ORIGINAL ARTICLE DOI: 10.20515/otd.1841308

Osmangazi Journal of Med, 2026;48(4):740-748

Osmangazi Journal of Medicine

e-ISSN: 2587-1579

# Mortality Prediction Using Systemic Inflammation Based Biomarkers in Idiopathic Pulmonary Fibrosis

İdiopatik Pulmoner Fibroziste Sistemik İnflamasyon Temelli Biyobelirteçler ile Mortalite Riskinin Belirlenmesi

Aysegul Erinc, Ali Kirac, Sule Gul, Erdogan Cetinkaya

Department of Pulmonology, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Health Sciences University, Istanbul, Türkiye

**Correspondence / Sorumlu yazar:**
Ayşegül ERİNÇ

Department of Pulmonology, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital,Health Sciences University, Istanbul, Türkiye

**e-mail:** draysgul@hotmail.com

**Received** : 22.03.2025

**Accepted** :..21.05.2026

**Abstract:** Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with poor survival despite the availability of antifibrotic therapies. Disease progression is heterogeneous, and the need for reliable prognostic biomarkers remains unmet. Systemic inflammation-based indices including C-reactive protein to albumin ratio, systemic immune-inflammation index, systemic inflammation response index, systemic inflammation aggregate index (CAR, SII, SIRI, SIAI) have demonstrated prognostic value in various chronic diseases, yet evidence in IPF patients receiving antifibrotic therapy is limited. This retrospective single-center cohort study included 108 patients diagnosed with IPF according to international criteria and treated with antifibrotic agents between 2015 and 2025. Demographic characteristics, comorbidities, pulmonary function tests, laboratory measurements, and treatment details were extracted from electronic medical records. CAR, SII, SIRI, and SIAI were calculated using standard formulas. Univariable and multivariable Cox regression analyses were performed to evaluate predictors of three-year mortality. The mean age was 66.09 ± 8.26 years, and 24.1% of patients were female. Baseline systemic inflammation markers and inflammation-based indices (CAR, SII, SIRI, SIAI) did not significantly differ between survivors and non-survivors. In univariable analysis, ex-smoking status, smoking pack-years, and COPD were significantly associated with mortality. Although pirfenidone demonstrated a protective trend, it did not retain significance after adjustment. Procalcitonin was the only independent predictor of three-year mortality in the multivariable model (HR = 0.094; p = 0.03). Other inflammation-based indices showed no prognostic value. In patients with IPF undergoing antifibrotic therapy, CAR, SII, SIRI, and SIAI did not predict long-term mortality, indicating limited prognostic utility of these inflammation-based biomarkers. Procalcitonin emerged as the only independent predictor. These findings highlight the need for more disease-specific and treatment-relevant biomarkers to improve prognostic stratification in IPF.

**Keywords:** Idiopathic pulmonary fibrosis; Antifibrotic therapy; Systemic inflammation biomarkers

**Özet:** İdiopatik pulmoner fibrozis (İPF), ilerleyici seyirli ve yüksek mortalite ile karakterize bir interstisyel akciğer hastalığıdır. Antifibrotik tedavilerin kullanılmasına rağmen hastalığın gidişatı öngörülemez olup, güvenilir prognostik biyobelirteçlere ihtiyaç devam etmektedir. Sistemik inflamasyon temelli biyobelirteçler C-reaktif protein / albümin oranı, sistemik immün-inflamasyon indeksi, sistemik inflamasyon yanıt indeksi, sistemik inflamasyon agregat indeksi (CAR, Sİİ, SİYİ, SİAİ) çeşitli kronik hastalıklarda prognostik değer göstermiş olsa da antifibrotik tedavi altındaki İPF hastalarında kanıtlar sınırlıdır. Bu retrospektif, tek merkezli kohort çalışmasına 2015–2025 yılları arasında antifibrotik tedavi alan, tanısı uluslararası kriterlere göre doğrulanmış 108 İPF hastası dahil edildi. Demografik veriler, komorbiditeler, solunum fonksiyon testleri, laboratuvar ölçümleri ve tedavi detayları elektronik kayıtlardan elde edildi. CAR, Sİİ, SİYİ ve SİAİ standart formüllerle hesaplandı. Üç yıllık mortalite için univaryant ve multivaryant Cox regresyon analizleri gerçekleştirildi. Çalışmaya dahil edilen hastaların yaş ortalaması 66.09 ± 8.26 yıl olup 24.1%'i kadındı. Bazal inflamasyon belirteçleri ve sistemik inflamasyon skorları sağ kalanlar ile yaşamını kaybedenler arasında anlamlı farklılık göstermedi. Univaryant analizde eks-sigara içiciliği, paket-yıl ve KOAH varlığı mortalite ile ilişkili bulundu. Pirfenidon kullanımının koruyucu etkisi gözlense de multivaryant analizde anlamlılık kayboldu. Multivaryant modelde yalnızca prokalsitonin, mortalitenin bağımsız belirleyicisi olarak saptandı (HR = 0.094; p = 0.03). Antifibrotik tedavi alan İPF hastalarında CAR, Sİİ, SİYİ ve SİAİ gibi yaygın inflamasyon temelli biyobelirteçlerin uzun dönem mortaliteyi öngörmede sınırlı yarar sağladığı gösterilmiştir. Prokalsitonin ise bağımsız bir prognostik belirteç olarak öne çıkmıştır. Bulgular, tedavi altındaki İPF hastalarında daha spesifik biyobelirteçlere ihtiyaç olduğunu göstermektedir.

**Anahtar Kelimeler:** İdiopatik pulmoner fibrozis; Antifibrotik tedavi; Sistemik inflamasyon biyobelirteçleri

**Ethics Committee Approval:** The single-centered, retrospective cohort study was conducted at the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital in accordance with the Declaration of Helsinki. The Hamidiye Non-interventional Clinical Research Ethics Committee of the University of Health Sciences approved the study protocol (Date/No: 23.10.2025; Decision No: 19/6) and waived the requirement for written informed consent due to the retrospective design.

**Informed Consent:** The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

**Authorship Contributions:** The authors confirm contribution to the paper as follows: Study conception and design: AE and AK data collection: AE, AK, SG and EC; Analysis and interpretation of results: AE and AK. Draft manuscript preparation: AE and AK. All authors reviewed the results and approved the final version of the manuscript.

**Copyright Transfer Form:** Copyright Transfer Form was signed by all authors.

**Peer-review:** Internally peer-reviewed.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

**How to cite/ Atıf için** Erinc A, Kirac A , Gul S , Cetinkaya E, Mortality Prediction Using Systemic Inflammation Based Biomarkers in Idiopathic Pulmonary Fibrosis, Osmangazi Journal of Medicine, 2026;48(4):740-748

## 1. Indroduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and fatal interstitial lung disease characterized by excessive extracellular matrix deposition and irreversible distortion of lung parenchyma (1). Its incidence is relatively low compared with other respiratory diseases, but the prognosis is dismal, with a median survival of only two to five years after diagnosis (2,3). This survival rate is poorer than that of many cancers, underscoring the devastating nature of the disease [4].

The development of antifibrotic therapies such as pirfenidone and nintedanib has transformed the treatment paradigm of IPF. These agents have been shown to slow the decline of lung function and reduce the risk of acute exacerbations (5). However, they do not halt or reverse disease progression, and a striking heterogeneity exists in treatment response and clinical outcomes (6). This variability highlights the urgent need for reliable and easily accessible prognostic biomarkers to support personalized treatment decisions and long-term patient management.

There is growing recognition that chronic inflammation contributes to the pathogenesis and progression of IPF (7). Pro-inflammatory cytokines, persistent alveolar epithelial injury, fibroblast proliferation, and dysregulated tissue repair all play roles in fibrosis development (8). Consequently, systemic inflammatory markers have gained increasing attention as potential prognostic tools in IPF and other chronic diseases.

Among these, the C-reactive protein (CRP) to albumin ratio (CAR) has emerged as a simple but robust indicator that reflects both systemic inflammation and nutritional status (9). Elevated CAR has been linked with adverse outcomes in a variety of malignant and chronic inflammatory conditions (10). More recently, composite indices such as the Systemic Immune-Inflammation Index (SII), the Systemic Inflammation Response Index (SIRI), and the Systemic Inflammation Aggregate Index (SIAI) have been proposed as hematological markers reflecting the balance between systemic inflammation and immune response (11–13).

Despite these developments, evidence regarding the prognostic significance of such indices in IPF, especially among patients receiving antifibrotic therapy, remains scarce. To the best of our knowledge, this study represents one of the few real-world investigations evaluating the prognostic significance of multiple systemic inflammation–based biomarkers specifically in patients with IPF receiving antifibrotic therapy. In particular, data regarding the prognostic utility of CAR, SII, SIRI, and SIAI in treated IPF populations remain highly limited. Most studies to date have focused on biomarker values at the time of diagnosis, without examining their potential utility during long-term treatment and follow-up (14).

Accurate prognostic stratification in IPF is not only clinically relevant but also economically important, given the high cost and variable efficacy of antifibrotic therapies (15). Identifying inexpensive and routinely available blood-based biomarkers could provide clinicians with valuable tools to predict disease trajectory, optimize treatment allocation, and improve patient counseling. Furthermore, although systemic inflammation-based indices have been extensively investigated in malignancies, sepsis, and other chronic conditions, their prognostic value in IPF remains largely underexplored, underscoring the novelty and clinical relevance of the present study (10-14).

The present study was therefore designed to evaluate the prognostic value of CAR, SII, SIRI, and SIAI in patients with IPF receiving antifibrotic therapy. The aim is to determine whether these readily available and inexpensive indices can be applied for risk stratification, prognosis estimation, and treatment monitoring in clinical practice.

## 2. Materials and methods

### *2.1. Study design and setting*

This study was designed as a retrospective, single-center, observational cohort study conducted at the Department of Pulmonology, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital. The study included patients followed between 1 January 2015 and 1 July 2025 and receiving antifibrotic therapy. The study protocol was approved by the Hamidiye Non-interventional Clinical Research Ethics Committee of the University of Health Sciences (Decision No: 19/6, dated 23.10.2025). All procedures were

conducted in accordance with the Declaration of Helsinki.

*2.2. Study population*

The study population consisted of adult patients aged 18 years or older with a confirmed or probable diagnosis of IPF according to international diagnostic criteria. Eligible patients were required to have received antifibrotic therapy for at least three months and to have complete clinical and laboratory follow-up data available in the institutional electronic medical record system. Patients were excluded if they had active malignancy, acute infection at the time of laboratory evaluation, significant hepatic or renal impairment, or incomplete laboratory or clinical datasets. The study flowchart is presented in Figure 1.

*2.3. Data collection*

Demographic characteristics, smoking history, comorbidities, pulmonary function test results, echocardiographic pulmonary artery pressure and antifibrotic treatment data were extracted from the hospital electronic medical record system. Baseline laboratory parameters used for biomarker calculations were obtained during the initial evaluation period at or immediately prior to antifibrotic treatment initiation. These parameters included complete blood count (neutrophils, lymphocytes, monocytes, and platelets), CRP, albumin, erythrocyte sedimentation rate (ESR), and procalcitonin. The death status of the patients was recorded, and the dates of antifibrotic treatment initiation and death were obtained from the system.

*2.4. Definitions*

Systemic inflammatory biomarkers were calculated using established formulas. The CAR was obtained by dividing serum CRP by albumin levels. SII was defined as (platelets × neutrophils) / lymphocytes, while the SIRI was calculated as (neutrophils × monocytes) / lymphocytes. The SIAI was defined as (neutrophils × monocytes × platelets) / lymphocytes (13,16). These indices were evaluated as markers of systemic inflammation and potential prognostic predictors in IPF.

*2.5. Outcomes*

The primary outcome of this study was to assess the prognostic value of systemic inflammation–based biomarkers—CAR, SII, SIRI, and SIAI—in patients with idiopathic pulmonary fibrosis receiving antifibrotic therapy. The secondary outcome was to compare these biomarker levels between survivors and non-survivors in order to explore their potential role in clinical risk stratification.

*2.6. Data analysis and statistical methods*

We used descriptive statistics to present the data. Categorical data were reported as proportions and numbers. The distribution of continuous variables was assessed using visual methods and the Shapiro–Wilk test. Variables with normal distribution were expressed as mean ± standard deviation, whereas non-normally distributed variables were presented as median and interquartile range (IQR). Univariate Cox regression analysis was performed to identify survival predictors. Variables included in the multivariable Cox regression model were selected based on both statistical significance in univariate analyses and clinical relevance. Despite the relatively limited number of mortality events, clinically meaningful covariates were included in order to minimize potential confounding effects. Analyses were conducted using IBM SPSS Statistics version 23. P values less than 0.05 were considered statistically significant.

## 3. Results

This study included a total of 108 patients with IPF who were receiving antifibrotic therapy. Of the entire cohort, 24.1% were female, and the mean age was 66.09 ± 8.26 years. Regarding smoking status, 44.4% of the patients had never smoked, 41.7% were ex-smokers, and 13.9% were active smokers. Ex-smoker status was notably more common in the death group (55.9% vs. 35.1%, p = 0.02). The median smoking pack-years was 22.5 in the death group, compared to 0 among survivors. The distribution of comorbidities was generally similar between groups, although COPD was more frequent among patients who died (8.8% vs. 1.4%, p = 0.04). Pirfenidone use was significantly more common among survivors (66.2% vs. 41.2%), whereas nintedanib was more frequently used among deceased patients (58.8% vs. 33.8%, p = 0.02). (Table 1).

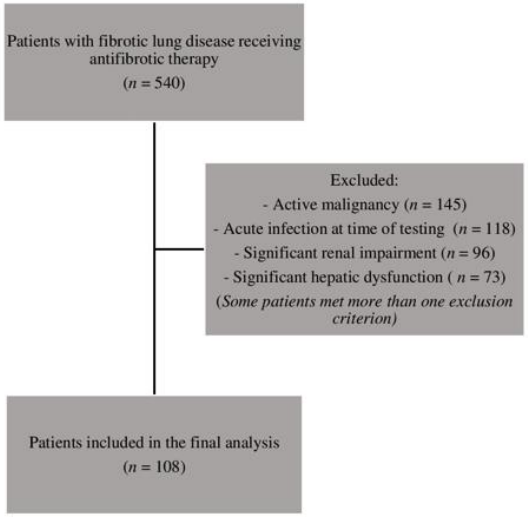



**Figure 1.** Flowchart of the study population.

**Table 1.** Demographic data of the patients.

| | Total Patients (*n* = 108) | Death (*n* = 34) | Alive (*n* = 74) | *p* |
|---|---|---|---|---|
| Age, years* | 66.09 ± 8.26 | 67.88 ± 8.75 | 65.27 ± 7.96 | 0.11 |
| Female gender, *n* (%) | 26 (24.1) | 6 (17.6) | 20 (27) | 0.24 |
| Smoking group, *n* (%) | | | | |
| Never smoker | 48 (44.4) | 10 (29.4) | 38 (51.4) | - |
| Ex-smoker | 45 (41.7) | 19 (55.9) | 26 (35.1) | **0.02** |
| Smoker | 15 (13.9) | 5 (14.7) | 10 (13.5) | 0.26 |
| Smoking package/year † | 10 (0-30) | 22.5 (0-40) | 0 (0-30) | **0.02** |
| Comorbidities, *n* (%) | | | | |
| Hypertension | 27 (25) | 9 (26.5) | 18 (24.3) | 0.92 |
| COPD | 4 (3.7) | 3 (8.8) | 1 (1.4) | **0.04** |
| Cardiovascular disease | 36 (33.3) | 14 (41.2) | 22 (29.7) | 0.18 |
| Diabetes mellitus | 23 (21.3) | 9 (26.5) | 14 (18.9) | 0.48 |

*COPD: chronic obstructive pulmonary disease. *Parameters that follow a normal distribution are presented as mean ± standard deviation. † Parameters that did not follow a normal distribution are presented as median and interquartile range.*

Pulmonary function parameters showed no statistically significant differences between survivors and non-survivors; however, FVC demonstrated a borderline trend (2.49 vs. 2.17 L, p = 0.06) and DLCO was slightly lower in the death group (3.29 vs. 5.30, p = 0.09). No statistically significant differences were observed in baseline laboratory parameters or inflammation-based biomarkers, including CRP, albumin, ESR, CAR, SII, SIRI, and SIAI (all p > 0.05) (Table 2).

**Table 2.** Laboratory and clinical parameters of the patients.

| Variables | Total Patients (*n* = 108) | Death (*n* = 34) | Alive (*n* = 74) | *p* |
|---|---|---|---|---|
| Laboratory | | | | |
| Neutrophil, $x10^3/mm^3$ | 5.83 ± 2.36 | 6.21 ± 2.72 | 5.66 ± 2.18 | 0.22 |
| Lymphocyte, $x10^3/mm^3$ | 2.38 (1.88-3.06) | 2.8 (1.90-3.10) | 2.37 (1.85-3.04) | 0.39 |
| Monocyte, $x10^3/mm^3$ | 0.71 (0.59-0.92) | 0.72 (0.63-0.97) | 0.69 (0.58-0.91) | 0.43 |
| Platelet, $x10^3/mm^3$ | 250.92 ± 62.02 | 245.82 ± 60.07 | 253.27 ± 63.17 | 0.60 |
| Albumin, g/dL | 40.81 ± 3.84 | 41.21 ± 4.3 | 40.62 ± 3.63 | 0.39 |
| ESR, mm/h | 30 (21.7-47) | 30.5 (22.7-48.5) | 30 (20.2-44.7) | 0.76 |
| CRP, mg/dL | 5.8 (3.32-11) | 4.9 (2.82-11.47) | 6.15 (3.47-11) | 0.65 |
| Procalcitonin, ng/mL | 0.07 (0.04-0.41) | 0.06 (0.04-0.14) | 0.09 (0.04-0.50) | 0.06 |
| CRP/Albumin | 0.14 (0.08-0.26) | 0.12 (0.06-0.29) | 0.15 (0.09-0.25) | 0.58 |
| SII | 530.6 (360.5-813.6) | 589.9 (406-851.7) | 524.7 (337.7-804.6) | 0.91 |
| SIRI | 1.55 (1-2.65) | 1.68 (1.15-2.75) | 1.50 (0.94-2.51) | 0.38 |
| SIAI | 403.8 (249.9-659.2) | 407.8 (266.1-668.6) | 385.8 (230-638.4) | 0.79 |
| PFT parameters | | | | |
| FEV1 lt. † | 1.93 ± 0.77 | 2.05 ± 0.75 | 1.88 ± 0.77 | 0.19 |
| FEV1% * | 71 (61-87) | 70 (59-88) | 71 (62-86) | 0.95 |
| FVC lt * | 2.27 ± 0.96 | 2.49 ± 1.04 | 2.17 ± 0.91 | 0.06 |
| FVC% * | 67 (55-84) | 65 (51.83) | 68 (55-84) | 0.75 |
| FEV1/FVC † | 89 (80-106) | 88 (80-109) | 89 (80-102) | 0.14 |
| DLCO unit † | 4.26 (2.93-9.38) | 3.29 (2.9-4.83) | 5.3 (2.91-9.99) | 0.09 |
| DLCO% * | 41 (31-55) | 40 (31-58.5) | 41 (29-55) | 0.59 |
| PAP, mmHg | 30 (25-45) | 25 (24-36) | 30 (25-45) | 0.09 |
| Antifibrotic treatment, *n* (%) | | | | **0.02** |
| Pirfenidone | 63 (58.3) | 14 (41.2) | 49 (66.2) | |
| Nintedanib | 45 (41.7) | 20 (58.8) | 25 (33.8) | |

*ESR; erythrocyte sedimentation rate; CRP: C reactive protein; SII: systemic inflammation index; SIRI: systemic inflammation response index; SIAI: systemic inflammation aggregate index; PFT: pulmonary function tests; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; PAP: pulmonary artery pressure. *Parameters that follow a normal distribution are presented as mean ± standard deviation. † Parameters that did not follow a normal distribution are presented as median and interquartile range.*

In the univariate Cox regression analysis, several smoking-related variables emerged as significant predictors of 3-year mortality. Ex-smoker status was associated with a significantly increased risk of death (HR = 2.35; p = 0.02). Smoking pack-years was also a significant predictor (HR = 1.01; p = 0.02). The presence of COPD increased mortality risk approximately threefold (HR = 3.35; p = 0.04). Furthermore, pirfenidone therapy was associated with a significantly lower mortality risk compared with nintedanib (HR = 0.45; p = 0.02). In

contrast, pulmonary function parameters such as FVC and DLCO demonstrated only borderline significance (p = 0.06 and p = 0.09, respectively), and inflammation-based biomarkers (CAR, SII, SIRI, SIAI) were not associated with mortality (Table 3).

**Table 3**. Univariate cox regression analysis for 3-year survival.

| **Variables** | **Hazard ratio** | **CI (95%)** | ***p*** |
|---|---|---|---|
| Age | 1.03 | 0.99-1.07 | 0.11 |
| Male gender | 1.69 | 0.70-4.09 | 0.24 |
| Smoking group | | | |
| Never smoker | Ref. | - | - |
| Ex-smoker | 2.35 | 1.09-5.06 | **0.02** |
| Smoker | 1.85 | 0.63-5.41 | 0.26 |
| Smoking package/year † | 1.01 | 1.00-1.02 | **0.02** |
| Comorbidities | | | |
| Hypertension | 1.04 | 0.48-2.22 | 0.92 |
| COPD | 3.35 | 1.00-11.1 | **0.04** |
| CVD | 1.59 | 0.80-3.15 | 0.18 |
| DM | 1.30 | 0.61-2.80 | 0.48 |
| PFT parameters | | | |
| FEV1 lt. † | 1.34 | 0.85-2.12 | 0.19 |
| FEV1% * | 1.01 | 0.98-1.01 | 0.95 |
| FVC lt * | 1.42 | 0.98-2.06 | 0.06 |
| FVC% * | 1.01 | 0.98-1.01 | 0.75 |
| FEV1/FVC † | 1.01 | 0.99-1.00 | 0.14 |
| DLCO unit † | 0.90 | 0.80-1.01 | 0.09 |
| DLCO% * | 1.01 | 0.98-1.02 | 0.59 |
| PAP | 0.98 | 0.95-1.01 | 0.09 |
| Laboratory | | | |
| Neutrophil | 1.08 | 0.95-1.23 | 0.22 |
| Lymphocyte | 0.86 | 0.60-1.21 | 0.39 |
| Monocyte | 1.61 | 0.48-5.39 | 0.43 |
| Platelet | 0.99 | 0.99-1.01 | 0.60 |
| Albumin | 1.04 | 0.94-1.14 | 0.39 |
| ESR | 1.01 | 0.98-1.01 | 0.76 |
| CRP | 1.01 | 0.97-1.03 | 0.65 |
| Procalcitonin | 0.25 | 0.05-1.07 | 0.06 |
| CRP/Albumin | 1.33 | 0.48-3.67 | 0.58 |
| SII | 1.01 | 0.99-1.01 | 0.91 |
| SIRI | 1.07 | 0.91-1.25 | 0.38 |
| SIAI | 1.01 | 1.0-1.01 | 0.79 |
| Pirfenidone treatment (vs. Nintedanib) | 0.45 | 0.22-0.90 | **0.02** |

*COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; DM: diabetes mellitus; PFT: pulmonary function tests; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; PAP: pulmonary artery pressure; ESR; erythrocyte sedimentation rate; CRP: C reactive protein;*

*SII: systemic inflammation index; SIRI: systemic inflammation response index; SIAI: systemic inflammation aggregate index; CI: confidence interval. *Parameters that follow a normal distribution are presented as mean ± standard deviation. † Parameters that did not follow a normal distribution are presented as median and interquartile range.*

Variables with a p-value < 0.15 in the univariate analysis, together with clinically relevant parameters, were included in the multivariate Cox regression model. After adjustment, procalcitonin was identified as an independent predictor of 3-year mortality (HR = 0.094; p = 0.03), indicating that lower procalcitonin levels were associated with improved survival. Smoking pack-years demonstrated a near-significant trend (HR = 1.015; p = 0.054). Although pirfenidone treatment showed a protective pattern, this association did not reach statistical significance in the adjusted model (HR = 0.521; p = 0.14). CAR, COPD, FVC, and age were not independently associated with survival in the multivariate analysis (Table 4).

**Table 4.** Multivariate cox regression for 3-year survival.

| Variables | Hazard ratio | CI (95%) | *p* |
|---|---|---|---|
| Age* | 1.042 | 0.988-1.099 | 0.12 |
| Smoking package/year† | 1.015 | 1.000-1.030 | 0.054 |
| COPD | 2.054 | 0.516-8.171 | 0.30 |
| CRP/Albumin | 0.643 | 0.125-3.299 | 0.59 |
| Procalcitonin | 0.094 | 0.011-0.836 | **0.03** |
| FVC | 1.425 | 0.842-2.413 | 0.18 |
| Pirfenidone treatment (vs. Nintedanib) | 0.521 | 0.218-1.248 | 0.14 |

*COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; CRP: C-reactive protein; CI: confidence interval. *Parameters that follow a normal distribution are presented as mean ± standard deviation. † Parameters that did not follow a normal distribution are presented as median and interquartile range.*

Overall, these findings indicate that baseline inflammation-based biomarkers were not significantly associated with 3-year mortality in patients with IPF receiving antifibrotic therapy. Smoking history and COPD were significant predictors in the univariate analysis, while procalcitonin emerged as the only independent prognostic factor in the multivariate model. Pirfenidone showed a favorable effect on survival, although this did not reach statistical significance after adjustment.

## 4. Discussion

In this retrospective cohort of patients with idiopathic pulmonary fibrosis receiving antifibrotic therapy, we found that systemic inflammation based biomarkers including CAR, SII, SIRI, and SIAI were not associated with 3-year mortality. Instead, procalcitonin emerged as the only independent prognostic factor in the multivariate Cox model, while smoking-related variables and COPD demonstrated significant associations in univariate analysis. Moreover, pirfenidone therapy appeared to show a protective trend, although this effect did not persist after adjustment for confounders.

The lack of prognostic significance for CAR and other inflammation-derived indices contrasts with findings in several chronic inflammatory and malignant diseases, where these biomarkers have consistently correlated with disease severity and outcomes (17,18). In IPF, however, the role of systemic inflammation remains controversial (19). Although inflammation contributes to disease pathogenesis, IPF is primarily characterized by aberrant wound healing and progressive fibrosis rather than sustained systemic inflammatory activation (20). This biological distinction may explain why inflammatory indices, which perform well in diseases dominated by systemic inflammation, may have limited prognostic utility in IPF—particularly in stable patients undergoing long-term antifibrotic treatment (21).

Procalcitonin, on the other hand, demonstrated an independent association with mortality. Traditionally recognized as a biomarker of bacterial infection, procalcitonin has also been linked to adverse outcomes in chronic lung diseases; however, direct mechanistic evidence underlying these associations particularly those involving immune dysregulation, metabolic stress, or impaired tissue response remains limited (22). The finding that lower procalcitonin levels were associated with better survival suggests that even low-grade systemic stress or microbial translocation may contribute to worse outcomes in

IPF (23). While evidence on procalcitonin in IPF is scarce, our results indicate that it may serve as a surrogate marker reflecting subclinical disease instability or increased susceptibility to respiratory complications. Several potential mechanisms may explain the observed association between procalcitonin and mortality in IPF. Although procalcitonin is traditionally regarded as a biomarker of bacterial infection, low-grade elevations may also reflect broader systemic stress responses, epithelial injury, or altered host–microbiome interactions in chronic lung diseases. In IPF, repeated alveolar epithelial injury and increased susceptibility to respiratory complications may contribute to subtle inflammatory activation even during clinically stable periods. Therefore, procalcitonin may potentially serve as an indirect marker of biological instability or increased vulnerability rather than overt infection alone. Nevertheless, the precise mechanisms underlying this association remain uncertain and warrant further investigation.

The observed association between smoking burden, COPD comorbidity, and mortality aligns with established knowledge (24). Smoking has been implicated in epithelial injury, abnormal repair, and fibroblast activation—key processes in IPF progression (25). COPD–IPF overlap is known to be associated with worse outcomes, partly due to impaired gas exchange, chronic inflammation, and increased susceptibility to exacerbations (26). The present study reinforces these observations, demonstrating that smoking pack-years and COPD were strongly associated with mortality in univariate analyses.

The protective trend observed for pirfenidone, although not statistically significant in the adjusted model, is broadly consistent with real-world evidence showing comparable effectiveness between pirfenidone and nintedanib, with some studies suggesting that specific patient subgroups may experience differential benefits (27). The lack of statistical significance may be attributable to the limited sample size, treatment selection bias, or the retrospective design. Nonetheless, this trend supports the ongoing discussion regarding treatment individualization in IPF. The apparent survival advantage observed among patients receiving pirfenidone should be interpreted cautiously. Because treatment allocation in this retrospective cohort was not randomized, the possibility of confounding by indication cannot be excluded. Patients with different baseline disease severity, comorbidity burden, tolerability profiles, or other clinical characteristics may have preferentially received one antifibrotic agent over the other. Therefore, the observed association should not be interpreted as evidence of a causal treatment effect.

This study has several strengths, including the homogeneous patient population, standardized follow-up within a single specialized center, and comprehensive evaluation of multiple inflammation-based biomarkers. However, limitations should be acknowledged. The retrospective design inherently limits causal inference, and the relatively limited sample size and number of observed mortality events may have reduced statistical power to detect subtle biomarker effects. Therefore, the absence of statistically significant associations does not necessarily exclude a potential biological or clinical relationship between these biomarkers and disease outcomes. Additionally, residual confounding cannot be entirely excluded, despite multivariate adjustment. The relatively limited number of mortality events compared with the number of covariates included in the multivariable model may have increased the risk of overfitting and reduced the stability of some effect estimates. Therefore, the multivariable findings should be interpreted cautiously and validated in larger prospective cohorts. Furthermore, a substantial proportion of the initially screened patients were excluded due to predefined eligibility criteria aimed at ensuring a more homogeneous study population. While this approach strengthens internal validity, it may limit the generalizability of the findings to the broader real-world IPF population. Additional analyses such as ROC-based threshold determination and survival stratification according to biomarker cut-off values may provide further clinically relevant information and should be explored in larger prospective cohorts. Given these considerations, the present findings should be interpreted cautiously and regarded as exploratory and hypothesis-generating.

## 5. Conclusion

In this cohort of patients with idiopathic pulmonary fibrosis receiving antifibrotic therapy, systemic inflammation–based biomarkers—including CAR, SII, SIRI, and SIAI—did not demonstrate a statistically significant association with long-term mortality. However, given the retrospective design and limited sample size, these findings should be interpreted cautiously. Procalcitonin emerged as the only independent prognostic factor, while smoking burden and COPD were significant predictors in univariate analysis. Although pirfenidone demonstrated a protective trend, this effect did not

remain significant after multivariable adjustment. Overall, these findings indicate that commonly used inflammatory indices may have limited prognostic utility in treated IPF, highlighting the need for more specific and disease-relevant biomarkers. Further prospective studies are warranted to validate the prognostic value of procalcitonin and to refine risk stratification strategies for patients undergoing antifibrotic therapy.

## REFERENCES


1. Sankari A, Chapman K, Ullah S. Idiopathic Pulmonary Fibrosis. [Updated 2024 Apr 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448162/
2. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;157:199–203.
3. Flaherty KR, Toews GB, Travis WD, Colby TV, Kazerooni EA, Gross BH, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur Respir J. 2002;19:275–283.
4. Abu Qubo A, Numan J, Snijder J, Padilla M, Austin JHM, Capaccione KM, et al. Idiopathic pulmonary fibrosis and lung cancer: future directions and challenges. Breathe (Sheff). 2022;18(4):220147.
5. Akbar I, Mann J, Niewodowski D, Mackintosh J, Glaspole IN, Barnes H. Antifibrotic therapies for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev. 2021;2021(10):CD015076.
6. Di Martino E, Provenzani A, Vitulo P, Polidori P. Systematic Review and Meta-analysis of Pirfenidone, Nintedanib, and Pamrevlumab for the Treatment of Idiopathic Pulmonary Fibrosis. Ann Pharmacother. 2021;55(6):723-731.
7. Bringardner BD, Baran CP, Eubank TD, Marsh CB. The role of inflammation in the pathogenesis of idiopathic pulmonary fibrosis. Antioxid Redox Signal. 2008;10(2):287-301.
8. Chambers RC, Mercer PF. Mechanisms of alveolar epithelial injury, repair, and fibrosis. Ann Am Thorac Soc. 2015;12 Suppl 1(Suppl 1):S16-S20.
9. Zavalaga-Zegarra H, Palomino-Gutierrez J, Ulloque-Badaracco J, Mosquera-Rojas M, Hernandez-Bustamante E, Alarcon-Braga E, et al. C-reactive protein-to-albumin ratio and clinical outcomes in COVID-19 patients: A systematic review and meta-analysis. Trop Med Infect Dis. (2022) 7:186.
10. Kim M, Ahn J, Song J, Choi H, Ann H, Kim J, et al. The C-reactive protein/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock treated with early goal-directed therapy. PLoS One. 2015;10:e0132109.
11. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. J Clin Lab Anal. 2019;33(8):e22964.
12. Sannan NS. Assessment of aggregate index of systemic inflammation and systemic inflammatory response index in dry age-related macular degeneration: a retrospective study. Front Med (Lausanne). 2023;10:1143045.
13. Zinellu A, Collu C, Nasser M, Paliogiannis P, Mellino S, Zinellu E, et al. The Aggregate Index of Systemic Inflammation (AISI): A Novel Prognostic Biomarker in Idiopathic Pulmonary Fibrosis. J Clin Med. 2021;10(18):4134.
14. Zheng Z, Peng F, Zhou Y. Biomarkers in idiopathic pulmonary fibrosis: Current insight and future direction. Chin Med J Pulm Crit Care Med. 2024;2(2):72-79.
15. Moua T, Ryu JH. Obstacles to early treatment of idiopathic pulmonary fibrosis: current perspectives. Ther Clin Risk Manag. 2019;15:73-81.
16. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-6222.
17. Wang K, Diao F, Ye Z, Zhang X, Zhai E, Ren H, et al. Prognostic value of systemic immune-inflammation index in patients with gastric cancer. Chin J Cancer. 2017;36(1):75.
18. Song YD, Bai XM, Ma J. The association of systemic immune-inflammation index with lung function, risk of COPD and COPD severity: A population-based study. PLoS One. 2024;19(6):e0303286.
19. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med. 2018;379(8):797-798.
20. Mei Q, Liu Z, Zuo H, Yang Z, Qu J. Idiopathic Pulmonary Fibrosis: An Update on Pathogenesis. Front Pharmacol. 2022;12:797292.
21. Behr J, Salisbury ML, Walsh SLF, Podolanczuk AJ, Hariri LP, Hunninghake GM, et al. The Role of Inflammation and Fibrosis in Interstitial Lung Disease Treatment Decisions. Am J Respir Crit Care Med. 2024;210(4):392-400.
22. Sivapalan P, Jensen JU. Biomarkers in Chronic Obstructive Pulmonary Disease: Emerging Roles of Eosinophils and Procalcitonin. J Innate Immun. 2022;14(2):89-97.
23. Yang L, Zhai Z, Zhang J. The Role of Serum 1,25-Dihydroxy Vitamin D3 and PCT in Idiopathic Pulmonary Fibrosis. Int J Gen Med. 2022;15:8081-8092.
24. Kang HR, Kim SJ, Nam JG, Park YS, Lee CH. Impact of Smoking and Chronic Obstructive Pulmonary Disease on All-Cause, Respiratory, and Cardio-Cerebrovascular Mortality. Int J Chron Obstruct Pulmon Dis. 2024;19:1261-1272.
25. Checa M, Hagood JS, Velazquez-Cruz R, Ruiz V, García-De-Alba C, Rangel-Escareño C, et al. Cigarette Smoke Enhances the Expression of Profibrotic Molecules in Alveolar Epithelial Cells. PLoS One. 2016;11(3):e0150383.
26. Choi JY, Song JW, Rhee CK. Chronic Obstructive Pulmonary Disease Combined with Interstitial Lung Disease. Tuberc Respir Dis (Seoul). 2022;85(2):122-136.
27. Kou M, Jiao Y, Li Z, Wei B, Li Y, Cai Y, et al. Real-world safety and effectiveness of pirfenidone and nintedanib in the treatment of idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2024;80(10):1445-1460




©Copyright 2026 by Osmangazi Tıp Dergisi - Available online at tip.ogu.edu.tr©Telif Hakkı 2026ESOGÜ Tıp Fakültesi - Makale metnine dergipark.org.tr/otdweb sayfasından ulaşılabilir.