Original Article

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 (SpO_2) <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.[1-3] 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).[4-8] 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

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subtype and studied population.[9,10] Interestingly, studies in PH-ILD have also identified FVC, TLC, DLco, 6MWD, and desaturation during the 6MWT as important physiological markers associated with increased mortality.[11-14] Thus, it is unclear whether these physiological parameters will remain a significant predictor of reduced survival in ILD patients without PH.

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.[18-28]

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 Sjogren'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/m^2	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
DL_{CO}, 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/m^2	2.9±0.6

*n=159; ‡n=165. Data are presented as means±SD or n (%). FVC=Forced vital capacity, FEV_1=TLC=Total lung capacity, DLco=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

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

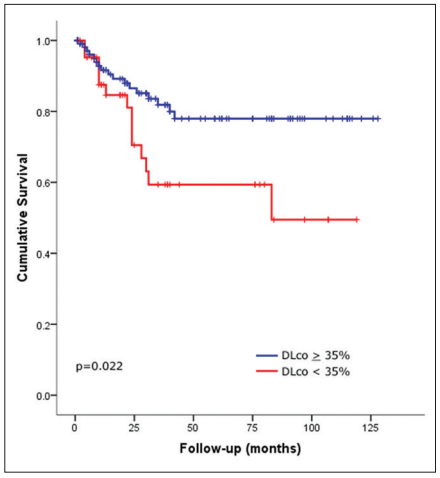

Figure 1: Kaplan–Meier survival estimates for interstitial lung disease patients with predicted diffusion capacity of the lung for carbon monoxide <35% (red line) and those with predicted diffusion capacity of the lung for carbon monoxide ≥ 35% (blue line)

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

Variable	Unadjusted		Adjusted	
	HR (95% CI)	*P*	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
DL_{CO}, percent predicted	0.986 (0.974-0.998)	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/m^2	0.704 (0.528-0.937)	0.016		

HR=Hazard ratio, 95% CI=95% confidence interval, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWT=Six-minute walk test, SpO2=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

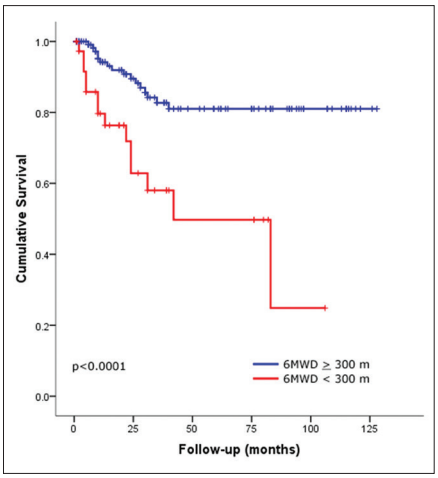

Figure 2: Kaplan–Meier survival estimates for interstitial lung disease patients with 6-min walk distance <300 m (red line) and those with 6-min walk distance ≥ 300 m (blue line)

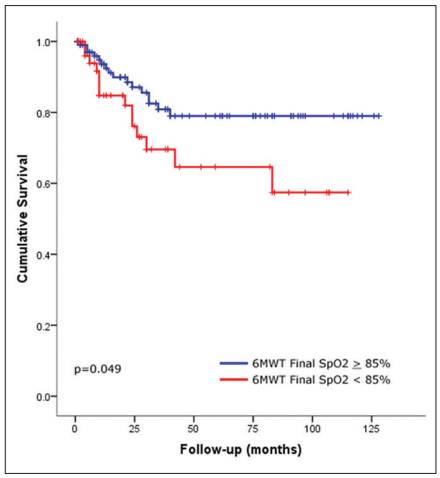

Figure 3: Kaplan–Meier survival estimates for interstitial lung disease patients with a 6-min walk test final oxygen saturation by pulse oximetry (SpO_2) <85% (red line) and those with SpO_2 ≥ 85% (blue line)

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.

Table 4: Variables predicting survival in the study cohort (*n*=169)

Variable	Unadjusted		Adjusted	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	1.086 (1.052-1.121)	<0.0001	1.072 (1.029-1.118)	0.001
Male sex	3.189 (1.507-6.751)	0.002		
Ever smoker	2.410 (1.174-4.946)	0.016		
BMI, kg/m^2	0.938 (0.883-0.996)	0.038		
IPF diagnosis	4.085 (2.042-8.169)	<0.0001	3.233 (1.241-8.428)	0.016
CTD-ILD diagnosis	0.666 (0.327-1.358)	0.264		
Sarcoidosis diagnosis	0.207 (0.028-1.515)	0.121		
FVC, percent predicted	0.972 (0.954-0.991)	0.004	0.955 (0.930-0.979)	<0.0001
DL_{CO}, percent predicted	0.982 (0.962-1.003)	0.089		
6MWD<300 m	3.733 (1.810-7.698)	<0.0001		
6MWT final saturation<85%	2.022 (0.985-4.150)	0.055		
mPAP, mmHg	1.046 (0.944-1.158)	0.390		
sPAP, mmHg	1.070 (1.017-1.126)	0.009		
dPAP, mmHg	1.045 (0.944-1.158)	0.395		
PCWP, mmHg	1.079 (0.960-1.213)	0.202		
PVR, Wood units	1.781 (0.933-3.403)	0.080		
CI, L/min/m^2	0.468 (0.281-0.780)	0.004	0.462 (0.251-0.852)	0.013
Oxygen supplementation	1.376 (0.684-2.769)	0.371		

HR=Hazard ratio, 95% CI=95% confidence interval, BMI=Body mass index, IPF=Idiopathic pulmonary fibrosis, CTD=Connective tissue disease, ILD=Interstitial lung disease, FVC=Forced vital capacity, DLco=Diffusion capacity of the lung for carbon monoxide, 6MWD=Six-minute walk distance, 6MWT=Six-minute walk test, SpO_2=Oxygen saturation by pulse oximetry, mPAP=Mean pulmonary artery pressure, sPAP=Systolic pulmonary artery pressure, dPAP=Diastolic pulmonary artery pressure, PCWP=Pulmonary capillary wedge pressure, PVR=Pulmonary vascular resistance, CI=Cardiac index

Another important observation in our study is that when we applied a cutoff value for the 6MWD at 300 m and 6MWT final SpO_2 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 mPAP ≥ 25 mmHg with low cardiac index (<2.0 L/min/m^2).[9] 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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Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Alhamad EH. Interstitial lung diseases in Saudi Arabia: A single-center study. Ann Thorac Med 2013;8:33-7.
2. Dhooria S, Agarwal R, Sehgal IS, Prasad KT, Garg M, Bal A, *et al*. Spectrum of interstitial lung diseases at a tertiary center in a developing country: A study of 803 subjects. PLoS One 2018;13:e0191938.
3. Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, Sanyal S, Brillet PY, Brauner M, *et al*. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. Eur Respir J 2017;50:1602419.
4. Nathan SD, Shlobin OA, Weir N, Ahmad S, Kaldjob JM, Battle E, *et al*. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest 2011;140:221-9.
5. Schwartz DA, Van Fossen DS, Davis CS, Helmers RA, Dayton CS, Burmeister LF, *et al*. Determinants of progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994;149:444-9.
6. Chan C, Ryerson CJ, Dunne JV, Wilcox PG. Demographic and clinical predictors of progression and mortality in connective tissue disease-associated interstitial lung disease: A retrospective cohort study. BMC Pulmonary Med 2019;19:192.
7. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, *et al*. Six-minute-walk test in idiopathic pulmonary fibrosis: Test validation and minimal clinically important difference. Am J Respir Crit Care Med 2011;183:1231-7.
8. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, *et al*. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:1084-90.
9. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, *et al*. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J 2019;53:1801914.
10. King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease: Dilemmas in diagnosis and the conundrum of treatment. Chest 2020. DOI:10.1016/j.chest.2020.04.046.
11. Hoeper MM, Behr J, Held M, Grunig E, Vizza CD, Vonk-Noordegraaf A, *et al*. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. PLoS One 2015;10:e0141911.
12. Kimura M, Taniguchi H, Kondoh Y, Kimura T, Kataoka K, Nishiyama O, *et al*. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. Respiration 2013;85:456-63.
13. Shlobin OA, Kouranos V, Barnett SD, Alhamad EH, Culver DA, Barney J, *et al*. Physiological predictors of survival in patients with sarcoidosis-associated pulmonary hypertension: Results from an international registry. Eur Respir J 2020;55:1901747.
14. Rose L, Prins KW, Archer SL, Pritzker M, Weir EK, Misialek JR, *et al*. Survival in pulmonary hypertension due to chronic lung disease: Influence of low diffusion capacity of the lungs for carbon monoxide. J Heart Lung Transplant 2019;38:145-55.
15. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
16. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, *et al*. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720-35.
17. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, *et al*. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511-22.
18. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, *et al*. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
19. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, *et al*: 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol 2019;71:1400-12.
20. Doria A, Mosca M, Gambari PF, Bombardieri S. Defining unclassifiable connective tissue diseases: Incomplete, undifferentiated, or both? J Rheumatol 2005;32:213-5.
21. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, *et al*. The WASOG sarcoidosis organ assessment instrument: An update of a previous clinical tool. Sarcoidosis, vasculitis, and diffuse lung diseases: Offic J WASOG 2014;31:19-27.
22. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al*. An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824.
23. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al*. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198:e44-68.
24. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, *et al*. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017;76:9-16.
25. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, *et al*. American College of Rheumatology classification criteria for Sjögren's syndrome: A data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2012;64:475-87.
26. Tani C, Carli L, Vagnani S, Talarico R, Baldini C, Mosca M, *et al*. The diagnosis and classification of mixed connective tissue disease. J Autoimmun 2014;48-49:46-9.
27. Travis WD, Costabel U, Hansell DM, King TE Jr., Lynch DA, Nicholson AG, *et al*. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-48.
28. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, *et al*. 2013 classification criteria for systemic sclerosis: An American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737-47.
29. King CS, Nathan SD. Idiopathic pulmonary fibrosis: Effects and optimal management of comorbidities. Lancet Respir Med 2017;5:72-84.