, inflamatuar belirteçler ile pozitif, pulmoner fonksiyon parametreleri (Zorunlu Vital Kapasite), Karbonmonoksit Difüzyon Kapasitesi (DLCO%)) ve 6 dakikalık yürüme mesafesi ile negatif korelasyon gösterdi. ROC analizi ile SIRI'nin fibrotik HP'yi ayırt etmede (AUC = 0,858) ve mortaliteyi öngörmede (AUC = 0,932) yüksek tanısal doğruluğa sahip olduğu gösterildi; mortalite için optimal kesme değeri ise 1,92 olarak belirlendi. Kaplan–Meier sağkalım eğrileri, SIRI >1,92 olan hastalarda sağkalımın anlamlı şekilde daha kısa olduğunu gösterirken, Log-Rank testi bu farkı doğruladı (ortalama sağkalım süresi 74,6 ± 3,2 ay vs. 127,7 ± 2,9 ay; $p < 0,001$). Çok değişkenli Cox regresyon analizinde ise fibrotik fenotip, azalmış DLCO% ve SIRI >1,92 mortalitenin bağımsız belirleyicileri olarak bulundu.

Sonuç: SIRI, sistemik inflamasyonun kantitatif bir göstergesi olup, HP hastalarında hastalık şiddeti ve mortalite riskinin öngörülmesinde anlamlı bir biyobelirteç olarak değerlendirilebilir. Rutin klinik kullanıma entegrasyonu için daha fazla kanıta ihtiyaç duyulmakla birlikte, risk sınıflaması, fibrotik progresyonun erken saptanması ve uzun dönem yönetim stratejilerinin belirlenmesinde destekleyici bir araç olarak potansiyel taşıyabilir.

Anahtar Kelimeler: Fibrozis, Hipersensitivite pnömonisi, Nötrofil/lenfosit oranı, Sistemik inflamasyon yanıt indeksi, İnterstisyel akciğer hastalığı

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INTRODUCTION

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease that develops in susceptible individuals following inhalation of various environmental or occupational antigens (1). The disease triggers intense inflammation in the small airways and lung parenchyma and may progress to pulmonary fibrosis in some patients. Both cellular and humoral immune mechanisms contribute to HP pathogenesis, with T lymphocytes, macrophages, and cytokines playing central roles. This immune response can lead to persistent inflammation and fibrosis in certain individuals. However, predicting which patients will develop fibrotic disease or experience poor clinical outcomes remains challenging (1). Clinically, HP is classified into fibrotic and non-fibrotic phenotypes, with the presence of fibrosis being the most important prognostic factor influencing disease progression and mortality (2). Biomarkers are essential tools for early diagnosis, prognosis, and treatment monitoring. An ideal biomarker should be non-invasive, easily accessible, reliable, and cost-effective. Currently, no specific laboratory test exists for diagnosing HP, assessing disease activity, or predicting progression.

Recently, hematologic inflammatory markers derived from neutrophil, monocyte, and lymphocyte counts such as the systemic inflammatory response index (SIRI) have gained attention for their prognostic value in various diseases (3,4). Investigating the diagnostic and prognostic utility of SIRI in HP could provide valuable insights to improve patient management and outcomes. Recently, novel biomarkers combining various white blood cell types have been introduced. Hematological inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and SIRI have been linked to the prognosis of several chronic diseases. These markers, derived from neutrophil, monocyte, and lymphocyte counts, have demonstrated significant prognostic value across multiple malignancies (5,6). Furthermore, SIRI has shown predictive utility in cardiovascular diseases, stroke, breast cancer, and nasopharyngeal carcinoma (7,8,9). For instance, a retrospective study involving 2.802 patients with acute ischemic stroke identified a SIRI cutoff value of ≥2.74 as an independent predictor of increased risk for stroke-associated pneumonia (10).

Despite these promising findings, no specific biomarker currently exists for the diagnosis or monitoring of hypersensitivity pneumonitis. Therefore, the aim of this study was to evaluate the prognostic value of the SIRI in patients with hypersensitivity pneumonitis and to investigate its association with clinical parameters, pulmonary function, and survival outcomes.

MATERIALS AND METHODS

Patients and Study Design

This retrospective, single-center study was conducted with the approval of the Clinical Research Ethics Committee of Gazi University (decision number 986, dated November 6, 2024). The study included 73 patients who were diagnosed with and treated for HP between February 2014 and December 2022. The data analyzed included clinical findings, imaging results, and histopathological diagnoses (when available). Patients followed at our hospital for HP were categorized into fibrotic or non-fibrotic HP groups based on symptom duration, imaging findings, bronchoalveolar lavage (BAL) results, and histological data, in accordance with the 2020 American Thoracic Society (ATS) / Japanese Respiratory Society (JRS) / Latin American Thoracic Association (ALAT) Clinical Practice Guideline for the Diagnosis of Hypersensitivity Pneumonitis in Adults (2).

Demographic data (age, sex, region of residence, occupation, etc.), tobacco use, comorbidities, current and prior treatments, history of environmental or occupational exposure, HP phenotypes, pulmonary function test results (Forced Vital Capacity (FVC ml, FVC %), Forced Expiratory Volume in 1 Second (FEV1 ml, FEV1 %), FEV1/FVC), carbon monoxide diffusion capacity (DLCO, DLCO/VA), six-minute walk test (6MWT) performance, and neutrophil, platelet, and monocyte counts were recorded on standardized patient follow-up forms. Reported symptoms included dyspnea, cough, chest pain, sputum production, and fatigue.

Bronchoscopic Evaluation and Diagnostic Sample Collection

Patients were evaluated for suspected interstitial lung disease (ILD) based on medical history, clinical presentation, and radiological findings. In cases where differential diagnosis could not be established, tissue sampling was performed using bronchoscopic or surgical methods. Bronchoscopic procedures were conducted in the hospital's pulmonology unit using a 2.8 mm fiberoptic flexible bronchoscope (Olympus). Bronchoalveolar lavage (BAL) was performed by instilling 100–150 mL of sterile saline into the most affected segment as identified on high-resolution computed tomography (HRCT). Microscopic cell counts in BAL fluid were analyzed by the pathology department. A lymphocyte count greater than 20% in BAL was considered supportive for the diagnosis of HP. Although not routinely recommended, a decreased CD4/CD8 ratio was also considered helpful in differential diagnosis.

In selected cases, transbronchial biopsy was performed via fiberoptic bronchoscopy targeting regions identified on HRCT. For patients requiring surgical sampling, video-assisted thoracoscopic surgery (VATS) was performed by the thoracic surgery team to obtain lung tissue for histopathological analysis.

Analysis of Hematologic Parameters and Inflammatory Indices

Complete blood count analyses were performed in our hospital laboratory using the spectrophotometric/impedance method (Beckman Coulter LH 780 Analyzer; Beckman Coulter, Inc., CA, USA). Erythrocyte sedimentation rate (ESR) was measured using a spectrophotometric method and C-reactive protein (CRP) levels were determined by a turbidimetric assay from peripheral blood samples collected at the time of diagnosis. Importantly, all blood samples were obtained prior to the initiation of any pharmacological treatment, including corticosteroids and immunosuppressive agents, to avoid potential confounding effects of treatment on hematologic and inflammatory parameters. Additionally, patients with

active infections, malignancies, or active rheumatologic diseases were carefully excluded based on clinical evaluation, laboratory tests, and medical history to minimize potential confounding factors affecting CRP and other inflammatory markers. NLR, MLR, and SIRI values were calculated based on neutrophil, monocyte, and lymphocyte counts at diagnosis using the following formulas:

NLR (Neutrophil-to-Lymphocyte Ratio) = Neutrophil count / Lymphocyte count

MLR (Monocyte-to-Lymphocyte Ratio) = Monocyte count / Lymphocyte count

SIRI (Systemic Inflammatory Response Index) = (Neutrophil count × Monocyte count) / Lymphocyte count

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as means (± standard deviation) for normally distributed continuous variables, and medians (minimum-maximum) for non-normally distributed continuous variables. Categorical variables are presented as counts and percentages (%). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test, and parametric tests were applied for normally distributed data.

The Pearson's χ^2 (chi-square) test was used to analyze categorical variables. The Student's t-test was used for comparisons of normally distributed continuous variables between two groups. The relationships between variables were evaluated using Pearson's correlation coefficient.

Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off values of the markers for differentiating between fibrotic and nonfibrotic HP and predicting mortality. The area under the curve (AUC), sensitivity, and specificity were calculated for each biomarker. Univariable and multivariable Cox proportional hazards regression analyses were performed to identify factors associated with mortality and determine independent predictors. A two-tailed p-value < 0.05 was considered statistically significant throughout the analyses.

RESULTS

A total of 73 patients diagnosed with hypersensitivity pneumonitis were included in this study. The mean age was 63 ± 12.7 years, with females comprising 65.8% of the study population (Table-1). The most frequently reported symptoms were dyspnea (82.2%) and cough (79.4%) (Table-1). A majority of patients (84.9%) had a history of exposure to one or more predefined environmental factors. Bird breeding was the most prevalent exposure, reported in 58.9% of patients, followed by farming (27.4%), poultry handling (16.4%), and agricultural or livestock activities (13.7%). Notably, one patient (1.36%) was a trombone player. Pharmacological treatment was administered to 63 patients, including corticosteroids in 62, azathioprine in 18, mycophenolate mofetil in 9, and nintedanib in 4 patients. Pulmonary function assessment revealed significantly greater impairment in patients with fibrotic HP (n = 42) compared to those with nonfibrotic HP (n = 31). Likewise, the 6MWT distance was significantly reduced in patients with fibrotic HP (238.5 ± 140.3 meters) compared to those with nonfibrotic HP (342.7 ± 132.8 meters; p = 0.015), indicating a substantial decline in functional exercise capacity in the presence of fibrotic involvement.

In the overall cohort, the mean values of MLR, NLR, and SIRI were 0.30 ± 0.13, 3.27 ± 2.44, and 2.27 ± 2.18, respectively. Stratification by radiological phenotype revealed significantly higher levels of all three inflammatory indices in the fibrotic HP group (NLR: 4.69 ± 3.02; MLR: 0.38 ± 0.18; SIRI: 3.50 ± 2.79)

Table 1. Patients' Demographic, Clinical, and Hematologic Characteristics

Variables	n (%) / Mean ± SD/ Med(Min-Max) n=73
Demographic Data	
Mean age (years)	63 ± 12.7
Gender, n (%)	
Female	48(65.8%)
Male	25(34.2%)
BMI	26.7±6.8
Smoking history (pack-years)	12.1±17.4
Symptoms	
Dyspnea	60(82.2%)
Cough	58(79.4%)
Chest pain	51(71.8%)
Fatigue	39(54.9%)
Sputum	23(32.4%)
Comorbid Conditions, n (%)	
Hypertension	21(28.8%)
Coronary Artery Disease	12(16.4%)
Diabetes Mellitus	9(12.3%)
Hyperlipidemia	7(9.6%)
Hypothyroidism	6(8.2%)
Pulmonary Function Test Parameters	
FVC, ml	1931.6±1103.7
FVC, %	70.8±24.1
FEV1, mL	2113.6±1223.6
FEV1, %	71.6±31.1
DLCO, %	35.1(20.6-90.3)
DLCO/VA	50.3(40.2-117.4)
6MWT, m	291.4±138.6
Laboratory Findings	
Hemoglobin (g/dL)	14.1±1.5
Hematocrit (%)	41.5±4.5
WBC (109 /L)	11.9±3.7
Neutrophils (109 /L)	7.3±4.1
Platelets (109 /L)	286.4±95.8
Lymphocytes (109 /L)	2.1±0.9
Monocytes (109 /L)	0.6±0.35
NLR	3.27 ± 2.44
MLR	0.30 ± 0.13
SIRI	2.27 ± 2.18
CRP (mg/L)	8.55(1.61-70.4)
ESR (mm/h)	16.9 ±9.7

SD: Standard deviation;BMI: Body Mass Index; FVC: Forced vital capacity;FEV1:Forced Expiratory Volume in 1 Second; 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; MLR: Monocyte-to- Lymphocyte Ratio; NLR: Neutrophil-to-Lymphocyte Ratio; SIRI: Systemic Inflammation Response Index; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate

Table 2. Comparison of Clinical and Laboratory Parameters Between Deceased and Surviving Patients Diagnosed with Hypersensitivity Pneumonitis

Parameter	Deceased (n = 22) Mean ± SD Med (Min-Max)	Survived (n = 51) Mean±SD Med (Min-Max)	P-value
Mean age (years)	65 ± 14.2	60.4 ± 11.3	0.161
BMI	24.3±7.7	27.3±6.8	0.647
Smoking history (pack-years)	12.7 ± 17.9	11.8 ± 16.9	0.780
FVC, %	56.77±14.43	69.48±19.7	0.004
DLCO, %	24.3 (20.6- 76.1)	39.5 (32.6-90.3)	0.038
6MWT, m	224.2±141.5	353.7±138.8	0.002
Hemoglobin (g/dL)	14.7±1.9	13.6±1.6	0.677
Neutrophils (109 /L)	9.1±4.7	5.7±2.2	0.001
Lymphocytes (109 /L)	2.1±0.7	2.6±0.8	0.077
Monocytes (109 /L)	0.97±0.3	0.59±0.2	0.003
CRP (mg/L)	16.7 (2.4-70.4)	7.3 (1.6-41.2)	0.034
NLR	4.53±2.33	2.48±0.91	0.001
MLR	0.38±0.18	0.22±0.04	0.001
SIRI	3.63±2.94	1.40±0.62	0.001

BMI: Body Mass Index ,FVC: Forced Vital Capacity,DLCO: Diffusing Capacity of the Lung for Carbon Monoxide, 6MWT: 6-Minute Walk Test, CRP: C-Reactive Protein, NLR: Neutrophil to Lymphocyte Ratio,MLR: Monocyte to Lymphocyte Ratio, SIRI: Systemic Inflammation Response Index

compared to the nonfibrotic group (NLR: 2.15 ± 0.89; MLR: 0.23 ± 0.08; SIRI: 1.30 ± 0.63), with all comparisons achieving statistical significance ($p < 0.001$). In the comparison between deceased and surviving patients, all three inflammatory markers NLR, MLR, and SIRI were significantly elevated in the deceased group. The mean NLR was 4.53 ± 2.33 in deceased patients compared to 2.48 ± 0.91 in survivors ($p = 0.001$). The mean MLR and SIRI values were both significantly higher in deceased patients compared to survivors ($p = 0.001$ for both) (Table-2).

Correlation analysis was performed to evaluate the relationships between SIRI and various clinical and laboratory parameters. Significant positive correlations were observed between SIRI and CRP ($r = 0.122$, $p=0.031$), ESR ($r = 0.298$, $p=0.012$), NLR ($r = 0.789$, $p < 0.001$), MLR ($r =0.642$, $p < 0.001$), and neutrophil count ($r = 0.455$, $p < 0.001$). Conversely, SIRI showed significant negative correlations with FVC% ($r = 0.266$, $p= 0.034$), DLCO% ($r =0.166$, $p < 0.05$), and 6MWT ($r = 0.114$, $p= 0.046$). These findings suggest that elevated SIRI levels are not only indicative of systemic inflammation but are also associated with diminished pulmonary function in patients with hypersensitivity pneumonitis. The overall median survival time in the study population was 99 (6-130) months, with 22 of 73 patients (30.1%) dying during the follow-up period. To evaluate the prognostic utility of SIRI, ROC analysis was conducted. The AUC was 0.858 (95% CI: 0.771–0.945, $p < 0.001$), indicating good discriminatory ability. Using a cut-off value of 1.86, SIRI demonstrated a sensitivity of 90.5% and a specificity of 76.9% for distinguishing fibrotic from non-fibrotic hypersensitivity pneumonitis patients (Figure 1).

Furthermore, the optimal cut-off value for mortality discrimination was identified as 1.92, with an AUC of 0.932 (95% CI: 0.878–0.987, $p < 0.001$), yielding a sensitivity of 90.9% and specificity of 80.4% (Figure 2).

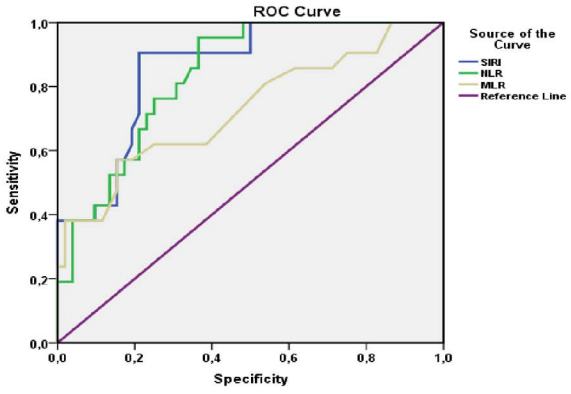

Figure 1. ROC curve for SIRI distinguishing fibrotic and non-fibrotic hypersensitivity pneumonitis.

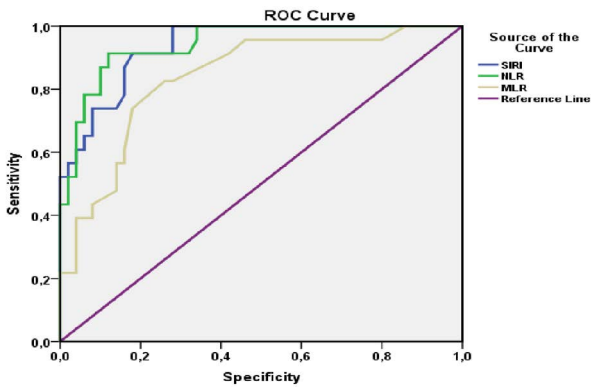

Figure 2. ROC curve of SIRI for mortality discrimination in hypersensitivity pneumonitis patients

Table 3. Univariable and Multivariable Cox Proportional Hazards Regression Analyses for All-Cause Mortality

Variable	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Age (per year)	1.04 (1.01 – 1.08)	0.015	1.03 (1.00 – 1.07)	0.061
Gender (Female)	1.21 (0.58 – 2.53)	0.610	1.05 (0.67 – 1.87)	0.722
Fibrotic HP	2.65 (1.32 – 5.31)	0.006	2.21 (1.08 – 4.52)	0.030
DLCO (%)	0.96 (0.93 – 0.99)	0.012	0.97 (0.94 – 0.99)	0.021
FVC (%)	0.92 (0.94 – 0.98)	0.010	0.98 (0.95 – 1.00)	0.067
6MWT	0.998 (0.994 – 1.002)	0.210	0.996 (0.993 – 0.999)	0.112
SIRI > 1.92	4.78 (2.01 – 11.36)	0.001	3.89 (1.57 – 9.63)	0.003
NLR	1.38 (1.12 – 1.69)	0.002	1.12 (0.91 – 1.38)	0.280
MLR	1.22 (0.97 – 1.52)	0.085	1.11 (0.89 – 1.39)	0.350

FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the Lung for Carbon Monoxide, 6MWT: 6-Minute Walk Test, CRP: C-Reactive Protein, NLR: Neutrophil to Lymphocyte Ratio,MLR: Monocyte to Lymphocyte Ratio, SIRI: Systemic Inflammation Response Index

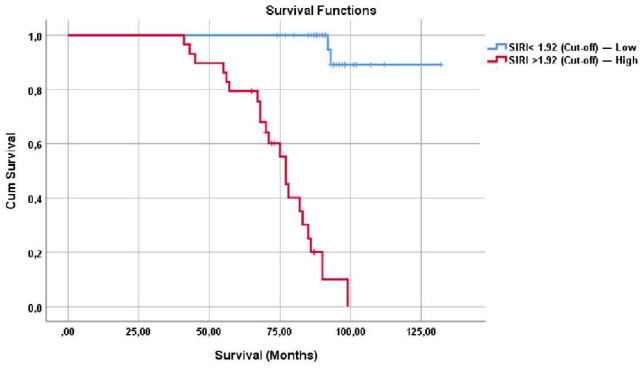

Figure 3. Kaplan–Meier survival curves based on SIRI cut-off value (1.92) in hypersensitivity pneumonitis patients.

Kaplan–Meier survival curves were plotted to illustrate the difference in survival between patients with SIRI >1.92 and those with SIRI ≤1.92. The mean survival time in the high SIRI group was 74.6 ± 3.2 months, with a median survival of 77.0 months (95% CI: 73.0–81.0). In contrast, patients in the low SIRI group had a significantly longer mean survival time of 127.7 ± 2.9 months, and the median survival was not reached due to low mortality. The Log-Rank test revealed a statistically significant difference between the groups ($\chi^2 = 50.98$, $p < 0.001$), confirming that elevated SIRI levels were strongly associated with increased mortality risk in patients with hypersensitivity pneumonitis (Figure-3).

In order to further investigate predictors of mortality, Cox proportional hazards regression analysis was performed. In the univariable analysis, older age, fibrotic HP pattern, reduced DLCO%, reduced FVC%, elevated NLR, and SIRI >1.92 were significantly associated with an increased risk of death (Table-3). However, in the multivariable Cox model, only fibrotic HP (HR: 2.21; 95% CI: 1.08–4.52; p = 0.030), lower DLCO% (HR: 0.97; 95% CI: 0.94–0.99; p = 0.021), and SIRI >1.92 (HR: 3.89; 95% CI: 1.57–9.63; p = 0.003) remained independently associated with mortality (Table-3).

DISCUSSION

HP is a complex inflammatory and/or fibrotic lung disease affecting the parenchyma and small airways. Identification of novel prognostic biomarkers in HP is critical to improving patient management by facilitating more precise disease phenotyping, risk stratification, evaluation of disease severity, monitoring of treatment response, and prediction of progression to fibrosis. While inflammatory markers such as NLR, MLR and SIRI have been investigated in various pulmonary diseases, their prognostic utility in HP remains inadequately studied. Our findings suggest that these markers, particularly SIRI, hold promise as reliable prognostic indicators in HP, effectively differentiating fibrotic from non-fibrotic disease and predicting patient mortality. NLR, MLR, and SIRI can be easily calculated from complete blood counts and serve as indicators of systemic inflammation. These markers have been extensively studied in a variety of diseases, including cardiovascular, rheumatologic, infectious conditions, and malignancies, for their predictive value regarding morbidity and mortality (11-14). Notably, elevated NLR and platelet-to-lymphocyte ratio (PLR) values have been associated with decreased survival in both small-cell and non-small cell lung cancers, as well as increased mortality in pulmonary thromboembolism (15,16). Consistent with our findings, Yao et al. (17). reported significantly higher NLR values in nonsurvivors compared to survivors, and found a positive correlation between NLR and CRP levels.

In a large cross-sectional study involving 7,153 patients with type 2 diabetes mellitus (T2DM), the mean NLR, MLR, and SIRI values were reported as 2.19 ± 1.34, 0.27 ± 0.12, and 1.24 ± 0.98, respectively, and were found to be associated with diabetic kidney disease (18). In comparison, our study population exhibited higher mean values for these inflammatory markers (NLR: 3.27 ± 2.44, MLR: 0.30 ± 0.13, and SIRI: 2.27 ± 2.18), which may reflect the distinct inflammatory burden in hypersensitivity pneumonitis patients. Systemic inflammation plays a key role in the pathogenesis and progression of ILD, including pulmonary fibrosis (19). In a study on idiopathic pulmonary fibrosis (IPF), the mean NLR was reported as 2.5 (range 1.8–3.3), and elevated NLR levels were significantly associated with worse clinical outcomes, including increased mortality, higher hospitalization rates, greater pulmonary function

decline, impaired 6MWT performance, and reduced quality of life (20). These findings are consistent with our results, which showed that increased NLR levels were significantly associated with the fibrotic phenotype of hypersensitivity pneumonitis, lower DLCO and 6MWT values, and higher mortality. Recent evidence has emphasized the prognostic relevance of SIRI in various chronic inflammatory conditions. Elevated SIRI has been independently associated with increased cardiovascular and all-cause mortality in chronic kidney disease (21), as well as higher mortality risk in asthma patients (22), underscoring its utility as a systemic inflammatory biomarker. In line with these data, our study is the first, to our knowledge, to investigate the prognostic significance of SIRI in patients with hypersensitivity pneumonitis. We found that elevated SIRI levels were significantly associated with fibrotic disease phenotype, impaired pulmonary function (DLCO%, FVC%, 6MWT), and most importantly, independently predicted mortality. Taken together, these results suggest that SIRI may serve as a simple and effective biomarker to aid in the risk stratification and prognostic assessment of patients with HP.

Furthermore, complementary studies have expanded the understanding of SIRI's role in respiratory and systemic inflammatory diseases. A cross-sectional study utilizing NHANES data demonstrated that SIRI is an independent risk factor for chronic obstructive pulmonary disease (COPD), showing stronger predictive value than other inflammatory markers, particularly among current smokers (23). Similarly, in patients with rheumatoid arthritis (RA), elevated SIRI levels were associated with increased all-cause and cardiovascular mortality, with the association being more pronounced in females and individuals with higher BMI (24). These findings reinforce the broad clinical relevance of SIRI as a marker of systemic inflammation and prognosis across diverse chronic diseases, supporting its potential utility in managing patients with hypersensitivity pneumonitis. In the study of Biyik et al. involving 332 patients with pancreatitis, SIRI demonstrated a significant predictive value for both severe acute pancreatitis and acute kidney injury (AUC = 0.782; 95% CI = 0.699–0.865, and AUC = 0.776; 95% CI = 0.715–0.837, respectively) (25). Similarly, a 2022 study reported that SIRI served as an independent predictor of poor functional outcomes in ischemic stroke patients, with a moderate discriminative performance (AUC = 0.714; 95% CI: 0.658–0.765) (26). These findings reinforce the utility of SIRI as a systemic inflammatory biomarker across a wide range of acute and chronic conditions.

In light of these previous reports, our study adds to the growing body of evidence by demonstrating that SIRI not only distinguishes between fibrotic and non-fibrotic hypersensitivity pneumonitis with high accuracy (AUC = 0.858), but also independently predicts mortality (AUC = 0.932), which, to our knowledge, has not been previously described in the context of HP. These results underscore the potential clinical utility of SIRI in the risk stratification and prognostic evaluation of HP patients and support its integration into routine clinical assessment. Immunopathological studies have demonstrated that neutrophils and monocytes/macrophages are the primary cells involved in the early inflammatory response in HP. For instance, in experimental HP models, IL-17A production predominantly originates from neutrophils and monocytes/macrophages, and neutrophil depletion has been reported to significantly reduce the development of fibrosis (27). In this context, elevated neutrophil and monocyte counts may trigger the pro-fibrotic transformation of inflammation processes characterized by alveolar tissue damage and increased cytokine release, which subsequently leads to remodeling. Conversely, a decreased lymphocyte ratio may indicate mechanisms such as impaired regulatory T cell function, inadequate regulation of adaptive immune responses, or lymphocyte exhaustion. These cellular dynamics biologically underpin the strong association observed between the SIRI calculated as (neutrophils × monocytes) / lymphocytes and clinical outcomes including fibrotic phenotype, poor pulmonary function, and mortality.

This study has several limitations. First, its retrospective and single-center design may introduce selection and information bias, and limits the generalizability of the findings to broader populations. Second, the relatively small sample size reduces statistical power, particularly for subgroup and multivariable analyses, and increases the risk of type II errors. Third, although inflammatory markers were measured prior to treatment initiation, only baseline values were analyzed; dynamic changes over time were not assessed. Additionally, the lack of an external validation cohort limits the ability to generalize the proposed SIRI cut-off values. Finally, despite efforts to account for comorbidities, unmeasured confounders such as subclinical infections or other inflammatory conditions may have influenced the biomarker levels. Therefore, prospective, multicenter studies with larger patient cohorts are needed to validate these results.

CONCLUSION

This study demonstrates that the SIRI, a simple, accessible, and cost-effective biomarker derived from routine blood parameters, is significantly associated with disease severity, fibrotic phenotype, impaired pulmonary function, and mortality in patients with hypersensitivity pneumonitis. Notably, SIRI showed strong discriminatory power in differentiating fibrotic from non-fibrotic HP and served as an independent predictor of mortality, outperforming other commonly used inflammatory indices such as NLR and MLR. These findings suggest that SIRI may have potential as a valuable tool for risk stratification and prognostic evaluation in clinical practice.

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