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The Relationship Between Pan-Immune Inflammation Value and Mortality in Idiopathic Pulmonary Fibrosis

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Abstract

Objectives: Idiopathic Pulmonary Fibrosis (IPF) is a progressive and potentially fatal interstitial lung disease of unknown origin etiology. Immunological and inflammatory pathways are central to its pathogenesis. The pan-immune inflammation value (PIV) is an emerging index that measures immune-inflammatory status through counts of platelets, neutrophils, monocytes, and lymphocytes. This study aimed to assess the prognostic significance of PIV in predicting disease outcomes and survival in IPF.

Methods: IPF patients aged 18 years or older, followed from January 2016 to June 2024, were retrospectively analyzed. Patients with malignancy or hematologic disorders were excluded. PIV was determined at diagnosis, with patients divided into low- and high-PIV groups based on the median. Clinical, demographic, and laboratory data were compared, and the predictive value of PIV for survival was evaluated.

Results: Among 142 patients, the median age was 70 years, the disease duration was 30 months, and the PIV was 302.8. Those with high PIV had a shorter disease duration (24 vs. 36 months, p=0.006) and higher rates of mortality, ICU admission, and nosocomial infections (p<0.05). The high PIV group showed increased troponin, white blood cell, neutrophil, monocyte, and platelet levels, along with decreased lymphocyte counts (p<0.05). Patients who died had shorter disease durations (22 months vs. 54 months, p<0.001) and more comorbidities, ICU admissions, and infections (p<0.05). LDH and PIV were higher, while magnesium was lower, in patients who died (p<0.05). Kaplan-Meier analysis showed that the median survival was 72 months for the low PIV group, whereas it was only 27 months for the high PIV group (p<0.01).

Conclusion: A high PIV at diagnosis signals a worse outlook in IPF, highlighting the importance of inflammation in how the disease develops.

Keywords: Idiopathic Pulmonary Fibrosis, Survival, Pan-Immune Inflammation Value

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İdiyopatik Pulmoner Fibroziste Pan-İmmün İnflamasyon Değeri ile Mortalite Arasındaki İlişki

Öz

Giriş: İdiyopatik Pulmoner Fibrozis (İPF); nedeni bilinmeyen, ilerleyici ve yaşamı tehdit eden bir interstisyel akciğer hastalığıdır. İmmünolojik ve inflamatuvar yolaklar, hastalığın gelişiminde merkezi bir rol oynamaktadır. Pan-immün inflamasyon değeri (PIV), trombosit, nötrofil, monosit ve lenfosit sayıları kullanılarak immün-inflamatuvar durumu değerlendiren yeni bir indekstir. Bu çalışma, İPF'de hastalık sonuçlarını ve sağkalımı öngörmede PIV'in prognostik önemini değerlendirmeyi amaçlamaktadır.

Yöntemler: Ocak 2016 ile Haziran 2024 tarihleri arasında takip edilen, 18 yaş ve üzerindeki IPF hastaları retrospektif olarak incelendi. Malignite veya hematolojik hastalığı bulunan hastalar çalışma dışı bırakıldı. Tanı anındaki PIV değerleri hesaplandı ve hastalar, medyan PIV değerine göre düşük ve yüksek PIV gruplarına ayrıldı. Klinik, demografik ve laboratuvar verileri karşılaştırıldı ve PIV'in sağkalımı öngörme değeri değerlendirildi.

Bulgular: Çalışmaya dâhil edilen 142 hastanın medyan yaşı 70 yıl, hastalık süresi 30 ay ve PIV değeri 302.8 idi. Yüksek PIV değerine sahip hastalarda hastalık süresi daha kısa (24 aya karşı 36 ay, p=0.006) ve mortalite, yoğun bakım yatışı ile nozokomiyal enfeksiyon oranları daha yüksek bulundu (p<0.05). Yüksek PIV grubunda troponin, beyaz kan hücresi, nötrofil, monosit ve trombosit düzeyleri artmış, lenfosit sayıları ise azalmıştı (p<0.05). Mortalite gelişen hastalarda hastalık süresi daha kısa (22 aya karşı 54 ay, p<0.001); komorbidite, yoğun bakım yatışı ve enfeksiyon oranları daha yüksekti (p<0.05). LDH ve PIV düzeyleri mortalite gelişen hastalarda daha yüksek, magnezyum düzeyi ise daha düşüktü (p<0.05). Kaplan-Meier analizinde, düşük PIV grubunda medyan sağkalım 72 ay iken yüksek PIV grubunda 27 ay olarak saptandı (p<0.01).

Sonuç: Tanı anında yüksek PIV düzeyi, İPF'de kötü prognozu öngörmekte olup inflamasyonun hastalık progresyonundaki rolünü desteklemektedir.

Anahtar kelimeler: İdiyopatik Pulmoner Fibrozis, Sağkalım, Pan-İmmün İnflamasyon Değeri.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a serious and advancing interstitial lung disease. The survival rate after initial diagnosis is about 2 to 3 years[1]. Although many pathogeneses have been implicated in IPF, it is believed that IPF results from multiple cellular interactions. Several cell types are involved in the development of pulmonary fibrosis, including inflammatory cells, fibroblasts, epithelial cells, and immune cells. These cells contribute to fibrosis through cell signaling and cytokine release[2]. In this disease, healthy lung tissue is replaced by a deteriorated extracellular matrix (ECM). Fibrosis results from chronic inflammation, as myofibroblasts form scars due to excessive protein accumulation in the ECM. Gas exchange is impaired in fibrotic lungs; the disease leads to respiratory failure and death[1,3].

The Pan-Immune Inflammation Value (PIV) serves as an index to assess a patient's immune response and inflammation level. It is a new biomarker obtained by multiplying the neutrophil, platelet, and monocyte counts (all in $10^3/mm^3$), then dividing that product by the lymphocyte count (also in $10^3/mm^3$). This biomarker integrates counts of neutrophils, platelets, monocytes, and lymphocytes, which are among the most frequently used markers of systemic inflammation[4]. It was first studied in colorectal cancer patients in 2020 and identified as a reliable predictor of survival. It also demonstrated a higher predictive value than other inflammation-related biomarkers[5].

The systemic inflammatory response alters circulating white blood cell (WBC) counts[6]. Neutrophils are the primary cells of the immune system; they produce cytokines, chemokines,

and growth factors. Platelets also contribute to inflammation by promoting cytokine release[7]. Lymphocytes are responsible for both cellular and humoral immunity[8]. Other immune cells that develop in response to inflammation include monocytes. Monocytes differentiate into macrophages and help in the inflammatory response[9]. The inflammation is characterized by an increase in neutrophils, platelets, and monocytes, while the number of lymphocytes decreases[7].

As mentioned earlier, all of these cells (neutrophils, platelets, monocytes, and lymphocytes), which can only be obtained through a hemogram test, play a role in immunity and inflammation. This study aimed to assess the predictive value of PIV for survival in patients with IPF, considering that immunity and inflammation are known to affect disease progression.

METHODS

The study was carried out following the Declaration of Helsinki and the Guidelines for Good Clinical Practice, with approval from the local ethics committee (Ethics Number: B.10.1.TKH.4.34.H.GP.0.01/201). Since the study was retrospective, participants did not provide informed consent.

Patients diagnosed with IPF and monitored in the Department of Chest Diseases and the pulmonary ICU at a tertiary training and research hospital from January 2016 to June 2024 were reviewed retrospectively. The IPF diagnosis was made following the guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) issued in 2011, 2018, and 2022. The research involved 142 adult patients who were at least 18 years old. Patients with hematological or solid-organ cancers that could influence neutrophil counts, or who were neutropenic, were excluded from the study (Figure 1: Study Flowchart).

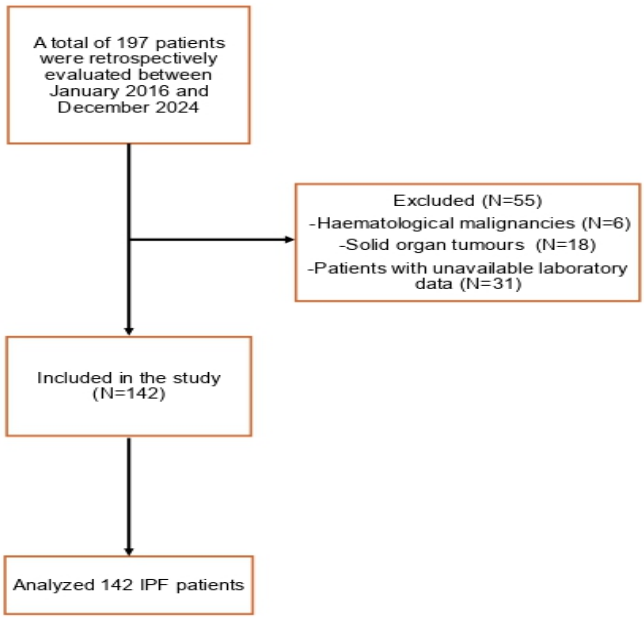

Figure 1. Study Flowchart (IPF: Idiopathic Pulmonary Fibrosis)

Additionally, patients with rheumatologic diseases and those presenting with active viral and bacterial infections were excluded. Demographic and clinical details such as age, gender, and smoking history, comorbidities, home oxygen therapy, disease duration, follow-up period, survival time among those who died, exacerbation reports, and mortality status were recorded. Blood test results, including complete blood count (CBC) parameters, creatinine, albumin, C-reactive protein (CRP), procalcitonin (PCT), electrolytes, blood gas analysis, lactate, and lactate dehydrogenase (LDH), were documented. PIVs were calculated, and the median was determined. Patients were split into two groups according to the median PIV: those below the median were classified as the low-PIV group, and those above as the high-PIV group. Additionally, clinical-demographic data, laboratory results, and PIV at diagnosis were compared between patients with and without a fatal outcome. Factors associated with mortality were identified, and the predictive value of PIV for survival was analyzed.

Statistical Analyses

Patient data collected as part of the study were analyzed using IBM SPSS Statistics for macOS 29.0 (IBM Corp., Armonk, NY) and MedCalc

statistical software version 12.7.0.0 (MedCalc Software, Ostend, Belgium). Descriptive statistics included frequencies and percentages for categorical variables and medians, minimums, and maximums for continuous variables. Intergroup comparisons were made using the Mann-Whitney U test, and comparisons of categorical variables were made using the chi-square test or Fisher's exact test. Receiver Operating Characteristic (ROC) analysis was performed for PIV, which was considered to have a discriminative effect on survival, and the ROC curve was plotted. The PIV group conducted an analysis of overall survival using the Kaplan-Meier method. Furthermore, Cox regression analysis was conducted to evaluate mortality. Results were considered statistically significant if the p-value was less than 0.05.

RESULTS

Patient Characteristics

Table 1 summarizes the demographic and clinical features of the patients. The study included 142 patients. The age at diagnosis ranged from 47 to 94 years, with a median of 70 years. of these, 73.9% (105) were male, and 26.1% (37) were female. Disease duration varied from 1 to 120 months, with a median of 30 months. Out of 142 patients, 43% (n=61) survived while 57% (n=81) did not. Coronary artery disease (CAD) was present in 59 patients (41.5%), arrhythmias in 20 patients (14.1%), hypertension (HT) in 93 patients (65.5%), diabetes mellitus (DM) in 60 patients (42.3%), chronic airway diseases in 13 patients (9.2%), congestive heart failure (CHF) in 22 patients (15.5%), and pulmonary hypertension (PHT) in 51 patients (40.2%). Only 41 patients (29.7%) had never smoked. Home oxygen therapy was used by 37.3% (n=53) of patients. During the treatment period, 56% of patients (n = 79) required ICU admission, and nosocomial infections developed in 10.6% (n = 15). Most patients were receiving anti-fibrotic therapy (n=119), and some were diagnosed during exacerbations (n=17) (Table 1).

Laboratory Results

Median values based on laboratory data at the time of diagnosis are as follows: PIV 302.8 (18.4-2823), CRP 5.5 (0.4-187), PCT 0 (0-9), pH 7.4 (7.30-7.60), PaO2 68 (47-133), Brain Natriuretic Peptide (BNP) 120.5 (10-4132), d-dimer 0.4 (0.1-2.7), troponin 14 (0.8-99), WBC 8910 (4666-16800), neutrophil 5575 (1770-15100), eosinophil 220 (0-7800), monocyte 560 (30-1530), lymphocyte 2210 (130-5300), platelet 239000 (95000-579000), blood urea nitrogen (BUN) 17 (6-45), creatinine 1 (0,5-2,2), LDH 369,5 (164-945), magnesium 1,8 (1-2,4), and albumin 4,1 (2,6-4,9) (Table 1).

Table I: Demographic and Clinical Findings of the Patients

Variables (N=142)	n (%)	Median (Min-Max)
Age at diagnose		70(47-94)
Duration of illness (month)		30(1-120)
Gender		
Male	105(73.9)	
Female	37(26.1)	
Latest situation		
Alive	61(43)	
Deceased	81(57)	
Exacerbation		1(1-5)
O_2 therapy at home	53(37.3)	
CAD	59(41.5)	
AF	20(14.1)	
HT	93(65.5)	
DM	60(42.3)	
Chronic Respiratory Disease/COPD	13(9.2)	
CHF	22(15.5)	
PHT	51(40.2)	
Smoking		
No	41(29.7)	
Yes	12(8.7)	
Quit	85(61.6)	
Smoke (package/year)		20(0-90)
ICU requirements	79(56)	
Nosocomial infections	15(10.6)	
Cause of Death		
Acute Respiratory Failure	62(76.5)	
Septic Shock	19(23.5)	
CRP mg/L		5.5(0.4-187)
PCT μg/L		0(0-9)
pH		7.4(7.3-7.6)
PO_2		68(47-133)
Lactate mmol/L		1.1(0-4.6)
BNP pg/ml		120.5(10-4132)
D-Dimer ng/ml		0.4(0.1-2.7)
Troponin ng/ml		14(0.8-99)
WBC		8910(4666-16800)
Neutrophil x $10^3/mm^3$		5575(1770-15100)
Eosinophil x $10^3/mm^3$		220(0-7800)
Monocyte x $10^3/mm^3$		560(30-1530)
Lymphocyte x $10^3/mm^3$		2210(130-5300)
Platelet x $10^3/mm^3$		239000(95000-579000)
LDH IU/L		369.5(164-945)
Magnesium mEq/L		1.8(1-2.4)
Calcium mg/dl		9.3(7.8-10.7)
Albumin gr/dl		4.1(2.6-4.9)
PIV x $10^6/mm^3$		302.8(18.4-2823)

CAD: Coronary Artery Disease, AF: Atrial Fibrillation, HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CHF: Congestive Heart Failure, PHT: Pulmonary Hypertension, ICU: Intensive Care Unit, CRP: C-Reactive Protein, PCT: Procalcitonin, PaO2: Partial Oxygen Pressure, BNP: Brain Natriuretic Peptide, WBC: White Blood Cell, LDH: Lactate Dehydrogenase, PIV: Pan-Immune Inflammation Value.

Comparison of Patients Based on Low and High PIV Values

Table 2 shows the distribution of demographic and clinical findings among patients in the high- and low-PIV groups. Patients in the high-PIV group experienced a shorter disease duration, averaging 24 months, whereas those in the low-PIV group averaged 36 months (p=0.006). The median age at diagnosis was comparable between the groups (69 vs. 70 years, p=0.485). Furthermore, the high PIV group experienced higher rates of mortality and ICU admission (66.2% vs 47.9%, p=0.028; 64.8% vs 47.1%, p=0.035, respectively). The primary causes of death were acute respiratory failure and septic shock, with similar distributions between the groups (73.5% vs 78.7%, 26.5% vs 21.3%; p = 0.780, respectively). The number of IPF exacerbations and gender did not differ significantly between the groups (1 vs 1, p = 0.698; male: 76.1% vs 71.8%; female: 23.9% vs 28.2%; p = 0.703, respectively). When chronic comorbidities were evaluated, no notable differences were found between the groups for CAD, arrhythmias, HT, DM, chronic respiratory diseases/COPD, CHF, and PHT (40.8% vs 42.3%, p = 0.865; 8.5% vs 19.7%, p = 0.091; 64.8% vs 66.2%, p = 1.00; 39.4% vs 45.1%, p = 0.497; 4.2% vs 14.1%, p = 0.081; 11.3% vs 19.7%, p = 0.246; 38.1% vs 42.2%, p = 0.638, respectively). Nosocomial infections and home oxygen therapy were similar across groups (7 vs 8, p = 1.00; 31% vs 43.7%, p = 0.118, respectively).

Median levels of CRP, troponin, WBC, neutrophils, monocytes, and platelet counts were higher in the high PIV group (7.4 vs 3.5, p=0.014; 15.5 vs 10, p=0.011; 10100 vs 7490, p<0.001; 6900 vs 4450, p<0.001; 650 vs 440, p<0.001; 259 vs 229, p<0.001, respectively), while lymphocyte counts were lower (2080 vs 2400, p<0.05). For other laboratory parameters, including PCT, pH, PO2, lactate, BNP, d-dimer, eosinophil, LDH, magnesium, calcium, and albumin, there were no meaningful differences between the low- and high-PIV groups. (0 vs 0, p=0.808; 7.4 vs 7.4, p=0.073; 71 vs 65, p=0.108; 1 vs 1.1, p=0.079; 102.9 vs 131.7, p=0.337; 0.4 vs 0.4, p=0.911; 210 vs 230, p=0.838; 363 vs 377, p=0.496; 1.8 vs 1.8, p=0.567; 9.3 vs 9.3, p=0.837; 4.2 vs 4, p=0.446, respectively) (Table 2).

Table II: Demographic and Clinical Findings According to Low and High PIV Groups

Variables (N=142)	Low PIV (n=71)	High PIV (n=71)	p-value
	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	
Age at diagnosis	69 (47-94)	70 (48-89)	0.485
Duration of illness (months)	36 (3-120)	24 (1-105)	**0.006**
Gender			0.703
Male	54 (76.1)	51 (71.8)	
Female	17 (23.9)	20 (28.2)	
Latest Situation			**0.028**
Alive	37 (52.1)	24 (33.8)	
Deceased	34 (47.9)	47 (66.2)	
Cause of Death			0.780
Acute Respiratory Failure	25 (73.5)	37 (78.7)	
Septic Shock	9 (26.5)	10 (21.3)	
Exacerbations	1 (1-4)	1 (1-5)	0.698
O_2 therapy at home	22 (31)	31 (43.7)	0.118
CAD	29 (40.8)	30 (42.3)	0.865
AF	6 (8.5)	14 (19.7)	0.091
HT	46 (64.8)	47 (66.2)	1.000
DM	28 (39.4)	32 (45.1)	0.497
Chronic Respiratory Disease/COPD	3 (4.2)	10 (14.1)	0.081
CHF	8 (11.3)	14 (19.7)	0.246

PHT	24 (38.1)	27 (42.2)	0.638
Smoking No Yes Quit	 21 (30) 7 (10) 42 (60)	 20 (29.4) 5 (7.4) 43 (63.2)	0.843
Smoke (package/year)	20 (0-90)	20 (0-80)	0.445
ICU Requirements	33 (47.1)	46 (64.8)	**0.035**
Nosocomial Infections	7 (10)	8 (11.3)	1.000
CRP mg/L	3.5 (0.4-94.1)	7.4 (1-187)	**0.014**
Procalcitonin μg/L	0 (0-0.3)	0 (0-9)	0.808
pH	7.4 (7.4-7.6)	7.4 (7.3-7.6)	0.073
PO_2	71 (47-107)	65 (52-133)	0.108
Lactate mmol/L	1 (0.1-4.6)	1.1 (0-2.8)	0.079
BNP pg/ml	102.9 (13.5-4132)	131.7 (10-2048)	0.337
D-Dimer ng/ml	0.4 (0.1-2.7)	0.4 (0.1-2.5)	0.911
Troponin ng/ml	10 (0.8-70)	15.5 (2-99)	**0.011**
WBC	7490 (4666-12600)	10100 (6850-16800)	**<0.001**
Neutrophil x 10^3 /mm^3	4450 (1770-10100)	6900 (3130-15100)	**<0.001**
Eosinophil x 10^3 /mm^3	210 (0-930)	230 (0-7800)	0.838
Monocyte x 10^3 /mm^3	440 (30-860)	650 (50-1530)	**<0.001**
Lymphocyte x 10^3 /mm^3	2400 (1110-5300)	2080 (130-4130)	**0.014**
Platelet x 10^3 /mm^3	229 (95-367)	259 (114-579)	**<0.001**
LDH IU/L	363 (164-686)	377 (170-945)	0.496
Magnesium mEq/L	1.8 (1-2.4)	1.8 (1.2-2.4)	0.567
Calcium mg/dl	9.3 (8-10.4)	9.3 (7.8-10.7)	0.837
Albümin g/dl	4.2 (2.6-4.9)	4 (3-4.8)	0.446

CAD: Coronary Artery Disease, AF: Atrial Fibrillation, HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CHF: Congestive Heart Failure, PHT: Pulmonary Hypertension, ICU: Intensive Care Unit, CRP: C-Reactive Protein, PCT: Procalcitonin, PaO2: Partial Oxygen Pressure, BNP: Brain Natriuretic Peptide, WBC: White Blood Cell, LDH: Lactate Dehydrogenase, PIV: Pan-Immune Inflammation Value.

Demographic and Clinical Findings of Patients Regarding Mortality

Table 3 shows the distribution of demographic and clinical characteristics according to mortality status. The duration of illness was 22 months among patients who died and 54 months among those who survived (p<0.001). Patients who expired exhibited a higher likelihood of requiring oxygen support (54.3% vs 14.8%, p<0.001). The frequencies of chronic respiratory disease/COPD, CAD, CHF, and PHT, as well as ICU admission and nosocomial infections, were higher in patients who died (14.8% vs 1.6%, p=0.016; 51.9% vs 27.9%, p=0.004; 24.7% vs 3.3%, p<0.001; 52.9% vs 24.6, p=0.002; 97.5% vs 0%, p<0.001; 18.5% vs 0%, p<0.001; respectively). There were no differences between groups in the number of exacerbations, arrhythmias, HT, and DM (1.5 vs 1, p=0.764; 17.3% vs 9.8%, p=0.308; 70.4% vs 59%, p=0.218; 43.2% vs 41%, p=0.790; respectively).

Among the laboratory findings, lactate, BNP, LDH, and PIV levels were markedly elevated in patients who succumbed (1.1 vs 0.8, p<0.001; 147 vs 100, p=0.027; 424 vs 316, p<0.001; 365.2 vs 274.4, p=0.027, respectively), while PO2, magnesium, and albumin levels were lower. (64 vs 74.5, p<0.001; 1.8 vs 1.9, p<0.001; 4 vs 4.2, p=0.017; respectively) (Table 3). There is no statistically significant difference between groups for CRP, PCT, pH, d-dimer, troponin, WBC, neutrophils, eosinophils, monocytes, lymphocytes, platelets, and calcium (6.2 vs 3.5, p=0.059; 0 vs 0, p=0.223; 7.4 vs 7.4, p=0.088; 0.4 vs 0.4, p=0.802; 9470 vs 8360, p=0.153; 6100 vs 5190, p=0.098; 240 vs 180, p=0.069; 560 vs 540, p=0.462; 2190 vs 2290, p=0.495; 247 vs 232, p=0.224; 9.2 vs 9.4, p=0.332; respectively) (Table 3).

Table III: Clinical and demographic findings according to whether the patients survived or not

Variables (N=142)	Alive (n=61)	Deceased (n=81)	p-value
	n (%) or Median (Min-Max)	n (%) or Median (Min-Max)	
Age at Diagnosis	69 (47-80)	71 (53-94)	0.076
Duration of illness (months)	54 (5-120)	22 (1-84)	**<0.001**
Gender			1.000
Male	45 (73.8)	60 (74.1)	
Female	16 (26.2)	21 (25.9)	
Exacerbations	1 (1-4)	1.5 (1-5)	0.764
O_2 Therapy at Home	9 (14.8)	44 (54.3)	**<0.001**
CAD	17 (27.9)	42 (51.9)	**0.004**
AF	6 (9.8)	14 (17.3)	0.308
HT	36 (59)	57 (70.4)	0.218
DM	25 (41)	35 (43.2)	0.790
Chronic Respiratory Disease/COPD	1 (1.6)	12 (14.8)	**0.016**
CHF	2 (3.3)	20 (24.7)	**<0.001**
PHT	14 (24.6)	37 (52.9)	**0.002**
Smoking			0.317
No	20 (33.3)	21 (26.9)	
Yes	7 (11.7)	5 (6.4)	
Quit	33 (55)	52 (66.7)	
Smoke (Package/Year)	20 (0-90)	20 (0-80)	0.375
ICU Requirements	0 (0)	79 (97.5)	**<0.001**
Nosocomial Infections	0 (0)	15 (18.5)	**<0.001**
Cause of Death			NA
Acute Respiratory Failure	0 (0)	62 (76.5)	
Septic Shock	0 (0)	19 (23.5)	
CRP mg/L	3.5 (0.4-94.1)	6.2 (0.6-187)	0.059
PCT μg/L	0 (0-5.1)	0 (0-9)	0.223
pH	7.4 (7.4-7.6)	7.4 (7.3-7.6)	0.088
PO_2	74.5 (48-104)	64 (47-133)	**<0.001**
Lactate mmol/L	0.8 (0.1-4.6)	1.1 (0-3.1)	**<0.001**
BNP pg/ml	100 (10-4014)	147 (10-4132)	**0.027**
D-Dimer ng/ml	0.4 (0.1-2.2)	0.4 (0.1-2.7)	0.802
Troponin ng/ml	10 (1.4-33.6)	14.2 (0.8-99)	0.071
WBC	8360 (4800-16800)	9470 (4666-16190)	0.153
Neutrophil x $10^3/mm^3$	5190 (1950-15100)	6100 (1770-11750)	0.098
Eosinophil x $10^3/mm^3$	180 (0-650)	240 (0-7800)	0.069
Monocyte x $10^3/mm^3$	540 (30-1260)	560 (50-1530)	0.462
Lymphocyte x $10^3/mm^3$	2290 (1080-4320)	2190 (130-5300)	0.495
Platelet x $10^3/mm^3$	232 (131.9-579)	247 (95-469)	0.224
LDH IU/L	316 (164-623)	424 (173-945)	**<0.001**
Magnesium mEq/L	1.9 (1.2-2.4)	1.8 (1-2.4)	**<0.001**
Calcium mg/dl	9.4 (8-10.4)	9.2 (7.8-10.7)	0.332
Albumin gr/dl	4.2 (2.9-4.9)	4 (2.6-4.9)	**0.017**
PIV x $10^6/mm^3$	274.4 (33.6-2823)	365.2 (18.4-2131.1)	**0.027**

CAD: Coronary Artery Disease, AF: Atrial Fibrillation, HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CHF: Congestive Heart Failure, PHT: Pulmonary Hypertension, ICU: Intensive Care Unit, CRP: C-Reactive Protein, PCT: Procalcitonin, PaO2: Partial Oxygen Pressure, BNP: Brain Natriuretic Peptide, WBC: White Blood Cell, LDH: Lactate Dehydrogenase, PIV: Pan-Immune Inflammation Value.

Cox Regression Analysis

In the univariate Cox regression analysis, various clinical and laboratory parameters showed a significant association with mortality in patients with IPF. Older age (p=0.051), frequent exacerbations (p<0.001), CAD (p=0.011), chronic respiratory diseases/COPD (p<0.001), CHF (p<0.001), PHT (p=0.003), nosocomial infections (p<0.001), elevated CRP (p=0.004), lactate (p<0.001), BNP (p=0.019), troponin (p=0.006), BUN (p<0.001), and LDH (p<0.001), as well as lower PaO_2 (p=0.002), magnesium (p<0.001), and albumin (p<0.001) were linked to increased mortality. Long-term home oxygen therapy was also significantly linked to mortality (p<0.001). Within the multivariate Cox regression model, COPD (HR: 2.471, 95% CI: 1.196–5.105, p=0.015), PHT (HR:

2.097, 95% CI: 1.267–3.470, p=0.004), lower magnesium (HR: 0.349, 95% CI: 0.143–0.851, p=0.021), and hypoalbuminemia (HR: 0.411, 95% CI: 0.233–0.726, p=0.002) remained independent predictors of mortality. Furthermore, being in a higher PIV group (PIV ≥ 302.8) was independently linked to reduced survival (HR: 1.735, 95% CI: 1.034–2.911, p=0.037). These findings suggest that systemic inflammation, comorbid cardiopulmonary conditions, and nutritional status are key factors influencing survival in patients with IPF (Table 4).

Table IV: Evaluation of Variables Associated with Mortality by Cox Regression Analysis

Variables	Univariate			Multivariate		
	HR (CI %)	B	p-value	HR (CI %)	B	p-value
Age at diagnose	1.029 (1.000-1.058)	0.028	**0.051**			
Gender	0.716 (0.430-1.737)	-0.334	0.199			
Exacerbations	1.319 (1.137-1.530)	0.277	**< 0.001**			
O_2 therapy at home	2.676 (1.721-4.161)	0.984	**< 0.001**			
CAD	1.766 (1.141-2.734)	0.569	**0.011**			
AF	1.211 (0.680-2.158)	0.192	0.515			
HT	1.157 (0.716-1.872)	0.146	0.552			
DM	1.026 (0.660-1.596))	0.026	0.908			
Chronic Respiratory Diseases/COPD	2.974 (1.600-5.529)	1.090	**< 0.001**	2.471 (1.196-5.105)	0.905	**0.015**
CHF	2.476 (1.486-4.126)	0.907	**< 0.001**			
PHT	2.027 (1.267-3.244)	0.707	**0.003**	2.097 (1.267-3.470)	0.740	**0.004**
Nosocomial Infections	2.676 (1.497-4.784)	0.984	**< 0.001**	1.765 (0.923-3.373)	0.568	0.086
CRP mg/lt	1.009 (1.003-1.015)	0.009	**0.004**			
PCTμg/lt	1.033 (0.816-1.308)	0.032	0.787			
pH	16.019 (0.068-3751.170)	2.774	0.319			
PaO_2	0.966 (0.946-0.987)	-0.034	**0.002**			
Lactate mmol/lt	1.796 (1.375-2.346)	0.586	**< 0.001**			
BNP pg/ml	1.000 (1.000-1.001)	0.000	**0.019**			
D-dimer ng/ml	0.954 (0.584-1.560)	-0.047	0.852			
Troponin ng/ml	1.016 (1.005-1.028)	0.016	**0.006**			
WBC	1.000 (1.000-1.000)	0.000	0.292			
Neutrophil x 10^3 /mm^3	1.000 (1.000-1.000)	0.000	0.262			
Eosinophil x 10^3 /mm^3	1.000 (1.000-1.000)	0.000	0.258			
Monocyte x 10^3 /mm^3	1.000 (1.000-1.001)	0.000	0.392			
Lymphocyte x 10^3 /mm^3	1.000 (1.000-1.000)	0.000	0.344			
Platelet x 10^3 /mm^3	1.000 (1.000-1.000)	0.000	0.841			
BUN mg/dl	1.049 (1.020-1.078)	0.047	**< 0.001**			
Creatinin mg/dl	1.726 (0.843-3.534)	0.546	0.135			
LDH IU/L	1.003 (1.001-1.004)	0.003	**< 0.001**			
Magnesium mEq/lt	0.170 (0.074-0.390)	-1.771	**< 0.001**	0.349 (0.143-0.851)	-1.054	**0.021**
Calcium mg/dl	0.886 (0.634-1.238)	-0.121	0.479			
Albumin g/dl	0.385 (0.241-0.615)	-0.955	**< 0.001**	0.411 (0.233-0.726)	-0.888	**0.002**
High PIV Group	1.800 (1.155-2.803)	0.588	**0.009**	1.735 (1.034-2.911)	0.551	**0.037**

CAD: Coronary Artery Disease, AF: Atrial Fibrillation, HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CHF: Congestive Heart Failure, PHT: Pulmonary Hypertension, CRP: C-Reactive Protein, PCT: Procalcitonin, PaO2: Partial Oxygen Pressure, BNP: Brain Natriuretic Peptide, BUN: Blood Urea Nitrogen, LDH: Lactate Dehydrogenase, PIV: Pan-Immune Inflammation Value.

Evaluation of Patients Regarding Survival

The ROC curve results analyzing the differential effect of PIV on mortality are presented in Table 5.

Table V: Cut-off Value for PIV Based on Mortality

Risk Factor	AUC (%95 CI)	Cut-off value	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)	p-value
PIV	0.609 (0.514-0.703)	>326.67	55.6	70.5	71.4	54.4	0.041

PPV: Positive Predictive Value, NPV: Negative Predictive Value, PIV: Pan-immune Inflammation Value

The area under the curve (AUC) for the PIV value was 60.9%, with a cutoff of 326.67 (Figure 2. Survival ROC Curve of PIV). The AUC reflects the diagnostic test's statistical significance in distinguishing outcomes. Because the diagnostic test in our study aimed to predict patient mortality, the PIV showed limited discriminative ability, falling within the 60%-70% range.

Table 6 presents the distribution of patient survival by PIV status (low vs. high). The table analysis indicates a discrepancy in survival rates between the low- and high-PIV groups. The low PIV group experienced a median survival of 72 months, whereas the high PIV group had a median survival of 27 months (p=0.008) (see Figure 3 for the Kaplan-Meier Overall Survival Curve by PIV groups).

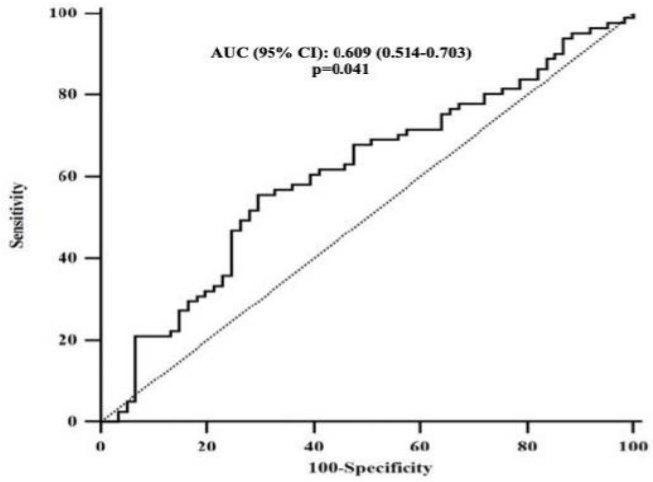

Figure 2. Survival ROC Curve of PIV

Table VI: Overall Survival of the Patients

	Survival estimate (%95 CI)	N of events (%)	Log-rank Test p-value
OS (months)			0.008
All patients	40 (30.2-49.8)	81	
Low-PIV	72 (46.5-97.5)	34	
High-PIV	27 (18.4-35.6)	47	

OS: Overall Survival, PIV: Pan-immune Inflammation Value.

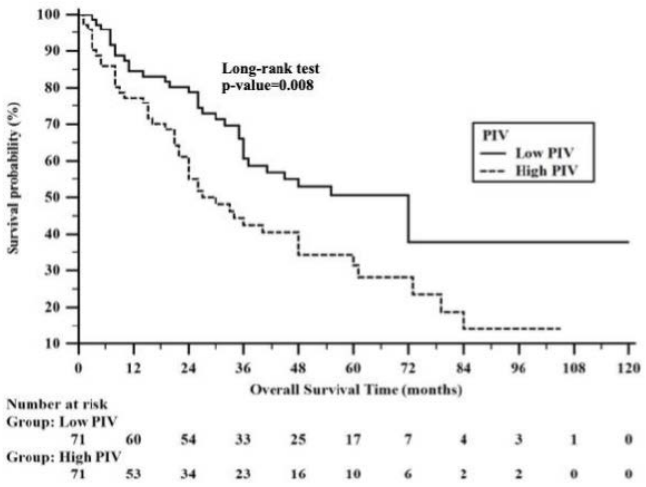

Figure 3. Kaplan Meier Overall Survival Curve According to PIV Groups

DISCUSSION

Idiopathic pulmonary fibrosis is a complex condition marked by ongoing injury to alveolar epithelial cells, leading to increasing fibrosis. It involves both innate and adaptive immune responses, making it a challenging disease to understand and treat. Inflammatory processes are mainly fueled by immune cells such as neutrophils, monocytes, and lymphocytes. As a result, increases in various inflammatory markers are observed in routine complete blood counts, reflecting systemic inflammation[10]. This indicates that higher levels of inflammation markers in IPF may provide useful insights into disease prognosis. In the present study, an increase in PIV, calculated from neutrophil, monocyte, platelet, and lymphocyte counts, was found to significantly influence mortality among patients with IPF.

A CBC is a simple, inexpensive, and widely accessible method for the indirect assessment of systemic inflammation. Hematological indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation response index (SIRI), systemic inflammation index (SII), and aggregate index of systemic inflammation (AISI), have been proposed as valuable markers of chronic inflammation. Monteleone et al. demonstrated that NLR is associated with lung function decline, hospitalization, and mortality in patients with IPF[11]. These findings suggest that CBC-derived inflammatory indices are practical tools for assessing disease activity and prognosis in IPF.

In recent years, NLR and PLR have been extensively investigated as systemic inflammatory markers in IPF. Several studies have shown that elevated baseline NLR and increases during follow-up are associated with worse clinical outcomes, including faster disease progression and higher mortality[12]. Nevertheless, conflicting data exist in the literature[13], highlighting the need for more comprehensive inflammation-based biomarkers. In this regard, the PIV has emerged as an integrated index that may provide a more accurate reflection of systemic immune activation. In our study, a PIV cutoff value of 326.67 yielded an AUC of 60.9%, indicating moderate discriminative ability. This result suggests that inflammation indices, such as PIV, may be influenced by multiple factors, including antifibrotic therapy use, disease heterogeneity, and the limited sample size (n=142). Despite these limitations, the results indicate that PIV could still be a useful tool in practice, a readily available biomarker for assessing inflammation and predicting mortality in patients with IPF.

Monocyte counts are elevated in patients with IPF. Furthermore, several studies have demonstrated that monocyte count may have even greater prognostic value than neutrophil count in predicting outcomes in patients with IPF[12]. In addition, Karampitsakos et al.[14] showed that a monocyte subgroup (CD14+CD163-HLA-DRLOW) predicts mortality in IPF from the entire monocyte pool, and it has been suggested that loss of HLA-DR on monocytes creates an immunosuppressive state and leads to immunoparalysis. Based on these data, IPF may produce a sepsis-like clinical

situation. Additionally, this may be linked to a greater need for intensive care hospitalization in the high PIV group due to immunoparalysis caused by inflammation. On the other hand, studies have also demonstrated that the monocyte-to-lymphocyte ratio (MLR) is not superior to the NLR. It has been shown that MLR is only weakly correlated with changes in FVC[15]. In our study, monocyte count was significantly higher in the high PIV group; however, it did not yield a significant association with mortality. Given the inconsistencies observed in the literature, it is not surprising that our results followed a similar pattern.

Blood cells are essential for the immune system and fighting disease. Leukocytes help prevent infections and phagocytose bacteria. Erythrocytes (RBCs) are responsible for oxygen transport and removing respiratory by-products. Platelets are involved in clotting, wound healing, and inflammation. Blood homeostasis requires maintaining the number and activity of these cells within a narrow physiological range. In disease states, these indicators can fall outside that range. Haematological indicators are essential clinical parameters that reflect an individual's overall health status[16]. Recently, a new biomarker, PIV (peripheral neutrophils × platelets × monocytes/lymphocytes), has been recognized as a promising indicator for predicting long-term outcomes in cancer patients, effectively reflecting their inflammatory and immune status. It has also been reported that PIV is a more effective prognostic marker compared to simpler ratios like Neutrophil/Lymphocyte, Platelet/Lymphocyte, and Monocyte/Lymphocyte[17,18]. Pan-immune inflammation value has been linked to disease activity not only in cancers but also in many inflammatory diseases, such as cardiovascular and rheumatological conditions[19-22]. In a recent study, a low PIV value was also linked to higher survival rates in patients with septic shock[4]. As far as we know, there are no studies linking PIV and IPF in the current literature. Hence, this article is anticipated to make meaningful contributions to the field.

Differences between PIV groups were also seen in laboratory results. The increases in CRP, WBC, neutrophils, and troponin levels, particularly in the high PIV group, indicate systemic inflammation. Similar to markers often highlighted by previous studies, such as the NLR, the role of these markers in predicting prognosis is also clear[23,24]. These findings indicate that inflammation is quite prevalent in IPF. Furthermore, the higher mortality observed in the high PIV group, along with the tendency for CRP levels to be elevated in this group—despite not being statistically significant—suggests that PIV might serve as a better predictor of mortality and a more dependable inflammatory biomarker than CRP. Additionally, the Cox regression analysis indicated that higher PIV values independently predicted mortality.

In IPF, LDH is a valuable biomarker for assessing disease activity, particularly during acute exacerbations. Additionally, LDH is linked to severe pulmonary fibrosis, which has been directly connected to hypoxia[25]. These data suggest that increased LDH levels are associated with greater inflammation. In our study, both LDH and PIV were found to be significantly elevated in patients who experienced mortality. Previous research has reported that LDH levels can reflect inflammatory processes and serve as indicators, such as PIV[26].

Magnesium deficiency can worsen inflammation and cellular dysfunction by increasing oxidative stress. Previous research has shown that magnesium deficiency triggers inflammatory processes and increases tissue damage through oxidative stress[27]. This suggests that magnesium may be associated with inflammatory markers, such as PIV.

Another important consideration is the role of magnesium in the pathophysiology of IPF. In an experimental animal model in which Magnesium Lithospermate B (MLB) was studied, inflammatory and pro-fibrotic cytokines decreased, as shown by pathological examination of rat lungs given MLB[28]. These results indicate that magnesium might be a valuable treatment option for chronic inflammatory conditions, such as IPF. Given magnesium's anti-inflammatory and anti-fibrotic effects, it's not surprising that magnesium deficiency was observed in the group with higher mortality.

CONCLUSION

This study indicates that PIV may reflect the inflammatory status at diagnosis in IPF patients and could help predict clinical outcomes. Patients with high PIV values are at a notably greater risk of poor outcomes. PIV could serve as an important tool for monitoring patients and evaluating mortality risk. However, further research with larger, more diverse patient groups is needed to improve the generalizability of these findings.

LIMITATIONS

Our study has certain limitations. First, some patients were diagnosed during exacerbations, which may, unfortunately, affect laboratory results. Because of the small number of IPF patients, they could not be excluded from the study. Another limitation is that not all patients received medication, and the treatment varied among those who did. Although treatments do not affect survival, in clinical settings such as exacerbations, they may influence outcomes. Another limitation of the study is that, due to its retrospective design, data on patients' occupational histories and exposure to chemicals and dust were not available.

List of Abbreviations

IPF: Idiopathic Pulmonary Fibrosis

ECM: Extracellular Matrix

PIV: Pan-immune Inflammation Value

WBC: White Blood Cell

ICU: Intensive Care Unit

ATS: American Thoracic Society

ERS: European Respiratory Society

CBC: Complete Blood Count

CRP: C-Reactive Protein

PCT: Procalcitonin

LDH: Lactate Dehydrogenase

SPSS: Statistical Package for the Social Sciences

ROC: Receiver Operating Characteristics

CAD: Coronary Artery Disease

HT: Hypertension

DM: Diabetes Mellitus

CHF: Chronic Heart Failure

PHT: Pulmonary Hypertension

BNP: Brain Natriuretic Peptide

BUN: Blood Urea Nitrogen

AUC: Area Under Curve

NLR: Neutrophil/Lymphocyte Ratio

PLR: Platelet/Lymphocyte Ratio

SIRI: Systemic Inflammation Response Index

SII: Systemic Inflammation Index

AISI: Aggregate Index of Systemic Inflammation

MLR: Monocyte/Lymphocyte Ratio

RBC: Red Blood Cell

MLB: Magnesium Lithospermate B

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The study was approved by the local ethics committee (Ethics Number: B.10.1.TKH.4.34.H.GP.0.01/201). Since the study was a retrospective study, informed consent was not obtained from the participants.

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