Original Article

Acute exacerbation in interstitial lung disease

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Abstract:

BACKGROUND: Information regarding acute exacerbation (AE) in patients with interstitial lung disease (ILD) is limited.

OBJECTIVES: The objective of the study was to elucidate the clinical features and outcome of AE among ILD patients.

METHODS: We retrospectively analyzed the data of 667 consecutive ILD (nonidiopathic pulmonary fibrosis [IPF] ILD, *n* = 463; IPF, *n* = 204) patients. ILD patients meeting the 2016 definition of AE-IPF were identified. Information analyzed included pulmonary function tests, 6-min walk tests, and right heart catheterization data, among others. Cox regression models were used to identify independent predictors of survival.

RESULTS: AE was identified in non-IPF ILD (*n* = 113) and IPF (*n* = 74). Compared with AE-IPF patients, non-IPF ILD patients with AE were of younger age, predominantly women, and primarily nonsmokers (all, $P < 0.0001$). The estimated survival probabilities at 1, 3, and 5 years were 88%, 75%, and 70%, respectively, in the ILD without AE group; 80%, 57%, and 50%, respectively, in the non-IPF ILD with AE group; and 53%, 38%, and 28%, respectively, in the AE-IPF group ($P < 0.0001$ by log-rank analysis). Age, body mass index, IPF diagnosis, AE, diffusion capacity of the lung for carbon monoxide <35% predicted, 6-min walk distance <300 meters, and cardiac index were independent predictors of survival in the ILD cohort.

CONCLUSIONS: Non-IPF ILD patients with AE have distinct clinical features compared to AE-IPF patients. Importantly, AE is one of many independent risk factors associated with worsened outcomes regardless of the underlying ILD type.

Keywords:

6-min walk test, acute exacerbation, idiopathic pulmonary fibrosis, interstitial lung disease, survival

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Interstitial lung disease (ILD) comprises a large group of disorders characterized by repetitive injury to the lung parenchyma with variable degrees of inflammation and scarring depending on the underlying ILD type. Idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD)-associated ILD, chronic hypersensitivity pneumonitis, and sarcoidosis are the most common ILD subtypes seen in ILD clinics. The natural course of fibrotic ILD involves progressive worsening of underlying lung fibrosis that occurs over many years; however, a subset of ILD patients may develop acute exacerbation (AE), defined as acute deterioration of respiratory symptoms of <1 month in duration with new ground-glass opacity and/or consolidation based on computed tomography and in the absence of heart failure or fluid overload.[1]

Although the term AE was originally described in IPF patients, accumulating evidence has shown that AE can also occur in other forms of fibrotic ILDs such as idiopathic nonspecific interstitial pneumonia (NSIP), CTD-ILD, chronic hypersensitivity pneumonitis, and sarcoidosis.[2-7] As such, it is now generally accepted that the definition of AE in IPF

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can also be applied in other types of fibrotic ILDs.[8] Although some studies[9-12] have shown that IPF with AE is associated with poor survival compared with other ILDs, other studies[13-16] found no significant difference in overall survival between AE in IPF and AE in fibrotic ILDs. Nonetheless, when AE occurs, regardless of the underlying ILD diagnosis, it creates significant challenges for patients, families, clinicians, and the health-care system. As such, identifying the factors that predict the risk of AE would help clinicians understand the pathobiology of AE to provide the best preventive management strategy that can be offered, which would ultimately have a positive impact on ILD patient survival.

The aim of the present study was to determine the clinical characteristics, risk factors, and outcome of AE in a large cohort of ILD patients with variable degrees of parenchymal inflammation and fibrosis.

Methods

The present study is a retrospective analysis of data acquired from a prospective database collected at the ILD and pulmonary hypertension (PH) center at King Saud University Medical City. Consecutive patients diagnosed with various ILD subtypes between March 2008 and December 2019 were included. This study was approved by the Institutional Research Board at the College of Medicine, King Saud University, Riyadh, Saudi Arabia (approval number E-20-4608). The need to obtain written informed consent was waived because of the retrospective nature of the current study.

Demographic characteristics and physiological studies of the ILD cohort from the first ILD clinic visit were retrieved from our database. Pulmonary function testing (PFT) variables include forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio, and diffusion capacity of the lung for carbon monoxide (DLco).[17-19] In addition, 6-min walk test (6MWT) parameters, including initial and final oxygen saturation by pulse oximetry (SpO_2) and 6-min walk distance (6MWD), were collected.[20]

During the follow-up period, all ILD patients who met the proposed diagnostic criteria for AE of IPF, whether idiopathic in origin or triggered (infection, drug toxicity, or postoperative, among others), as previously described, were included.[1] ILD patients hospitalized with symptoms resembling AE but found to be solely secondary to heart failure were excluded ($n = 11$).

When PH was suspected, right heart catheterization (RHC) was performed. RHC parameters were obtained from all ILD patients in stable condition. Patients were categorized as without PH (defined as the mean pulmonary artery pressure [mPAP] <21 mmHg, or mPAP 21–24 mmHg with pulmonary vascular resistance (PVR) <3 Wood units [WU]), with PH (defined as mPAP 21–24 mmHg with PVR >3 WU, or mPAP 25–34 mmHg) and with severe PH (defined as mPAP >35 mmHg or mPAP >25 mmHg with low cardiac index [CI] [<2.0 L/min/m^2]) as previously described.[21] Patients with postcapillary PH (defined as mPAP >20 mmHg with pulmonary capillary wedge pressure [PCWP] >15 mmHg and PVR <3 WU as previously described[22]) were included in the current study.

A multidisciplinary approach involving various specialties, including pulmonology, rheumatology, radiology, and pathology, was implemented for all ILD patients after a thorough analysis of clinical, radiological, histopathological (when available), and serological test results according to established guidelines,[23-33] and a management plan was adopted after the multidisciplinary consensus recommendation.

Statistical analysis

Data are presented as the means ± standard deviations or numbers (percentages), where appropriate. Between-group differences were compared using *t*-test, the Chi-square test, or Fisher's exact test, as appropriate. Survival was compared using Kaplan–Meier estimates and log-rank testing. All survival analyses were performed from the time of ILD diagnosis to death, transplant, loss to follow-up, or end of the study period (i.e., follow-up duration). Survival status was determined by contacting the patient or was retrieved from medical records. Survival time was censored on May 31, 2020; at the time, the patient underwent lung transplant or at the date of the last visit if they were lost to follow-up. Unadjusted hazard ratios were obtained for all study parameters using Cox proportional hazards regression analysis to determine risk factors for AE and ILD survival. Univariate parameters with a $P < 0.05$ were considered for inclusion in multivariate models to identify the independent predictors of AE and mortality among the ILD patients. $P < 0.05$ was considered significant, and 95% confidence intervals were used to report the precision of our results. SPSS (Statistical Package for the Social Sciences) version 18 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Six hundred and sixty-seven consecutive ILD patients were identified. The incidence of AE in non-IPF-ILD and IPF was 9.6 and 16 events per 100 patient-years, respectively. Among the CTD-ILD patients, 106 patients had the usual interstitial pneumonia (UIP) pattern (without AE, $n = 65$; with AE, $n = 41$), 102 patients

had an NSIP pattern (without AE $n = 75$; with AE, $n = 27$), 10 patients had organizing pneumonia (without AE $n = 7$; with AE, $n = 3$), and 7 patients had lymphocytic interstitial pneumonia (without AE, $n = 6$; with AE, $n = 1$). The underlying subtypes of CTD included 84 patients with primary Sjogren's syndrome (without AE, $n = 52$; with AE, $n = 32$), 43 patients with rheumatoid arthritis (without AE, $n = 28$; with AE, $n = 15$), 44 patients with systemic sclerosis (without AE, $n = 32$; with AE, $n = 12$), 23 patients with mixed CTD (without AE, $n = 18$; with AE, $n = 5$), 18 patients with systemic lupus erythematosus (without AE, $n = 13$; with AE, $n = 5$), and 13 patients with polymyositis (without AE, $n = 10$; with AE, $n = 3$).

Among the patients with interstitial pneumonia with autoimmune features, 26 had the UIP pattern (without AE, $n = 21$; with AE, $n = 5$), 12 patients had an NSIP pattern (without AE, $n = 10$; with AE, $n = 2$), 6 patients had organizing pneumonia (without AE, $n = 4$; with AE, $n = 2$), and two patients had lymphocytic interstitial pneumonia without AE. The clinical characteristics of the ILD patients without AE and with AE are summarized in Table 1. Compared to ILD patients without AE, marked baseline physiological impairments in PFTs, and 6MWT parameters were noted in the AE group [Table 1].

In total, 370 ILD patients underwent RHC and were categorized as 181 patients without PH (without AE, $n = 124$; with AE, $n = 57$), 104 patients with PH (without AE, $n = 58$; with AE, $n = 46$), 60 patients with severe PH (without AE, $n = 34$; with AE, $n = 26$), and 25 patients with postcapillary PH (without AE, $n = 16$; with AE, $n = 9$).

The ILD with AE comparisons of demographic, clinical, and physiological parameters between non-IPF ILD and IPF patients are summarized in Table 2. Non-IPF ILD patients were significantly younger, predominantly women, and primarily nonsmokers and had a higher body mass index (BMI) (all, $P < 0.0001$). Based on available RHC parameters, AE was more frequently noted in IPF patients without PH than in non-IPF ILD patients without PH (56.6% and 31.7%, respectively, $P = 0.004$). However, AE was more frequently observed in non-IPF ILD with PH than in IPF patients with PH (40% and 22.6%, respectively, $P = 0.035$) [Table 2]. Interestingly, baseline PFTs and 6MWT parameters were remarkably similar in the two groups [Table 2].

Table 1: Clinical characteristics of the interstitial lung disease cohort

	Without AE (*n*=480)	With AE (*n*=187)	*P*
Age	56.6±15.6	59.8±13.6	0.013
Female sex	264 (55)	99 (52.9)	0.632
Ever smoker	123 (25.6)	50 (26.7)	0.806
Follow-up duration (months)	22.2±24.0	29.0±28.0	0.002
BMI (kg/m^2)	29.1±6.4	29.3±7.3	0.701
Interstitial lung disease type			
IPF	130 (27.0)	74 (39.5)	0.002
CTD-ILD	153 (31.8)	72 (38.5)	0.104
Sarcoidosis	84 (17.5)	18 (9.6)	0.011
IPAF	37 (7.7)	9 (4.8)	0.185
Chronic hypersensitivity pneumonitis	31 (6.4)	8 (4.2)	0.281
Idiopathic NSIP	17 (3.5)	4 (2.1)	0.351
Others			
Organizing pneumonia	9 (1.8)	1 (0.5)	0.297
Chronic eosinophilic pneumonia	6 (1.2)	1 (0.5)	0.680
RB-ILD	9 (1.8)	0	0.068
DIP	4 (0.8)	0	0.581
Pulmonary function test			
FVC (percentage predicted)	63.6±19.9$^{\alpha}$	54.8±19.4$^{\beta}$	<0.0001
FEV_1 (percentage predicted)	68.5±19.6$^{\alpha}$	61.8±21.0$^{\beta}$	<0.0001
FEV_1/FVC	86.5±9.0$^{\gamma}$	88.8±10.8$^{\beta}$	0.007
DLco (percentage predicted)	51.0±23.5$^{\varphi}$	40.6±21.0$^{\kappa}$	<0.0001
6MWT	*n*=447	*n*=177	
Initial SpO_2 (%)	95.6±5.4	94.7±3.0	0.034
Final SpO_2 (%)	88.8±8.9	84.4±8.9	<0.0001
Distance (m)	338.4±114.2	291.3±118.3	<0.0001

Data are presented as the mean±SD or *n* (%). $^{\alpha}n$=467, $^{\beta}n$=184, $^{\varphi}n$=409, $^{\kappa}n$=160. ILD=Interstitial lung disease, AE=Acute exacerbation, BMI=Body mass index, IPF=Idiopathic pulmonary fibrosis, CTD=Connective tissue disease, IPAF=Interstitial pneumonia with autoimmune features, NSIP=Nonspecific interstitial pneumonia, RB-ILD=Respiratory bronchiolitis interstitial lung disease, DIP=Desquamative interstitial pneumonia, FVC=Forced vital capacity, FEV_1=Forced expiratory volume in one second, DLco=Diffusion capacity of the lung for carbon monoxide, SpO_2=Oxygen saturation by pulse oximetry, SD=Standard deviation, 6MWT=6-min walk test

Etiology of acute exacerbation

The etiology of AE among the non-IPF-ILD patients was classified as idiopathic (n = 48) or triggered (infection, n = 47; drug induced, n = 2), and 16 patients had multiple episodes of AE of different etiologies (i.e., one admission was found to be idiopathic, and another admission at a different time was found to be triggered). However, the etiology of AE among the IPF patients was classified as idiopathic (n = 37) or triggered (infection, n = 16), and 21 patients had multiple episodes of AE of different etiologies (i.e., idiopathic and triggered).

Predictors of acute exacerbation among the interstitial lung disease cohort

A multiregression analysis for predictors of AE was performed. In the entire ILD cohort, we found that advanced age and lower percent predicted FVC, 6MWD <300 meters, and 6MWT final SpO_2 <85% were independently associated with an increased risk of AE [Table 3]. In the IPF group, a lower percent predicted FVC was the only variable independently associated with an increased risk of AE [Table 4]. However, in the non-IPF ILD group, we found that advanced age and lower percent predicted FVC and higher PCWP were independently associated with an increased risk of AE [Table 5].

Survival analysis of the interstitial lung disease cohort

In total, 147 patients died (without AE, n = 64; with AE, n = 83; $P < 0.0001$), and three underwent transplantation. Notably, the estimated survival probabilities at 1, 3, and 5 years were 88%, 75%, and 70%, respectively, in the ILD (IPF and non-IPF ILD) without AE group; 80%, 57%, and 50%, respectively, in the non-IPF ILD with AE group; and 53%, 38%, and 28%, respectively, in the IPF with AE group [$P < 0.0001$ by log-rank analysis; Figure 1].

In the univariate Cox regression analysis, among the entire ILD cohort, a number of factors were associated with survival. However, in the multivariable analysis, age, BMI, IPF diagnosis, AE, DLco <35%, 6MWD <300 m, and CI were independently associated with survival [Table 6]. In the IPF group, percent predicted FVC and 6MWD <300 m were independently associated with survival [Table 7], and in the non-IPF ILD group, age, AE, and DLco <35% were independently associated with survival [Table 8].

Discussion

The present study describes the clinical characteristics, risk factors, and survival of AE in a large cohort of

Table 2: Clinical characteristics of the interstitial lung disease cohort with acute exacerbation

	Non-IPF ILD (*n*=113)	IPF (*n*=74)	*P*
Age	56.7±13.6	64.7±12.2	<0.0001
Female sex	79 (69.9)	20 (27.0)	<0.0001
Ever smoker	19 (16.8)	31 (41.8)	<0.0001
Follow-up duration (months)	30.2±27.4	27.2±29.0	0.478
BMI (kg/m^2)	30.9±8.2	27.0±5.0	<0.0001
Hemodynamic	*n*=85	*n*=53	
Without PH	27 (31.7)	30 (56.6)	0.004
Postcapillary PH	4 (4.7)	5 (9.4)	0.305
With PH	34 (40)	12 (22.6)	0.035
Severe PH	20 (23.5)	6 (11.3)	0.074
Pulmonary function test	*n*=111	*n*=73	
FVC (percentage predicted)	54.3±18.9	55.5±20.2	0.669
FEV_1 (percentage predicted)	59.9±20.0	64.7±22.1	0.134
FEV_1/FVC	88.4±12.0	89.4±8.7	0.570
DLco (percentage predicted)	43.1±21.8$^{\gamma}$	36.6±19.0$^{\delta}$	0.053
6MWT	*n*=107	*n*=70	
Initial SpO_2	95.1±2.9	94.2±2.9	0.054
Final SpO_2	84.9±9.5	83.6±8.0	0.358
Distance (m)	291.7±114.4	290.7±124.8	0.953
Treatment			
Corticosteroids (5-10 mg)	54 (47.7)	21 (28.3)	0.008
PH specific therapy†	26 (23.0)	16 (21.6)	0.824
Oxygen supplementation	46 (40.7)	37 (50.0)	0.211

Data are presented as the mean±SD or *n* (%). $^{\gamma}n$=98, $^{\delta}n$=62, †In the nonIPF ILD group: Patients received phosphodiesterase 5 inhibitor (n=11), endothelin receptor antagonist (n=2), prostanoids (n=1), phosphodiesterase 5 inhibitor+endothelin receptor antagonist (n=7), phosphodiesterase 5 inhibitor+prostanoids (n=1), phosphodiesterase 5 inhibitor+endothelin receptor antagonist+prostanoids (n=4), in the IPF group, patients received phosphodiesterase 5 inhibitor (n=16). IPF=Idiopathic pulmonary fibrosis, ILD=Interstitial lung disease, BMI=Body mass index, PH=Pulmonary hypertension, FVC=Forced vital capacity, FEV_1=Forced expiratory volume in one second, DLco=Diffusion capacity of the lung for carbon monoxide, SpO_2=Oxygen saturation by pulse oximetry, SD=Standard deviation, 6MWT=6-min walk test

Table 3: Variables predicting acute exacerbation among the interstitial lung disease cohort

Variable	Unadjusted		Adjusted	
	HR (95% confidence interval)	*P*	HR (95% confidence interval)	*P*
Age	1.019 (1.008-1.029)	<0.0001	1.015 (1.001-1.030)	0.035
Male sex	1.464 (1.095-1.957)	0.010		
Ever smoker	1.406 (1.012-1.953)	0.042		
BMI (kg/m^2)	0.994 (0.971-1.017)	0.595		
IPF diagnosis	1.867 (1.392-2.505)	<0.0001		
CTD-ILD diagnosis	0.967 (0.719-1.301)	0.824		
Sarcoidosis diagnosis	0.613 (0.376-0.998)	0.049		
FVC (percentage predicted)	0.974 (0.967-0.982)	<0.0001	0.984 (0.974-0.994)	0.002
DLco (percentage predicted) <35%	1.379 (1.003-1.895)	0.048		
6MWD <300 m	2.050 (1.524-2.758)	<0.0001	1.615 (1.108-2.354)	0.013
6MWT final SpO_2 <85%	1.922 (1.424-2.593)	<0.0001	1.557 (1.081-2.242)	0.017
mPAP (mmHg)	1.005 (0.986-1.024)	0.616		
RAP (mmHg)	0.996 (0.948-1.048)	0.886		
sPAP (mmHg)	1.004 (0.992-1.016)	0.519		
dPAP (mmHg)	1.013 (0.990-1.038)	0.273		
PCWP (mmHg)	1.028 (0.994-1.063)	0.112		
PVR (wood units)	1.040 (0.984-1.100)	0.165		
CI (L/min/m^2)	0.935 (0.739-1.183)	0.576		

HR=Hazard ratio, ILD=Interstitial lung disease, BMI=Body mass index, IPF=Idiopathic pulmonary fibrosis, CTD=Connective tissue disease, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=6-min walk distance, 6MWT=6-min walk test, SpO_2=Oxygen saturation by pulse oximetry, PAP=Pulmonary artery pressure, mPAP=Mean PAP, RAP=Right atrial pressure, sPAP=Systolic PAP, dPAP=Diastolic PAP, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

Table 4: Variables predicting acute exacerbation among idiopathic pulmonary fibrosis patients

Variable	Unadjusted		Adjusted	
	HR (95% confidence interval)	*P*	HR (95% confidence interval)	*P*
Age	1.005 (0.985-1.025)	0.641		
Male sex	1.621 (0.950-2.763)	0.076		
Ever smoker	1.241 (0.775-1.988)	0.368		
BMI (kg/m^2)	0.937 (0.896-0.979)	0.004		
FVC (% predicted)	0.976 (0.964-0.989)	<0.0001	0.977 (0.959-0.994)	0.010
DLco (% predicted) <35%	1.268 (0.760-2.115)	0.363		
6MWD <300 m	1.872 (1.148-3.054)	0.012		
6MWT final SpO_2 <85%	1.440 (0.891-2.325)	0.136		
mPAP (mmHg)	0.960 (0.926-0.995)	0.026		
RAP (mmHg)	0.898 (0.825-0.978)	0.013		
sPAP (mmHg)	0.970 (0.945-0.994)	0.017		
dPAP (mmHg)	0.973 (0.934-1.013)	0.187		
PCWP (mmHg)	0.981 (0.927-1.038)	0.509		
PVR (wood units)	0.951 (0.833-1.086)	0.458		
CI (L/min/m^2)	0.855 (0.558-1.310)	0.473		

HR=Hazard ratio, BMI=Body mass index, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=6-min walk distance, 6MWT=6-min walk test, SpO_2=Oxygen saturation by pulse oximetry, PAP=Pulmonary artery pressure, mPAP=Mean PAP, RAP=Right atrial pressure, sPAP=Systolic PAP, dPAP=Diastolic PAP, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

ILD patients with variable degrees of parenchymal inflammation and fibrosis. We show that 28% of the ILD patients developed AE. Importantly, the observed 1-, 3-, and 5-year survival rates of non-IPF ILD patients with AE were better than those of IPF patients with AE; however, both groups were significantly associated with decreased survival compared to ILD patients without AE.

Many precipitating factors (i.e., triggered) have been implicated in causing acute lung injury, including infection, aspiration, surgery, and drugs, among others; because acute lung injury resembles the clinical, radiological, and histopathological findings of idiopathic AE-IPF, the international working group has revised the definition and diagnostic criteria for AE-IPF where both terms idiopathic and triggered events are included.[1] Although there are no consensus recommendations regarding the definition of AE in non-IPF ILD, it has been recently proposed that applying the same definition of AE-IPF in non-IPF ILD will provide useful information for this poorly studied group of patients.[8]

Significant variation among studies was noted with regard to the incidence, clinical characteristics, and outcome of AE in non-IPF ILD patients.[9-11,13,15,16] Different methodologies, ILD types, sample sizes, environmental factors, smoking habits, races, and other factors may explain the observed variation. As such, the findings from other studies and ours should be interpreted in the context of the studied populations. Nonetheless, studies of AE in non-IPF ILD across different populations will enrich our understanding of the clinical behavior, risk factors, and outcomes, which offers the best hope of developing effective preventive measures against this devastating complication.

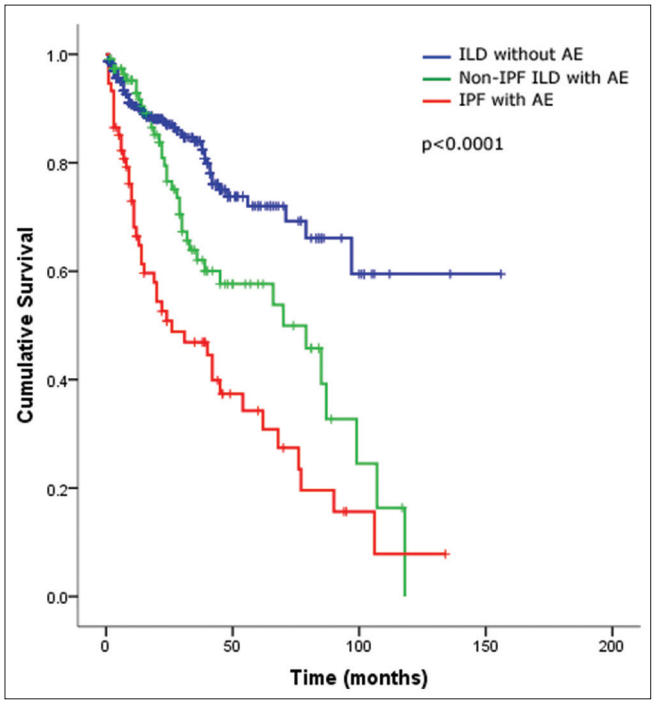

Figure 1: Kaplan–Meier survival estimates for interstitial lung disease (idiopathic pulmonary fibrosis and nonidiopathic pulmonary fibrosis interstitial lung disease) patients without acute exacerbation (blue line), nonidiopathic pulmonary fibrosis interstitial lung disease with acute exacerbation (green line), and Idiopathic pulmonary fibrosis with acute exacerbation (red line)

In the present study, we found that the incidence of AE in non-IPF-ILD and IPF was 9.6 and 16 events per 100 patient-years, respectively. Moreover, the clinical features of patients with AE in the non-IPF ILD group reveal that they are of younger age, predominantly female, and primarily nonsmokers. While the rate of idiopathic AE was similar between IPF and non-IPF-ILD, we noted that the triggered events were more frequently observed in the non-IPF ILD group (43.3%) than in the AE-IPF group (21.6%), likely a result of the use of various immunomodulatory therapies that put non-IPF ILD patients at higher risk of acquiring infection.

Several risk factors have been implicated in AE-IPF including nonsmoking status, low FVC, low DLco, reduced 6MWD, poor baseline oxygenation, PH, and recent decline in FVC.[1,34-37] Interestingly, studies examining risk factors for AE in non-IPF ILD noted baseline FVC, BMI, total lung capacity, DLco, and partial pressure of oxygen were independent predictors of AE.[6,10,16] Thus, the similarity in AE risk factors between IPF and non-IPF ILD is not surprising since both diseases share similar lung injury, and importantly, both involve background lung fibrosis. In the present study, we found that advanced age, lower FVC, 6MWD <300 m, and desaturation at the end of the 6MWT <85% were independent predictors of AE in ILD patients. As such,

Table 5: Variables predicting acute exacerbation among nonidiopathic pulmonary fibrosis interstitial lung disease patients

Variable	Unadjusted		Adjusted	
	HR (95% confidence interval)	*P*	HR (95% confidence interval)	*P*
Age	1.017 (1.004-1.031)	0.013	1.023 (1.003-1.044)	0.023
Male sex	1.056 (0.704-1.583)	0.793		
Ever smoker	1.151 (0.699-1.895)	0.581		
BMI (kg/m^2)	1.023 (0.997-1.051)	0.089		
FVC (% predicted)	0.973 (0.963-0.982)	<0.0001	0.982 (0.968-0.997)	0.021
DLco (% predicted) <35%	1.334 (0.880-2.023)	0.174		
6MWD <300 m	2.241 (1.533-3.276)	<0.0001		
6MWT final SpO_2 <85%	2.198 (1.495-3.231)	<0.0001		
mPAP (mmHg)	1.027 (1.005-1.050)	0.014		
RAP (mmHg)	1.063 (0.996-1.133)	0.065		
sPAP (mmHg)	1.017 (1.004-1.030)	0.013		
dPAP (mmHg)	1.036 (1.007-1.067)	0.016		
PCWP (mmHg)	1.061 (1.014-1.110)	0.011	1.068 (1.005-1.135)	0.035
PVR (wood units)	1.070 (1.007-1.137)	0.028		
CI (L/min/m^2)	1.023 (0.778-1.343)	0.873		

HR=Hazard ratio, BMI=Body mass index, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=6-min walk distance, 6MWT=6-min walk test, SpO_2=Oxygen saturation by pulse oximetry, PAP=Pulmonary artery pressure, mPAP=Mean PAP, RAP=Right atrial pressure, sPAP=Systolic PAP, dPAP=Diastolic PAP, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

Table 6: Variables predicting survival in the interstitial lung disease cohort

Variable	Unadjusted		Adjusted	
	HR (95% confidence interval)	*P*	HR (95% confidence interval)	*P*
Age	1.033 (1.020-1.045)	<0.0001	1.023 (1.001-1.045)	0.044
Male sex	2.235 (1.604-3.113)	<0.0001		
Ever smoker	1.991 (1.409-2.812)	<0.0001		
BMI (kg/m^2)	0.946 (0.919-0.974)	<0.0001	0.946 (0.900-0.995)	0.031
IPF diagnosis	3.374 (2.436-4.672)	<0.0001	2.635 (1.052-6.597)	0.039
CTD-ILD diagnosis	0.679 (0.478-0.966)	0.031		
Sarcoidosis diagnosis	0.520 (0.288-0.939)	0.030		
Acute exacerbation	2.588 (1.865-3.592)	<0.0001	1.712 (1.043-2.810)	0.033
FVC (% predicted)	0.968 (0.959-0.977)	<0.0001		
DLco (% predicted) <35%	2.419 (1.671-3.502)	<0.0001	2.075 (1.225-3.515)	0.007
6MWD <300 m	2.700 (1.904-3.827)	<0.0001	1.958 (1.120-3.424)	0.018
6MWT final SpO_2 <85%	2.413 (1.699-3.427)	<0.0001		
mPAP (mmHg)	1.026 (1.006-1.045)	0.009		
RAP (mmHg)	1.006 (0.953-1.063)	0.821		
sPAP (mmHg)	1.019 (1.007-1.031)	0.001		
dPAP (mmHg)	1.035 (1.009-1.061)	0.007		
PCWP (mmHg)	1.037 (1.000-1.075)	0.047		
PVR (wood units)	1.083 (1.026-1.142)	0.004		
CI (L/min/m^2)	0.651 (0.490-0.866)	0.003	0.618 (0.409-0.935)	0.023

HR=Hazard ratio, ILD=Interstitial lung disease, BMI=Body mass index, CTD=Connective tissue disease, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=6-min walk distance, 6MWT=6-min walk test, SpO_2=Oxygen saturation by pulse oximetry, PAP=Pulmonary artery pressure, mPAP=Mean PAP, RAP=Right atrial pressure, sPAP=Systolic PAP, dPAP=Diastolic PAP, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

Table 7: Variables predicting survival among idiopathic pulmonary fibrosis patients

Variable	Unadjusted		Adjusted	
	HR (95% confidence interval)	*P*	HR (95% confidence interval)	*P*
Age	1.006 (0.986-1.025)	0.574		
Male sex	1.576 (0.943-2.635)	0.083		
Ever smoker	1.232 (0.789-1.926)	0.359		
BMI (kg/m^2)	0.957 (0.917-0.998)	0.038		
Acute exacerbation	1.489 (0.950-2.333)	0.082		
FVC (% predicted)	0.967 (0.954-0.979)	<0.0001	0.982 (0.965-0.998)	0.030
DLco (% predicted) <35%	1.791 (1.083-2.962)	0.023		
6MWD <300 m	2.381 (1.473-3.851)	<0.0001	2.117 (1.220-3.674)	0.008
6MWT final SpO_2 <85%	2.046 (1.268-3.303)	0.003		
mPAP (mmHg)	1.017 (0.990-1.045)	0.226		
RAP (mmHg)	1.014 (0.950-1.083)	0.677		
sPAP (mmHg)	1.008 (0.989-1.027)	0.415		
dPAP (mmHg)	1.023 (0.991-1.056)	0.162		
PCWP (mmHg)	1.016 (0.972-1.061)	0.492		
PVR (wood units)	1.072 (0.977-1.176)	0.140		
CI (L/min/m^2)	0.720 (0.484-1.072)	0.106		

HR=Hazard ratio, BMI=Body mass index, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=6-min walk distance, 6MWT=6-min walk test, SpO_2=Oxygen saturation by pulse oximetry, PAP=Pulmonary artery pressure, mPAP=Mean PAP, RAP=Right atrial pressure, sPAP=Systolic PAP, dPAP=Diastolic PAP, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

our findings, along with the cited studies, support the notion that advanced ILD disease is more susceptible to the development of AE. Furthermore, our findings attest to the parameters obtained from the 6MWT as a test that captures patients at increased risk of AE.

Interestingly, in the non-IPF ILD group, we found that parameters obtained from RHC, such as right atrial pressure, mPAP, systolic PAP, diastolic PAP, PCWP, and PVR, were significantly associated with an increased risk of AE in the univariate analysis. However, in the multivariate analysis, only PCWP emerged as an independent predictor of AE. Although we excluded all cases admitted due to heart failure and volume overload from the analysis as stated in the definition of AE-IPF[1] and the number of patients (n = 4) diagnosed with postcapillary PH in this group was small, our results imply that a subset of patients with abnormal

Table 8: Variables predicting survival among nonidiopathic pulmonary fibrosis interstitial lung disease patients

Variable	Unadjusted		Adjusted	
	HR (95% confidence interval)	*P*	HR (95% confidence interval)	*P*
Age	1.028 (1.010-1.046)	0.002	1.038 (1.002-1.074)	0.036
Male sex	1.529 (0.932-2.508)	0.093		
Ever smoker	1.866 (1.050-3.317)	0.033		
BMI (kg/m^2)	0.949 (0.908-0.991)	0.018		
Acute exacerbation	3.246 (1.998-5.273)	<0.0001	2.142 (1.024-4.482)	0.043
FVC (% predicted)	0.969 (0.956-0.983)	<0.0001		
DLco (% predicted) <35%	3.019 (1.723-5.290)	<0.0001	2.480 (1.173-5.241)	0.017
6MWD <300 m	3.280 (1.942-5.542)	<0.0001		
6MWT final SpO_2 <85%	2.463 (1.466-4.137)	0.001		
mPAP (mmHg)	1.033 (1.005-1.062)	0.019		
RAP (mmHg)	0.946 (0.860-1.041)	0.255		
sPAP (mmHg)	1.028 (1.012-1.043)	<0.0001		
dPAP (mmHg)	1.035 (0.997-1.075)	0.074		
PCWP (mmHg)	1.042 (0.981-1.108)	0.182		
PVR (wood units)	1.095 (1.020-1.175)	0.012		
CI (L/min/m^2)	0.760 (0.508-1.135)	0.180		

HR=Hazard ratio, BMI=Body mass index, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=6-min walk distance, 6MWT=6-min walk test, SpO_2=Oxygen saturation by pulse oximetry, PAP=Pulmonary artery pressure, mPAP=Mean PAP, RAP=Right atrial pressure, sPAP=Systolic PAP, dPAP=Diastolic APA, PCWP=pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

filling pressure are at significantly increased risk of developing AE. A potential explanation is that the downstream effects of congestion on other organs due to elevated filling pressure may result in the release of inflammatory mediators such as interleukin (IL)-6 and activation of endothelial cells similar to those observed in heart failure and renal failure.[38-40] In line with this observation, previous studies have shown that IL-6, IL-8, markers of type II alveolar epithelial cell injury, endothelial cell injury, and coagulation were significantly elevated in patients with AE-IPF compared to stable IPF patients.[41,42] Nonetheless, the association between elevated PCWP and increased risk of AE in the non-IPF ILD patients noted in our study is intriguing and needs to be validated along with measurements of serum inflammatory mediators and markers of Type II alveolar epithelial cell injury.

Several studies have shown that the development of AE in both IPF and non-IPF ILD is associated with poor survival.[6,9-12,14-16] Although the overall survival in the non-IPF ILD patients with AE was significantly better than that in the AE-IPF patients in the present study, we showed that survival in both groups was significantly worse than that in the ILD group without AE. Furthermore, we demonstrate that the development of AE was associated with a 1.7-fold increased risk of mortality regardless of the underlying ILD type, highlighting the urgent need to develop effective preventive measures that would ultimately have a positive impact on ILD patient survival. In univariate Cox regression analysis, a number of factors were associated with ILD survival; however, in multivariate analysis, we found that age, BMI, IPF diagnosis, AE, DLCO <35% predicted, 6MWD <300 m, and CI emerged as independent predictors of survival. In a Japanese cohort with various ILD types, Suzuki *et al*.[16] noted that fibrotic ILD, age, male sex, FVC, DLco, BMI, modified Medical Research Council dyspnea scale, UIP pattern, and AE were independent predictors of survival. As such, our findings are consistent with other racial cohorts, and importantly, we have identified additional variables highlighting the importance of parameters obtained from the 6MWT and RHC as prognostic markers in ILD patients.[43]

The present study had several strengths and limitations. The strengths include enrolling a large consecutive cohort of ILD patients from one center. All physiological and hemodynamic variables used in the present study were collected at the time when the patient was first seen at our center. In addition, more than half of our ILD cohort underwent RHC at the time of establishing ILD diagnosis, which contributes added beneficial information to the risk of AE and overall ILD survival. Last, because the 6MWT is simple, inexpensive, well received by patients and mimics daily physical activity, our findings have several potential implications for clinicians evaluating ILD patients. We show that parameters obtained from this test are capable of identifying ILD patients at increased risk of AE and can serve as surrogate markers of increased mortality among ILD patients. Limitations including the retrospective analysis may have introduced selection and information bias, although data were acquired prospectively. All patients in the present study were from the Saudi population; thus, our results may not be extrapolated to other populations. Finally, institutional bias may have occurred due to the most

severe cases being referred to our center, which may have led to overestimation of the incidence of AE and mortality of ILD patients in this region.

Conclusions

This study describes the clinical features, risk factors, and outcome of AE in diverse ILD patients with variable degrees of parenchymal inflammation and fibrosis, which highlights a number of important issues pertaining to this serious complication. AE in non-IPF ILD patients has distinct clinical features; they are younger, predominantly women, and primarily nonsmokers. We show that AE in IPF and non-IPD ILD is common and associated with poor survival. Importantly, the development of AE was associated with a nearly 2-fold increased risk of mortality regardless of the underlying ILD type. Our study clearly demonstrates that parameters obtained from PFTs and the 6MWT are important surrogate markers for AE and mortality among ILD patients.

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Conflicts of interest

There are no conflicts of interest.

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