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Retrospective analysis of patients hospitalized with acute exacerbation of idiopathic pulmonary fibrosis

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Abstract:

BACKGROUND AND AIM: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease of unknown etiology. Acute exacerbation of IPF (AE-IPF) can cause sudden deterioration in the prognosis of the disease and is responsible for a significant proportion of deaths due to IPF. The aim of our study is to examine the medical histories, symptoms, clinical findings, laboratory tests, and radiological images of cases hospitalized in our clinic due to AE-IPF, and to determine mortality rates during and after the AE.

METHODS: We retrospectively examined the records of patients hospitalized with a diagnosis of AE-IPF. We recorded their demographic data, comorbidities, physical examination and laboratory findings, radiological findings, spirometry results, treatment status, intensive care needs, and mortality-related data. Statistical analyses were performed using Chi-square and Mann-Whitney U tests.

RESULTS: Out of 28 cases, 19 (67.9%) were male with a mean age of 67.1±11.4 years. The most common comorbidities were hypertension (39.3%), chronic obstructive pulmonary disease (35.7%), diabetes (32.1%), chronic renal failure (14.3%), and atrial fibrillation (14.3%). In respiratory function tests, mean forced vital capacity and carbon monoxide diffusion capacity was 65±17.1% and 47 47±14.2%, respectively. All patients had newly developed ground-glass opacity and/or consolidation areas in their chest computed tomography images. It was observed that the mean duration of steroid use initiated due to an AE was 7.1 days. Of the cases, 23 (82.1%) were discharged home, while the remaining 5 (17.9%) were transferred to the intensive care unit, where, unfortunately, all of them lost their lives. Among the discharged patients, 6 succumbed within three months. Consequently, the mortality rate within the hospital stay and the subsequent three months for patients hospitalized with AE-IPF was determined to be 39.3%. Notably, the mortality rate was significantly higher in patients with chronic renal failure compared to those without (p=0.016).

CONCLUSIONS: It was observed that the in-hospital and early post-discharge mortality rate for patients hospitalized with AE-IPF was approximately 40%. This finding underscores the serious negative impact of AEs on the prognosis of the disease.

Keywords:

Idiopathic pulmonary fibrosis, lung disease, mortality

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease characterized by fibrosis of unknown etiology, typically occurring in older adults. It is categorized under idiopathic interstitial pneumonias and is the most common disease in this group. The incidence of IPF increases with age, and it is often associated with a history of smoking.[1] According to data from our country, its incidence is estimated at 5 per 100,000.[2] The course of IPF varies; however, the mean survival is between 2.5 to 5 years. Common manifestations include dyspnea on exertion, cough, bibasilar inspiratory crackles, and clubbing. Factors such as advanced age, a history of smoking, low body mass index, the presence of pulmonary hypertension, and extensive radiological involvement are linked to a poorer prognosis.[3]

In patients diagnosed with IPF, an acute deterioration in dyspnea clinically, along with the appearance of new bilateral ground-glass densities and/or consolidation on top of the underlying usual interstitial pneumonia (UIP) pattern radiologically, is defined as an acute exacerbation (AE) of IPF. It is crucial to demonstrate that this condition, emerging clinically and radiologically, is not attributable to heart failure or fluid overload. Typically, this period should be less than one month to qualify as AE-IPF.[4] The incidence of AE-IPF varies in studies due to inadequate clinical data, uncertain AE-IPF cases, disease severity, and ambiguity in diagnostic criteria. However, it has been estimated to be between 10–20%,[4] with some studies reporting rates as high as 40%.[5] AE-IPF can lead to sudden deterioration in prognosis and is a significant cause of mortality and morbidity. Studies indicate that the early mortality rate is nearly 50%.[6]

Acute exacerbation of IPF is more common in patients with advanced functional disease. A low forced vital capacity (FVC) level has been shown to be a significant risk factor for AE.[7,8] Additional risk factors include a recent loss in FVC,[9,10] low levels in the carbon monoxide diffusion test (DLCO),[7] decreased distance in the six-minute walk test,[7] low partial oxygen pressure,[7,10] pulmonary hypertension,[11] and increased dyspnea.[8] Some studies have linked young age,[12] increased body mass index,[10] and accompanying coronary artery disease[7] with the development of exacerbations. However, data on the risk of AE associated with smoking and the presence of emphysema are inconsistent.[13,14] Furthermore, having had a previous AE is linked with an increased risk of subsequent exacerbations.[8]

The etiology of AE-IPF remains unknown. However, it is believed that factors such as respiratory viral infections, microaspiration due to gastroesophageal reflux, immunosuppressive treatments, surgical biopsy, and interventional procedures can trigger these exacerbations.[4]

The most common radiological finding in AEs is new ground-glass opacities and/or consolidations on computed tomography, added to the existing pattern.[15] Clinically, the most prominent symptoms in these patients are dyspnea and hypoxemia. Cough, phlegm, and fever can be seen in many patients, often without an underlying infection being detected. Most patients may develop respiratory failure and require intensive care.[16]

There is no strongly evidence-based guideline recommendation for the treatment of AE-IPF. Studies suggest that early initiation of corticosteroids and supportive treatment positively influence prognosis.[1–18] Acute exacerbations of IPF can cause sudden and rapid deterioration in respiratory functions and are associated with high mortality and morbidity. In our study, we aimed to examine the early mortality rates during and after the AE, factors associated with mortality, the medical history, symptoms, clinical findings, laboratory tests, and radiological presentations of patients admitted to our clinic with AE-IPF.

Materials and Methods

Our study, designed as a retrospective observational cohort, included 28 cases who presented to our clinic with a diagnosis of AE-IPF between March 2018 and December 2021. We recorded patient demographic data, comorbid diseases, respiratory complaints, physical examination and laboratory findings, spirometry results, radiological imaging, treatment regimens, need for intensive care, and mortality-related data. Patients whose partial oxygen pressure was below 55 mmHg during hospitalization, as indicated by arterial blood gas results, were classified as hypoxemic. Thoracic computed tomography (CT) was used as the standard radiological evaluation tool. Radiological involvement was defined as the presence of newly added ground-glass densities or consolidation areas over the existing radiological pattern, and was categorized into three levels: less than 50%, more than 50%, and nearly complete. All subjects received a standard steroid dose of 1 mg/kg/day methylprednisolone. The same antibiotic protocol, consisting of ceftriaxone disodium 1 mg bid and clarithromycin 500 mg bid, was administered to all pa-

tients. Mortality occurring within the first three months from the onset of AE was classified as early mortality. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 19.0 (IBM Corporation, Armonk, NY USA). Chi-square, Fisher's exact test, and Mann-Whitney U tests were utilized. The study (No: 2023/514/254/21, Date: 19 July 2023) received approval from the ethics committee. The study was conducted in accordance with the Declaration of Helsinki.

Results

Demographic, clinical, and radiological features of patients admitted with AE-IPF is seen in Table 1. Out of the cases included in our study, 9 (32.1%) were female and 19 (67.9%) were male, with a mean age of 67.1±11.4 years. Twenty-four (85.7%) patients had comorbidities. The most common were hypertension (39.3%), chronic obstructive pulmonary disease (35.7%), diabetes (32.1%), chronic renal failure (14.3%), and atrial fibrillation (14.3%). The mean duration from the diagnosis of IPF to the onset of the AE was 17.1 months (min-max: 1–60). All patients experienced dyspnea (100%). Other common symptoms included sputum production (46.4%) and dry cough (35.7%). On physical examination, velcro rales were heard in 26 (92.9%) patients, and clubbing was present in 9 (32.1%) patients (Table 2). All patients were found to be hypoxemic according to arterial blood gas results at the time of hospitalization. However, only 15 (53.9%) were receiving long-term oxygen therapy at home. Exactly half of the cases were receiving antifibrotic drug treatment, with 9 patients on pirfenidone and 5 on nintedanib. Respiratory function tests can be performed in 15 patients. Mean FVC was 65.4±17.1%, mean FEV_1 (forced expiratory volume in one second) was 69.0±15.6%, and mean DLCO was 47.7±14.2%. The mean C-reactive protein (CRP) at the time of hospitalization was 61.3± 44.7 mg/dL, and white blood cells (WBC) count was 11.0±3.3 $10^3/\mu L$ (Table 2). Thoracic CT scans of all patients revealed new ground-glass and/or consolidation areas added to the existing interstitial pattern. When proportioning the ground-glass areas to the total lung volume, involvement was less than 50% in 15 cases and more than 50% in 11 cases, with two cases showing almost complete involvement. Oxygen support therapy was administered using a nasal cannula in 19 cases, a reservoir mask in 7 cases, and a high-flow oxygen circuit in 2 cases. The mean hospitalization period was 10.3±5.1 days, and the mean duration of steroid use was 7.1±2.0 days. Out of all cases, 23 (82.1%) were discharged home, with 20 of these continuing to need long-term oxygen therapy. The remaining 5 (17.9%) cases were transferred to the intensive care unit due to worsening respiratory failure. Unfortunately, all of these 5 cases resulted in fatalities in the intensive care unit. Upon reviewing the outcomes of the discharged patients, it was found that 6 of them lost their lives within three months. Consequently, the mortality rate of patients admitted with AE-IPF was 39.3% during hospitalization and within the subsequent three months [Fig. 1]. In terms of factors affecting mortality, a statistical comparison revealed that the mortality rate was significantly higher in patients with chronic renal failure compared to those without ($p=0.016$). However, when assessing other parameters, such as laboratory tests, spirometric measurements, radiological involvement rates, and symptoms, no demonstrable effect on mortality could be observed.

Discussion

In our study, the mortality rate for patients admitted to our clinic with AE-IPF during hospitalization and the early period was found to be 39.3%. When analyzing factors affecting mortality, it was noted that patients with chronic renal failure had a significantly higher mortality rate than others.

When examining literature data on mortality rates in AE-IPF, a study by Song et al.,[19] which retrospectively evaluated 461 IPF patients, detected AE-IPF in 96 (20.8%) of them. Their analysis of mortality data of these patients revealed in-hospital and early period mortality rates of 50% and 60%, respectively. In another study, 598 IPF patients were examined, with AEs detected in 58 (9.8%) patients. The mortality rates during hospitalization and within three months were found to be 56.9% and 63%, respectively.[20] A study conducted in Japan investigating the death rates of IPF patients found a 40% mortality rate due to AE- IPF.[5] In our study, the early period mortality rate due to AE-IPF was found to be 39.3%. Although literature data variety, high mortality rates due to exacerbation are observed in patients with IPF.

In IPF, AEs and comorbidities play a significant role in the disease's progression. Many studies have shown that comorbidities are more prevalent in IPF patients compared to the general population.[21,22] While some conditions, like pulmonary hypertension, develop as a result

Table 1: Demographic, clinical, and radiological features of patients admitted with AE-IPF

	n	%
Age (mean±SD) years	67.1±11.4	
Gender (male)	19	67.8
Comorbidities		
Hypertension	11	39.3
Chronic obstructive pulmonary disease	10	35.7
Diabetes	9	32.1
Chronic renal failure	4	14.3
Atrial fibrillation	4	14.3
Time from IPF diagnosis to AE-IPF	mean 17.1 months	
Symptoms		
Dyspnea	28	100
Cough	10	35.7
Sputum	13	46.4
Fever	13	46.4
Physical examination		
Velcro rales	26	92.9
Clubbing	9	32.1
Radiological involvement (intensity of new ground glass areas added on the current radiological pattern)		
Less than 50% involvement	15	53.5
More than 50% involvement	11	39.2
Near-complete involvement	2	7.1
Pulmonary function tests		
FVC (%) mean±SD	65±17.1	
FEV_1 (%) mean±SD	69±15.6	
DLCO (%) mean±SD	47±14.2	
Laboratory data		
CRP (mg/dL) mean±SD	61.3±44.7	
WBC (mg/dL) mean±SD	11.0±3.3	
Time from IPF diagnosis to attack (month)	min: 1; max: 60 median 12	
Number of patients given steroid treatment	28	100
Duration of steroid use days (mean±SD)	7.1±2.0	
Number of patients given oxygen supportive treatment	28	100
Duration of hospitalization days (mean±SD)	10.3±5.1	

AE-IPF: Acute exacerbation of idiopathic pulmonary fibrosis, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second, DLCO: Diffusion capacity for carbon monoxide, CRP: C-reactive protein, WBC: White blood cells

of IPF, others may share common risk factors (e.g., combined emphysema fibrosis due to smoking, lung cancer, etc.). Current guidelines for IPF diagnosis and treatment acknowledge that patients may have comorbidities such as pulmonary hypertension, gastroesophageal reflux, obstructive sleep apnea, and emphysema, but the effects of these diseases on the progression of IPF are not yet fully understood.[1] Mortality in IPF is often attributed to the progression of the disease or to pneumonias, but it can also occur due to comorbidities. Studies have highlighted the impact of cardiovascular disease and lung cancer on mortality in IPF patients.[22] Interestingly, potential comorbidities such as chronic renal failure and liver diseases have not been examined in studies. Contrary to existing literature, our study found that the mortality rate of patients with chronic renal failure was

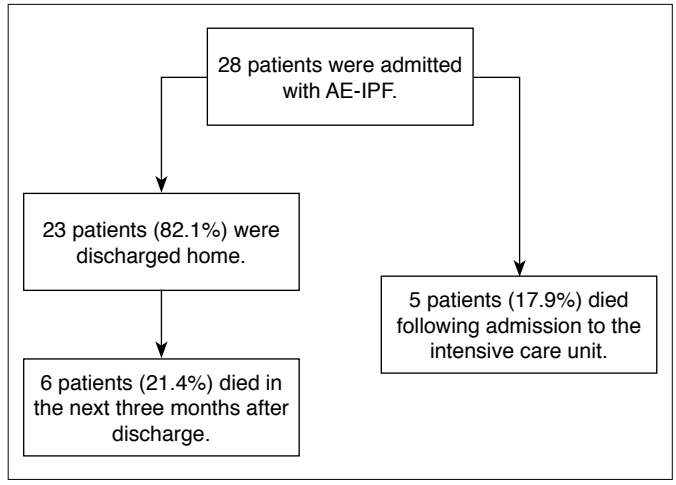

Figure 1: The early mortality rate for patients admitted with AE-IPF is 39.3%
AE-IPF: Acute exacerbation of Idiopathic pulmonary fibrosis

Table 2: Parameters related to mortality

	Alive patients	Exitus	p
Age (median)	67.8	66.0	0.677
Gender			
Male	11	8	0.657
Female	6	3	
Comorbidities (%)			
Diabetes	35.3	27.3	0.657
Chronic Renal Failure	0	36.4	**0.016**
Chronic obstructive pulmonary disease	41.2	27.3	0.453
Hypertension	47.1	27.3	0.295
Symptoms (%)			
Dyspnea	100	100	1.00
Cough	35.3	36.4	0.954
Sputum	47.1	45.5	0.934
Fever	35.3	36.4	0.954
Physical examination (%)			
Clubbing	29.4	36.4	0.700
Velcro rales	88.2	100	0.505
Laboratory data			
CRP (mg/dl)	67.2±48.0	52.3±39.7	0.487
Procalcitonin (µg/l)	0.14±0.17	0.52±1.46	0.461
WBC ($\times10^3$/µL)	10.4±3.0	11.8±3.6	0.353
Platelet ($\times10^3$/µL)	287.0±70.5	273±132.2	0.329
Radiological involvement >50% (%)	41.2	54.5	0.488
Pulmonary function test			
FVC%	67.7±20.1	62.0±12.0	0.689
FEV_1%	68.8±17.4	69.1±13.9	0.864
FEV_1/FVC	82.7±8.8	87.8±7.3	0.328
DLCO%	54.1±11.4	39.3±14.0	**0.059**
Patients given oxygen supportive treatment (%)	47.1	63.6	0.390
Antifibrotic drug usage (%)	47.1	54.5	0.699

significantly higher than others. The evaluation of these parameters in future studies will be crucial in understanding their impact on mortality.

The most classic radiological finding in AE-IPF is the appearance of newly added bilateral ground-glass densities and/or consolidation on top of a UIP pattern.[4] This appearance can be diffuse, multifocal, or peripheral. Studies have indicated that patients with diffuse radiological involvement have a worse prognosis than those with peripheral or multifocal involvement.[15,23] Moreover, mortality rates have been found to be significantly higher in patients with diffuse involvement compared to those with other types of involvement.[15,24] A recent study reported that asymmetric radiological involvement in AE-IPF is associated with a better prognosis and survival compared to symmetric involvement.[25] However, in our study, no significant correlation was found between the extent of radiological involvement and mortality.

AE-IPF is more frequent in patients with clinically and functionally advanced disease. Numerous studies have shown that having a low FVC in respiratory function test is a risk factor for AE-IPF.[7,19] In a study by Song et al.,[19] a low FVC value was associated with decreased survival. Other studies indicate that 5–10% decreases in FVC can predict mortality. Decreases in DLCO are also associated with increased mortality.[26,27] In our study, mean values of respiratory parameters were not different among survivors and non survivors. This can be due to the limited number of patients who were able to perform respiratory function tests.

Several potential prognostic factors have been identified in AE-IPF, with laboratory data being one of them. Studies have found that patients who succumbed to an AE had higher CRP levels and neutrophil percentages, and lower lymphocyte percentages. When examining the effect of these laboratory data on mortality, only the rela-

tionship of CRP level with mortality was demonstrated.[19] Another study investigating the prognostic factors and outcomes of AE-IPF found a relationship between high lactate dehydrogenase (LDH) levels and in-hospital mortality, but no relationship was shown between CRP level and mortality.[28] In a study conducted by Akira et al.,[15] it was shown that CRP, LDH, and WBC levels were higher during the AE when comparing the laboratory data of patients before and during the AE, and high LDH levels were associated with mortality. In our study, similar to the literature data, high CRP, LDH, and WBC levels were found during the AE. However, the relationship of these data with mortality could not be demonstrated.

In IPF, low oxygen levels are a common and expected finding, both during the course of the disease and during AEs. Numerous studies have indicated that low partial oxygen pressure is a risk factor for developing AEs.[4,7,10,12] In a study by Song et al.,[19] the ratio of partial arterial oxygen pressure to inspiratory oxygen fraction was found to be lower in patients who succumbed to AE-IPF compared to others. However, no significant relationship was established between mortality rates and low oxygen levels.[12] In our study, all patients admitted with a diagnosis of an AE-IPF were found to be hypoxemic in room air. Similar to literature data, no correlation between low oxygen levels and mortality could be demonstrated. Upon examining the mortality rates of our 15 patients who were on long-term oxygen therapy at home during the stable period before the AE, no significant difference was observed compared to others.

There are two antifibrotic drugs, pirfenidone and nintedanib, currently recommended for the treatment of IPF. These treatment options aim to prevent clinical and functional deterioration rather than cure the disease. Antifibrotic treatments are expected to help prevent the development of AEs, and studies have been conducted on this subject. A review of the literature data, particularly the "To Improve Pulmonary Fibrosis With BIBF 1120" (TOMORROW) study, a phase II study research, shows that nintedanib reduces the decrease in FVC and concurrently prevents the development of AEs.[29] These findings were also supported by another study.[30] Studies have also shown that pirfenidone reduces losses in respiratory function and the development of AEs.[31] However, in a Phase III study investigating the efficacy of pirfenidone, no difference was detected in either the number of AEs or the time to the onset of the AE in patients receiving pirfenidone compared to those receiving a placebo.[32,33] In terms of preventing the development of AE-IPF, the literature suggests that nintedanib may be more effective.[29,30] In our study, 14 patients (50%, 9 on pirfenidone, 5 on nindetanib) were receiving antifinrotic treatment when they were admitted with AE-IPF. There was no significant difference in mortality rates between patients receiving antifibrotic treatment and those not receiving it. Additional studies are needed to determine the impact of antifibrotic treatments on the incidence of AEs and mortality during AE.

In treating AE-IPF, there is no treatment method with a high level of evidence and proven effectiveness. Guidelines regarding the management of IPF recommend steroid treatment during the AE, albeit based on a low level of evidence.[1] There are also studies where cytotoxic agents have been used in conjunction with steroid therapy, due to increased cellular activity, activated T cells, and neutrophils.[34,35] Hemoperfusion with polymyxin B is another potential treatment method being explored.[36] Although there is not enough evidence from controlled studies supporting steroid use, it is considered the most commonly used medication, along with supportive treatment. In steroid treatment, after administering a high-dose (pulse), oral treatment can be continued with decreasing doses, or a low dose can be initiated in those with mild disease. There are also studies indicating that there is no decrease in early and late mortality rates in patients receiving steroid therapy alone.[37] In our study, all patients admitted with AE-IPF received low-dose steroid treatment (1 mg/kg), with the mean duration of steroid administration being 7.1 days. Although not administering high dose (pulse) steroids may be critical according to some authors, our data shows that our mortality rate is not higher than what is reported in the literature.

Limitations and strengths of the study

The limitations of our study include being a single-centered, retrospective study with a limited sample size. However, the administration of standard doses of systemic steroids and antibiotics to all patients may be considered a strength of the study.

Conclusion

This study revealed that in hospital and early mortality is high in hospitalized patients with AE-IPF. This finding supports the serious negative impact of AE on IPF prognosis. The significant impact of chronic renal failure on mortality need to be studied in further studies.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (No: 2023/514/254/21, Date: 19/07/2023).

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