Predictors of mortality in interstitial lung disease patients without pulmonary hypertension

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Abstract:
BACKGROUND: There is a paucity of information regarding prognostic factors associated with reduced survival in interstitial lung disease (ILD) patients without pulmonary hypertension (PH).
AIMS: The aim of this study was to determine physiological and hemodynamic parameters that impact survival among ILD patients without PH based on right heart catheterization (RHC).
METHODS: Consecutive ILD patients who underwent RHC (n = 169) at one center were included. The information analyzed included demographics and physiological and hemodynamic parameters. Cox regression models were used to identify independent predictors of survival.
RESULTS: The mean age was 55.0 years, and 49.7% of the patients were females. Thirty-three patients died, and two underwent transplantation. Patients with predicted diffusion capacity of the lung for carbon monoxide <35%, walking distance <300 m, and 6-min walk test (6MWT) final oxygen saturation measured by pulse oximetry (SpO₂) <85% were significantly associated with an increased mortality risk (P = 0.022, P < 0.0001, and P = 0.049, respectively; all by log-rank analysis). Advanced age, idiopathic pulmonary fibrosis diagnosis, reduced forced vital capacity, and low cardiac index were independent predictors of increased mortality in the ILD cohort.
CONCLUSIONS: Our study demonstrates that parameters obtained from baseline pulmonary function tests and 6MWTS are important determinants of survival in ILD patients without PH. Importantly, cardiac index was the only hemodynamic variable independently associated with survival. Thus, in the absence of PH, when ILD patients perform poorly during the 6MWT manifested as reduced walking distance and desaturation at the end of the test, cardiovascular impairment must be ruled out.
Keywords: Idiopathic pulmonary fibrosis, interstitial lung disease, pulmonary hypertension, 6-min walk test, survival

Interstitial lung disease (ILD) consists of a large group of disorders that cause inflammation and/or scarring of the lung parenchyma with variable degrees of severity, depending on the underlying ILD. According to epidemiological studies, idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD)-associated ILD, chronic hypersensitivity pneumonitis, and sarcoidosis were the most commonly reported ILD subtypes with variable rankings depending on the studied population.[1,2] Studies in ILD have identified important physiological prognostic markers associated with reduced survival, such as forced vital capacity (FVC), total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DLCO), 6-min walk distance (6MWD), and desaturation during the 6-min walk test (6MWT).[3,4] However, the cited studies did not specify what proportions of these patients have underlying pulmonary hypertension (PH). Estimates suggest that the prevalence of PH among ILD patients ranges between 30% and 74% depending on the ILD...
In this context, we reviewed a series of consecutive ILD patients without PH, defined as a mean pulmonary artery pressure (mPAP) <25 mmHg and pulmonary vascular resistance (PVR) <3 Wood units (WU), as previously described,[9] to determine the impact of physiological and hemodynamic parameters on ILD survival.

Methods

The present study is a retrospective review of the ongoing ILD and PH registry at the ILD and PH Centre at King Saud University Medical City. Consecutive ILD patients between March 1, 2009, and October 31, 2019, were included. Right heart catheterization (RHC) was performed within 7 days of establishing an ILD diagnosis. Inclusion criteria for the present analysis were a diagnosis of ILD, age >18 years, and availability of parameters from RHC showing a mPAP <25 mmHg and PVR <3 WU. Patients with pulmonary capillary wedge pressure (PCWP) >15 mmHg were excluded (n = 26).

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.

The demographics collected included age, sex, and smoking history. The baseline pulmonary function test (PFT) and 6MWT parameters performed at baseline were collected.[15‑17] A multidisciplinary approach was implemented for all ILD patients, and each patient received a specific ILD subtype diagnosis according to the established guidelines.[16‑28]

Statistical analysis

Data are presented as the means ± standard deviations or numbers (percentages), where appropriate. Kaplan–Meier survival curves and log-rank tests were used to investigate the time from the initial RHC 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; if they were lost to follow-up; or at the date of the last visit. Univariate Cox proportional hazard models were used to examine the association of selected variables with ILD survival. Significant variables (P < 0.05) in the univariate analysis were included in the multivariate model to identify the independent predictors of mortality among the ILD patients. P <0.05 was considered statistically significant, and 95% confidence intervals were used to report the precision of our results. SPSS (Statistical Package for the Social Sciences) version 18 software (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

A total of 169 patients without PH based on RHC inclusion criteria were identified. The mean age was 55 years, and 49.7% were females. The baseline demographic characteristics of the ILD patients are summarized in Table 1. The underlying subtypes of CTD included 18 patients with undifferentiated CTD, 12 patients with rheumatoid arthritis, 11 patients with mixed CTD, 9 patients with primary Sjögren’s syndrome, 8 patients with systemic sclerosis, 5 patients with systemic lupus erythematosus, and 3 patients with polymyositis. Among the CTD-ILD patients, 35 patients had the usual interstitial pneumonia pattern, 27 patients had a nonspecific interstitial pneumonia pattern, and 2 patients each had organizing pneumonia and lymphocytic interstitial pneumonia. Because of the advanced state of lung fibrosis, 10 patients were not able to perform DLco and 4 patients were not able to perform 6MWT. The baseline PFT, 6MWT, and hemodynamic parameter results are shown in Table 2.

Determinants of reduced 6-min walk distance

On univariate regression analysis, a reduced 6MWD was associated with advanced age and a positive smoking history [Table 3]. Regarding physiological

Table 1: Demographic characteristics of the study cohort

| Variable                        | n=169 |
|---------------------------------|-------|
| Age                             | 55.0±15.6 |
| Female sex                      | 84 (49.7)  |
| Ever smoker                     | 41 (24.3)  |
| Follow-up duration, months      | 38.0±35.9  |
| BMI, kg/m²                      | 29.3±6.2   |
| Underlying disease              |       |
| IPF                             | 49 (29.9)  |
| CTD-ILD                         | 66 (39.0)  |
| Sarcoidosis                     | 23 (13.6)  |
| Chronic hypersensitivity pneumonitis | 12 (7.1) |
| Others*                         | 19 (11.2)  |
| Oxygen supplementation          | 91 (53.8)  |

*Others: Unclassifiable fibrosis, n=6; organizing pneumonia, n=4; respiratory bronchiolitis interstitial lung disease, n=4; idiopathic nonspecific interstitial pneumonia, n=3; desquamative interstitial pneumonia, n=2. Data are presented as the means±SD or n (%). BMI=Body mass index, IPF=Idiopathic pulmonary fibrosis, CTD=Connective tissue disease, ILD=Interstitial lung disease, NSIP=Nonspecific interstitial pneumonia, SD=Standard deviation
test parameters, a lower percent predicted FVC, reduced diffusing capacity, and desaturation during the 6MWT were associated with reduced walking distance. Although higher systolic PAP and higher PCWP tended to be associated with reduced walking distance ($P = 0.062$ and $P = 0.055$, respectively), a reduced cardiac index was the only hemodynamic parameter significantly associated with reduced 6MWD. On multivariate linear regression, we found that advanced age and lower percent predicted FVC were independently associated with reduced 6MWD [Table 3].

### Table 2: Physiological and hemodynamic parameters of the study cohort

| Variable                        | n=169 |
|---------------------------------|-------|
| Pulmonary function test         |       |
| FVC, percent predicted          | 63.1±18.5 |
| TLC, percent predicted          | 65.5±18.2 |
| $D_{LCO}$, percent predicted*    | 47.2±19.4 |
| Six-minute walk test*           |       |
| Initial Borg score              | 0.9±1.4 |
| Final Borg score                | 3.2±2.3 |
| Initial $SpO_2$, %              | 95.9±2.6 |
| Final $SpO_2$, %                | 87.0±6.9 |
| Distance, meters                | 355.3±106.1 |
| Right heart catheterization     |       |
| sPAP, mmHg                      | 29.5±5.9 |
| dPAP, mmHg                      | 11.1±3.5 |
| mPAP, mmHg                      | 18.7±3.5 |
| PCWP, mmHg                      | 8.6±3.0 |
| PVR, wood units                 | 1.9±0.5 |
| CO, L/min                       | 5.2±1.2 |
| CI, L/min/m²                    | 2.9±0.6 |

* = n=159; ‡ = n=165. Data are presented as means±SD or n (%). FVC=Forced vital capacity, FEV₁=TLC=Total lung capacity, $D_{LCO}$=Diffusion capacity of the lung for carbon monoxide, $SpO_2$=Oxygen saturation by pulse oximetry, sPAP=Systolic pulmonary artery pressure, dPAP=Diastolic pulmonary artery pressure, mPAP=Mean pulmonary artery pressure, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CO=Cardiac output, CI=Cardiac index, SD=Standard deviation

### Table 3: Clinical determinants of reduced 6-min walk distance on univariate and multivariable regression analysis

| Variable                        | Unadjusted HR (95% CI) | $P$   | Adjusted HR (95% CI) | $P$   |
|---------------------------------|------------------------|-------|----------------------|-------|
| Age                             | 1.039 (1.023-1.054)    | <0.0001 | 1.053 (1.035-1.072) | <0.0001 |
| Male sex                        | 1.361 (0.906-2.043)    | 0.137  |                      |       |
| Ever smoker                     | 1.783 (1.120-2.839)    | 0.015  |                      |       |
| FVC, percent predicted          | 0.979 (0.968-0.990)    | <0.0001 | 0.970 (0.955-0.985) | <0.0001 |
| $D_{LCO}$, percent predicted    | 0.986 (0.874-0.970)    | 0.020  |                      |       |
| 6MWT final $SpO_2$              | 0.956 (0.931-0.982)    | 0.001  |                      |       |
| mPAP, mmHg                      | 1.017 (0.962-1.075)    | 0.550  |                      |       |
| sPAP, mmHg                      | 1.033 (0.998-1.068)    | 0.062  |                      |       |
| PCWP, mmHg                      | 1.067 (0.999-1.140)    | 0.055  |                      |       |
| PVR, Wood units                 | 1.045 (0.752-1.452)    | 0.795  |                      |       |
| CI, L/min/m²                    | 0.704 (0.528-0.937)    | 0.016  |                      |       |

HR= Hazard ratio, 95% CI=95% confidence interval, FVC=Forced vital capacity, $D_{LCO}$=Diffusion capacity of the lung for carbon monoxide, 6MWT=Six-minute walk test, $SpO_2$=Oxygen saturation by pulse oximetry, mPAP=Mean pulmonary artery pressure, sPAP=Systolic pulmonary artery pressure, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

### Survival analysis of the interstitial lung disease cohort

In total, 33 patients died, 2 underwent transplantation, and 76 patients were lost to follow-up. Survival in the ILD cohort revealed that physiological parameters were predictors of worse outcome, including predicted $DLCO <35\%$ [$P = 0.022$ by log-rank analysis; Figure 1], 6MWD <300 m [$P < 0.0001$ by log-rank analysis; Figure 2], and 6MWT final oxygen saturation by pulse oximetry ($SpO_2$) <85% [$P = 0.049$ by log-rank analysis; Figure 3].

In the univariate Cox regression analysis, baseline variables significantly predicting outcome among ILD patients were age, male sex, smoking history, body mass index, IPF diagnosis, percent predicted FVC, 6MWD <300 m, systolic PAP and cardiac index. However, in the multivariable analysis, only age, IPF...
diagnosis, percent predicted FVC, and cardiac index remained significantly associated with survival [Table 4].

**Discussion**

The present study describes a cohort of ILD patients without PH based on RHC findings. We show that reduced diffusing capacity, reduced walking distance, and desaturation during the 6MWT were associated with reduced survival. Notably, age, IPF diagnosis, FVC, and cardiac index were independently associated with a high mortality risk.

IPF is a chronic fibrosing ILD characterized by progressive lung scarring that leads to permanent architectural distortion of the lung parenchyma. Although IPF is rare, epidemiological studies show that IPF always ranks among the top three common causes of ILD depending on the studied population.[1‑3] The diagnosis of IPF is complex, and to establish an accurate diagnosis, a dedicated multidisciplinary team consisting of a pulmonologist, radiologist, and pathologist is needed. The prognosis of IPF is poor, with a median survival range between 2 and 3 years.[22] In the present study, we show that among a cohort of various ILD subtypes, the diagnosis of IPF is independently associated with a three-fold risk of mortality. As such, it is of paramount importance to recognize IPF at an early stage and refer the patient to the ILD center for accurate diagnosis, which may lead to improved outcomes.

Clinicians evaluating ILD patients commonly use baseline PFT parameters to determine disease severity, prognosis, and response to therapeutic medication during follow-up. The commonly reported PFT parameters that are associated with ILD prognosis include FVC and DLco.[4‑6] Nathan et al.[4] reported that the median survival among IPF patients with baseline FVC percent predicted <55% was 27.4 months and among those with DLco percent predicted <35% was 31.3 months compared to 55.6 months for FVC >70% and 67.3 months for DLco >50%. Although the cited study did not specify what proportions of their cohort have underlying PH, our findings attest that even in the absence of PH, baseline FVC, and DLco are important and useful tools in predicting the risk of mortality among ILD patients. However, although the percent predicted DLco at a threshold of 35% was associated with decreased survival among our cohort, only FVC emerged as an independent predictor of survival when multivariate analysis was applied. This underscores the importance of obtaining PFTs during routine evaluation and follow-up of ILD patients.

The 6MWT is a submaximal exercise that requires the integrated response of the cardiopulmonary, musculoskeletal, central nervous, and metabolic systems. Several important parameters can be obtained from the 6MWT, including dyspnea Borg score, initial and final oxygen saturation, walking distance, and heart rate recovery. Because the 6MWT is simple, inexpensive, well received by patients and mimics daily physical activity, it has become a popular tool among clinicians to assess functional capacity during initial and follow-up evaluations, responses to medication, and evaluations for oxygen supplementation as well as an important surrogate marker for predicting mortality. In the present study, we found a number of factors associated with reduced walking distance in univariate analysis, including advanced age, smoking history, reduced percent predicted FVC, reduced percent predicted DLco, desaturation, and low cardiac index. However, in multivariate regression, only age and FVC emerged as independent predictors of reduced walking distance.
Another important observation in our study is that when we applied a cutoff value for the 6MWD at 300 m and 6MWT final SpO₂ at 85%, we show that both parameters were significantly associated with poor survival. Interestingly, similar threshold values have also been suggested to screen for PH in IPF patients.²⁹ As such, our findings reveal that even in the absence of PH, walking distance <300 m, and desaturation <85% during the 6MWT are important surrogate markers of increased mortality among ILD patients, and perhaps, the 6MWT unmasks pulmonary vascular pathology that is undetected when RHC is performed at rest.

The recent guidelines on PH in chronic lung disease and hypoxia defined severe PH as mPAP ≥ 35 mmHg or sPAP ≥ 25 mmHg with low cardiac index (<2.0 L/min/m²).²⁹ Interestingly, among the hemodynamic parameters evaluated in the current study, cardiac index was significantly and independently predictive of adverse clinical outcomes in patients with ILD without PH. Furthermore, cardiac index was the only hemodynamic variable associated with reduced walking distance in univariate analysis. Collectively, our findings highlight the importance of recognizing cardiovascular impairment as one of the detrimental factors that limits functional capacity in ILD patients.

The present study had several strengths and limitations. The strengths include enrolling a large number of ILD patients who underwent RHC within 7 days of establishing an ILD diagnosis at one center. All variables used in the present study were collected at the time when the patient was first seen in our center. Each ILD patient underwent comprehensive evaluation and was subsequently discussed in the multidisciplinary meeting to ensure that each patient received an accurate diagnosis. Last, our findings have yielded important prognostic information on ILD patients without PH that can be utilized in clinical practice. Limitations include that studies on ILD without PH based on RHC are limited; thus, we were not able to compare our findings with others. The retrospective review of the database from a single center may introduce data bias. Although few patients were not able to perform DLco (n = 10) and 6MWT (n = 4), such a small number of missing variables are less likely to affect the results of our multivariate analysis. Finally, our center is highly specialized in the diagnosis and management of various ILDs; thus, institutional bias may have occurred due to the most severe cases being referred to our center.

Conclusions

This study describes a population of ILD patients with variable degrees of lung fibrosis characterized by the absence of PH based on RHC. Our study demonstrates that advanced age, IPF diagnosis, percent predicted FVC, and cardiac index were independently associated with reduced survival. Importantly, the findings in the present study have important implications for clinicians evaluating ILD patients. We show that parameters obtained from baseline PFTs and 6MWTs have powerful predictive value in identifying patients at increased risk...
of mortality. Moreover, when ILD patients without PH perform poorly during the 6MWT manifested as reduced walking distance and desaturation at the end of the test, clinicians should promptly investigate the possibility of an underlying cardiovascular disease that is known to limit the functional capacity among ILD patients.

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Conflicts of interest There are no conflicts of interest.

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