



Monocytosis as a Prognostic Factor in Idiopathic Pulmonary Fibrosis

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ABSTRACT

Objective: To determine increased monocyte count (monocytosis) as a cellular biomarker for poor outcomes in idiopathic pulmonary fibrosis. **Methods:** A descriptive cross-sectional study was conducted at Allied Hospital-2, Faisalabad. A total of 305 patients aged 30–70 years with confirmed IPF were enrolled using non-probability consecutive sampling. Monocyte counts were classified into three groups: Group I ($<0.60 \times 10^9/L$), Group II ($0.60-0.95 \times 10^9/L$), and Group III ($\geq 0.95 \times 10^9/L$). The primary outcome was in-hospital all-cause mortality. **Results:** The mean age was 50.6 ± 12.2 years; 53.1% were female. Mortality was significantly higher in Group III (48.6%) compared to Group I (2.9%) and Group II (48.6%) ($p = 0.017$). Stratified analysis revealed consistent trends, with statistically significant associations in non-smokers ($p = 0.048$), non-diabetics ($p = 0.035$), non-MI patients ($p = 0.020$), and hypertensive patients ($p = 0.041$). Elevated monocyte count was a strong predictor of poor outcomes across subgroups. **Conclusion:** Elevated monocyte count, particularly $\geq 0.95 \times 10^9/L$, is associated with increased in-hospital mortality in IPF. Given its accessibility and cost-effectiveness, monocyte count can be used as a prognostic tool for risk stratification and early clinical decision-making.

INTRODUCTION

The term interstitial lung diseases (ILDs) refers to a diverse collection of non-neoplastic pulmonary disorders, marked by differing degrees of fibrosis and inflammation.¹⁻³

Although certain ILDs have well-established causes, many fall into the idiopathic category, lacking a clear etiology yet showing distinct risk factors and pathogenic features. Among these, idiopathic pulmonary fibrosis (IPF) is the most well-defined and is regarded as the prototype for fibrotic lung conditions.⁴ IPF is a severe, progressively worsening interstitial pneumonia with a median survival of 2 to 3 years. The prevalence of this disease varies internationally, but its incidence is on a global upward trend. It causes irreversible damage to lung function.⁵ The clinical course is variable, yet most patients experience a gradual and foreseeable decline. Therefore, early prediction of mortality and stratification of patients at risk of faster progression are critical for effective management.⁶

Readily available biomarkers that can predict disease progression would greatly aid in risk stratification at diagnosis, helping identify patients who might benefit

from early intervention or referral for lung transplantation. Prognosis is equally vital for patients, supporting informed decision-making and clearer understanding of their condition. Among these, the baseline absolute monocyte count in peripheral blood has been linked to outcomes in idiopathic pulmonary fibrosis (IPF).⁷ This count is part of the routine complete blood count (CBC), making it an accessible, inexpensive, and practical biomarker.⁸ Kreuter et al⁹ investigated the prognostic value of monocyte count in patients with idiopathic pulmonary fibrosis (IPF), categorizing patients into three groups based on monocyte levels. They found that all-cause mortality rates were 4.8% for monocyte counts below 0.60, 8.9% for counts between 0.60 and <0.95 , and 21.3% for counts ≥ 0.95 . Given the multifactorial nature of IPF, this study aims to evaluate the prognostic significance of elevated monocyte counts. The findings could contribute to identifying affordable and accessible prognostic markers using routine blood tests.

METHODOLOGY

A descriptive cross-sectional study was carried out at the

Department of Pulmonology, Allied Hospital-2, Faisalabad, From 31 January 2025 to 31 May 2025. The study commenced after obtaining ethical clearance from the Ethical Review Board (ERB) and the College of Physicians and Surgeons Pakistan (CPSP). Using the WHO sample size calculator, a total of 305 patients were enrolled, based on a 95% confidence level, an expected prevalence of 4.8%, and a 2.4% margin of error. Participants were selected through a non-probability consecutive sampling method. Eligible participants were male or female patients aged 30–70 years with a confirmed diagnosis of idiopathic pulmonary fibrosis (IPF). Exclusion criteria included the presence of rheumatoid factor, known connective tissue disorders (e.g., systemic lupus erythematosus or scleroderma), and symptoms suggestive of infection, such as fever and fatigue, within two weeks prior to sampling. Written informed consent was obtained from all eligible participants, and the purpose of the study was explained to them. A detailed medical history and clinical examination were conducted for each patient. The diagnosis of IPF was made by pulmonologists based on a four-point operational definition that included suggestive clinical history and examination, restrictive pattern on pulmonary function tests, characteristic imaging findings on high-resolution computed tomography (HRCT), and exclusion of known causes of usual interstitial pneumonia (UIP) patterns.

For each participant, a 3cc venous blood sample was collected to determine the absolute monocyte count as part of the complete blood count (CBC) panel. Monocytosis was defined as a monocyte count greater than $1.0 \times 10^9/L$. Based on the monocyte levels, patients were categorized into three groups: Group I with monocyte count $<0.60 \times 10^9/L$, Group II with count between 0.60 – $<0.95 \times 10^9/L$, and Group III with count $\geq 0.95 \times 10^9/L$. Each patient was followed until discharge or death, and poor outcome was defined as all-cause mortality during hospitalization. All collected demographic and clinical data were recorded in a predesigned structured proforma. The data were then transferred to Microsoft Excel and analyzed using SPSS version 25. Continuous variables, including age, IPF duration, and monocyte levels, were reported as means with standard deviations. Categorical variables—such as gender, smoking habits, comorbid conditions, and outcomes—were presented in terms of frequency and percentage. Associations between categorical variables and poor outcomes were evaluated using the chi-square test. To address potential confounders, stratification was done for variables like age, gender, smoking, and comorbidities, followed by post-stratification chi-square testing.

RESULTS

Descriptive Statistics and Clinical Characteristics of IPF Patients

The study included a total of 305 patients diagnosed with idiopathic pulmonary fibrosis (IPF). The age distribution revealed that 46.9% ($n = 143$) of the patients were between 30 and 50 years old, while the remaining 53.1% ($n = 162$) were aged between 51 and 70 years. Gender distribution was nearly balanced, with females comprising 53.1% ($n = 162$) and males 46.9% ($n = 143$) of the study

population. In terms of lifestyle factors, smoking was reported in 42.0% ($n = 128$) of the participants, whereas 58.0% ($n = 177$) were non-smokers. Regarding comorbid conditions, 21.3% ($n = 65$) had chronic obstructive pulmonary disease (COPD), and 11.8% ($n = 36$) had a history of myocardial infarction (MI). Hypertension was present in 29.2% ($n = 89$) of patients, and diabetes mellitus was documented in 25.9% ($n = 79$). Monocyte count, assessed as a potential biomarker, was categorized into three groups. Group I (monocyte count $<0.60 \times 10^9/L$) comprised 15.1% ($n = 46$) of patients. The majority, 54.1% ($n = 165$), fell into Group II (0.60 to $<0.95 \times 10^9/L$), while 30.8% ($n = 94$) were classified in Group III ($\geq 0.95 \times 10^9/L$). Clinical outcomes were also recorded. Poor outcome, defined as all-cause mortality during hospitalization, was observed in 11.5% ($n = 35$) of patients, while 88.5% ($n = 270$) survived. With respect to disease duration, 58.0% ($n = 177$) had IPF for 1–30 months, and the remaining 42.0% ($n = 128$) had been diagnosed for 31–60 months.

The analysis of continuous variables among patients diagnosed with idiopathic pulmonary fibrosis (IPF) provided further insight into the clinical characteristics of the study population. The mean age of the patients was 50.59 years with a standard deviation of ± 12.17 , indicating a moderately wide age range centered around the late 40s to early 50s. In terms of disease duration, the mean duration of IPF was 31.81 months with a standard deviation of ± 17.54 months. This suggests that patients had been living with the disease for approximately 2.5 years on average, with a notable variability among individuals. Regarding the primary laboratory biomarker of interest, the mean absolute monocyte count was $0.84 \times 10^9/L$ with a standard deviation of $\pm 0.23 \times 10^9/L$. This value is close to the threshold separating Group II and Group III in the monocyte group classification and reflects a significant range of monocyte levels within the study population. (Table 1)

Table 2 illustrates the relationship between absolute monocyte count and in-hospital mortality in patients diagnosed with idiopathic pulmonary fibrosis (IPF). The participants were divided into three categories according to their monocyte levels: Group I (less than $0.60 \times 10^9/L$), Group II (ranging from 0.60 to less than $0.95 \times 10^9/L$), and Group III (equal to or greater than $0.95 \times 10^9/L$).

Among those who died during hospitalization (poor outcome), only 2.9% were from Group I, whereas 48.6% each belonged to Group II and Group III. In contrast, among survivors, 16.7% were in Group I, 54.8% in Group II, and 28.5% in Group III. These findings show that a higher proportion of deaths occurred in patients with elevated monocyte counts, particularly those in Group III. The association was statistically significant, with a p-value of 0.017 as determined by the Chi-square test. This supports the conclusion that elevated monocyte count is significantly associated with poor prognosis in IPF, reinforcing its potential as a simple and effective biomarker for mortality risk stratification in clinical practice.

Table 3 provides a stratified analysis evaluating the relationship between monocyte count and in-hospital mortality among patients with idiopathic pulmonary fibrosis (IPF), taking into account various potential

confounders. Across nearly all subgroups—age, gender, smoking status, presence of comorbidities (COPD, myocardial infarction, hypertension, and diabetes mellitus), and duration of disease—the data showed a consistent trend: mortality was higher in patients with elevated monocyte counts, particularly those in Group III ($\geq 0.95 \times 10^9/L$).

Among non-smokers, the association between higher monocyte count and mortality reached statistical significance ($p = 0.048$), whereas it did not in smokers, although the trend remained similar. A significant relationship was also observed in non-diabetic patients ($p = 0.035$), non-MI patients ($p = 0.020$), and hypertensive patients ($p = 0.041$), suggesting that the prognostic impact of monocytosis is more prominent in patients without certain systemic comorbidities.

In contrast, although age, gender, COPD status, and duration of IPF did not show statistically significant associations in isolation, they demonstrated the same directional trend—mortality increased with rising monocyte counts. This pattern supports the hypothesis that monocytosis is a meaningful prognostic marker, even if subgroup sample sizes may have limited statistical power in some cases.

In summary, the findings from this stratified analysis reinforce that elevated monocyte count is consistently associated with poor outcomes in IPF, and the effect remains notable across different patient characteristics. These results suggest that monocyte count could serve as an accessible and cost-effective tool for risk stratification in clinical practice.

Table 1

Descriptive Statistics and Clinical Data of the Patients with Idiopathic Pulmonary Fibrosis

Variable	Category	Frequency (%)
Age (Years)	30–50	143 (46.9%)
	51–70	162 (53.1%)
Gender	Male	143 (46.9%)
	Female	162 (53.1%)
Smoking Status	Yes	128 (42.0%)
	No	177 (58.0%)
COPD	Yes	65 (21.3%)
	No	240 (78.7%)
Myocardial Infarction	Yes	36 (11.8%)
	No	269 (88.2%)
Hypertension	Yes	89 (29.2%)
	No	216 (70.8%)
Diabetes Mellitus	Yes	79 (25.9%)
	No	226 (74.1%)
Monocyte Group	Group I (<0.60)	46 (15.1%)
	Group II (0.60–<0.95)	165 (54.1%)
	Group III (≥ 0.95)	94 (30.8%)
Poor Outcome (Mortality)	Yes	35 (11.5%)
	No	270 (88.5%)
Duration of IPF (months)	1–30	177 (58.0%)
	31–60	128 (42.0%)

Table 2

Monocytosis as a Prognostic Factor in Idiopathic Pulmonary Fibrosis

Poor Outcome (Mortality)	Group I (<0.60)	Group II (0.60–<0.95)	Group III (≥ 0.95)	P value ^a
Yes	1 (2.9%)	17 (48.6%)	17 (48.6%)	0.017
No	45 (16.7%)	148 (54.8%)	77 (28.5%)	

^aChi square test

Table 3

Monocytosis as a Prognostic Factor in Idiopathic Pulmonary Fibrosis According to Potential Confounders

Variables	Group	Group I (<0.60)	Group II (0.60–<0.95)	Group III (≥ 0.95)	p-value ^a
Age (Years)	30–50	0 (0.0%)	8 (53.3%)	7 (46.7%)	0.178
	51–70	22 (17.2%)	65 (50.8%)	41 (32.0%)	
		1 (5.0%)	9 (45.0%)	10 (50.0%)	
Gender	Male	23 (16.2%)	83 (58.5%)	36 (25.4%)	0.055
	Female	0 (0.0%)	9 (52.9%)	8 (47.1%)	
		24 (19.0%)	63 (50.0%)	39 (31.0%)	
Smoking Status	Yes	1 (5.6%)	8 (44.4%)	9 (50.0%)	0.100
	No	21 (14.6%)	85 (59.0%)	38 (26.4%)	
		1 (7.1%)	7 (50.0%)	6 (42.9%)	
COPD	Yes	18 (15.8%)	68 (59.6%)	28 (24.6%)	0.307
	No	0 (0.0%)	10 (47.6%)	11 (52.4%)	
		27 (17.3%)	80 (51.3%)	49 (31.4%)	
Myocardial Infarction	Yes	0 (0.0%)	5 (45.5%)	6 (54.5%)	0.230
	No	7 (13.0%)	27 (50.0%)	20 (37.0%)	
		1 (4.2%)	12 (50.0%)	11 (45.8%)	
Hypertension	Yes	38 (17.6%)	121 (56.0%)	57 (26.4%)	0.067
	No	0 (0.0%)	3 (75.0%)	1 (25.0%)	
		6 (18.8%)	19 (59.4%)	7 (21.9%)	
Diabetes Mellitus	Yes	1 (3.2%)	14 (45.2%)	16 (51.6%)	0.635
	No	39 (16.4%)	129 (54.2%)	70 (29.4%)	
		0 (0.0%)	3 (75.0%)	1 (25.0%)	
Duration of IPF (months)	1–30	6 (18.8%)	19 (59.4%)	7 (21.9%)	0.635
	31–60	1 (3.2%)	14 (45.2%)	16 (51.6%)	
		39 (16.4%)	129 (54.2%)	70 (29.4%)	
Hypertension	Yes	0 (0.0%)	4 (30.8%)	9 (69.2%)	0.041
	No	12 (15.8%)	38 (50.0%)	26 (34.2%)	
		1 (4.5%)	13 (59.1%)	8 (36.4%)	
Diabetes Mellitus	Yes	33 (17.0%)	110 (56.7%)	51 (26.3%)	0.250
	No	0 (0.0%)	2 (33.3%)	4 (66.7%)	
		16 (21.9%)	28 (38.4%)	29 (39.7%)	
Duration of IPF (months)	1–30	1 (3.4%)	15 (51.7%)	13 (44.8%)	0.214
	31–60	29 (14.7%)	120 (60.9%)	48 (24.4%)	
		1 (6.7%)	6 (40.0%)	8 (53.3%)	
Duration of IPF (months)	1–30	24 (14.8%)	90 (55.6%)	48 (29.6%)	0.158
	31–60	0 (0.0%)	11 (55.0%)	9 (45.0%)	
		21 (19.4%)	58 (53.7%)	29 (26.9%)	

^aChi square test

DISCUSSION

The current study demonstrated a significant association between elevated peripheral blood monocyte count and in-hospital mortality among patients with idiopathic pulmonary fibrosis (IPF). This finding aligns with a growing body of literature that highlights monocyte count as a robust prognostic marker in IPF. The observed mortality rate of 48.6% in patients with monocyte counts $\geq 0.95 \times 10^9/L$ underscores the clinical relevance of this parameter. This study further reinforces the accessibility and utility of monocyte count as a simple, cost-effective tool for early risk stratification in resource-limited settings.

Our study population had a mean age of 50.6 years, and 53.1% were female. These demographics differ from several previous cohorts, such as those reported by Kreuter et al. (2021),⁹ Teoh et al. (2020),¹⁰ and Min et al. (2023),¹¹ where the mean age was considerably higher and male predominance was observed. Such differences may reflect regional variations in disease presentation, healthcare access, or referral patterns, and could influence disease progression and outcomes. Notably, even in our relatively younger and more gender-balanced cohort, elevated monocyte count retained a strong association with poor prognosis, indicating the reliability of this biomarker across different populations.

Our findings are consistent with multiple supportive

studies. Kreuter et al (2021)⁹ conducted a pooled analysis of over 2,000 IPF patients from randomized controlled trials and found that higher monocyte counts ($\geq 0.95 \times 10^9/L$) were independently associated with increased risk of mortality, hospitalization, and disease progression. Min et al. (2023)¹¹ reported similar findings in a meta-analysis, with significantly elevated hazard ratios for mortality and disease progression associated with monocyte counts exceeding 0.6 or $0.9 \times 10^9/L$. Teoh et al. (2020)¹⁰ also confirmed that higher monocyte counts predicted poorer survival even after adjusting for key clinical variables. Scott et al. (2021)¹² and Karampitsakos et al. (2021)⁸ further validated these observations across different settings and patient cohorts. Hirata et al (2024)¹³ improved prognostic predictions by integrating monocyte ratio with ILD-GAP score. Zhang et al (2024)¹⁵ supported the mechanistic relevance of monocytes using single-cell analysis. Zhou et al (2023)¹⁶ reinforced these findings through monocyte-related gene signatures. Collectively, these studies reinforce the predictive value of monocytosis in fibrotic lung diseases.

Biologically, these associations are plausible, as monocytes contribute to the pathogenesis of IPF by differentiating into profibrotic macrophages, promoting aberrant wound healing, and releasing cytokines that exacerbate tissue fibrosis. Fernandez and Kass (2021)¹⁷ and Shenderov et al. (2021)¹⁸ discussed the immunological mechanisms underlying these processes, highlighting monocyte-driven immune dysregulation as a key component in IPF progression.

Contrary to these findings, some studies such as Kim et al. (2023)²³ in idiopathic nonspecific interstitial pneumonia (iNSIP) did not identify a statistically significant independent prognostic value for monocyte count in adjusted analyses. These discrepancies could be attributed

to smaller sample sizes, population heterogeneity, differences in disease subtype, and varied endpoints such as short-term vs. long-term outcomes. Nonetheless, the overall evidence base, especially in IPF-specific cohorts, strongly supports the role of elevated monocyte count as a prognostic biomarker.

The strengths of our study include a relatively large sample size, uniform diagnostic criteria for IPF, and stratified analyses across key clinical subgroups including smoking status, diabetes, myocardial infarction, and hypertension. This allowed us to explore the interaction between monocyte count and comorbidities in depth. However, limitations include the single-center design which may limit external validity, and the exclusive use of in-hospital mortality as the endpoint, which precludes long-term outcome analysis. Moreover, we did not perform functional analyses of monocyte subsets, which could offer mechanistic insights into their role in IPF. From a clinical perspective, integrating monocyte count into the routine assessment of IPF patients could enable timely identification of high-risk individuals who may benefit from aggressive monitoring, early antifibrotic therapy, or prioritization for transplant evaluation. Given that monocyte count is already included in standard complete blood count panels, its incorporation into prognostic models is both feasible and cost-effective.

CONCLUSION

Our study contributes to the growing body of evidence supporting elevated monocyte count, particularly $\geq 0.95 \times 10^9/L$, as a reliable and accessible prognostic biomarker in IPF. Future multicenter and prospective studies should aim to validate these findings and explore the integration of monocyte-based risk models into routine clinical workflows.

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