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Rising stars of DPLD survival: FVC and exercise desaturation (a single-center study)

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Background/aim: Diffuse parenchymal lung diseases (DPLDs) comprise a broad, heterogeneous group of diseases with common functional characteristics and a common final pathway, usually leading to irreversible fibrosis. We investigated the effects of the physiological and functional parameters and of pulmonary hypertension (PH) on survival in DPLDs.

Materials and methods: The study included 158 patients with DPLDs. Patient data were examined retrospectively, and survival status was obtained through phone calls.

Results: Patients were divided into five groups according to their diagnosis: idiopathic pulmonary fibrosis (IPF), non-IPF idiopathic interstitial pneumonias, connective tissue diseases, sarcoidosis, and other DPLDs. Median survival was 42.9 months. The significant negative effects of older age, presence of delta saturation (DeltaSat; difference between oxygen saturation at rest and after the 6-min walking test), 6-min walking distance (<350 m), systolic pulmonary artery pressure (sPAP; ≥50 mmHg), and baseline percentage of diffusing capacity of the lungs for carbon monoxide (<80%) with percentage of forced vital capacity (FVC%; <80%) were detected on survival ($P < 0.05$). A one-unit decrease in FVC% was related to a 6% increase in mortality. Another unique finding indicated that higher DeltaSat (>10%) correlated strongly with sPAP (>50 mmHg) and thus with a worse survival rate.

Conclusion: The current study determined that FVC% is important in the prediction of mortality. Moreover, it demonstrated a strong relationship between exercise desaturation and PH.

Key words: Desaturation, diffuse parenchymal lung diseases, forced vital capacity, survival, pulmonary hypertension

1. Introduction

Diffuse parenchymal lung disease (DPLD) is a heterogeneous category consisting of more than 200 diseases with similar clinical, radiological, and laboratory properties. These diseases lead to parenchymal lung injury and severe accumulation of interstitial protein and cells, associated with known or unknown causes (1,2). Although DPLD classification is somewhat complicated, a consensus report published by the American Thoracic Society (ATS) and the European Respiratory Society classified it into four main groups (3): DPLDs of known causes (collagen vascular diseases [CVDs], etc.), idiopathic interstitial pneumonias (IIPs), granulomatous DPLD (e.g., sarcoidosis), and other forms of DPLD (histiocytosis-X [HX], lymphangioleiomyomatosis [LAM], etc.). Idiopathic pulmonary fibrosis (IPF), which represents about half of the cases of IIPs, is a chronic progressive disease with poor treatment response and prognosis. Although sarcoidosis is a multisystemic granulomatous disease involving mostly the lungs and intrathoracic lymph nodes, it has a good prognosis. However, pulmonary parenchymal involvement is a poor prognostic factor in CVD; for example, life expectancy has been reported to decline by 3.5–4.9 years when pulmonary involvement is identified in cases with rheumatoid arthritis (4–6). Many survival studies have been conducted with subjects with IIPs and particularly with IPF. In these studies, factors such as diffusion capacity (DLCO), hypoxia (at room temperature and during exercise), exercise capacity, and pulmonary hypertension have an important effect on survival (7,8). The 6-min walking test (6MWT) is a simple, inexpensive, reproducible, and well-tolerated submaximal exercise test that is typically used in COPD and vascular diseases. In IIP patients (particularly severe cases), this test is also considered highly reliable and reproducible (9). Oxygen desaturation during the 6MWT according to cardiopulmonary exercise testing (CPET), even in the absence of resting hypoxia, is more

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often observed in IIP (10,11). Desaturation to 88% or less during baseline 6MWT is a more consistent and powerful predictor of mortality in IIP than desaturation during CPET (10,12,13). Exercise-induced desaturation has been identified as an important factor for predicting mortality (10–14). In an IPF-related study, a correlation was found between the 6MWT and pulmonary artery pressure (PAP). Pulmonary hypertension (PH) has recently been considered a potential complication of DPLD (15–17). This is encountered frequently in IPF, DPLD associated with CVD (particularly scleroderma and rheumatoid arthritis), sarcoidosis, and HX. PH development is a poor prognostic factor for determining mortality (18). Hence, current DPLD studies focus mainly on PH.

The goal of this retrospective study was to evaluate the effects of physiological and functional parameters and of PH on survival of DPLD patients.

2. Materials and methods

2.1. Patients' characteristics

The medical files of 158 patients who were admitted with the diagnosis of DPLD to the Interstitial Lung Disease Unit of Ankara University's Department of Chest Diseases from 2000 to 2008 were retrospectively evaluated.

Patient data on sex, age, diagnosis, and dates of diagnosis were recorded. Results of spirometric tests (FVC%, FEV1%, FEV1%/FVC%, FEF25–75, PEF) and results of single-breath carbon monoxide diffusion tests (DLCO, DLCO/VA) obtained in the upright sitting position at room temperature were recorded, as were arterial blood gas (pH, PaO2, PaCO2, SaO2) levels obtained at rest. Walking distance covered during the 6MWT, which was performed in a smooth corridor according to the ATS guidelines, was recorded. SaO2 was measured by a finger probe at rest and at the end of the test, and the difference (delta saturation [DeltaSat]) was recorded. The Borg dyspnea index was recorded at both the beginning and the end of the 6MWT.

Patients were divided into five groups according to diagnosis: IPF, non-IPF IIP, CVD, sarcoidosis, and other forms of DPLD. Patients were compared by grouping them as follows: age >65 years vs. <65 years; FVC <80% vs. >80% of predicted; DLCO <80% vs. >80% of predicted; FVC/DLCO ratio of <1.4 vs. >1.4; PaO2 <80 mmHg vs. >80 mmHg; 6MWT <350 m vs. >350 m; DeltaSat <4% (no desaturation), 4%–10%, and >10%.

The presence of PH was evaluated by the noninvasive method of echocardiography. On transthoracic echocardiography, systolic pulmonary artery pressure (sPAP) was calculated using the tricuspid regurgitation flow. Subjects with sPAP above 35 mmHg were diagnosed with PH, and patients were grouped according to sPAP as follows: <35 mmHg, 35–50 mmHg, and ≥50 mmHg.

The survival of patients was determined by phone calls and recorded.

This study was approved by the Ethics Committee of Ankara University.

2.2. Statistical evaluation

Statistical analysis was performed using SPSS 13.0 for Windows. Results were presented as mean ± SD. Comparison of parameters between groups was performed using the Mann–Whitney U test, Wilcoxon test, and Student t-test. Patient and diagnostic groups were compared using the chi-square test (Pearson chi-square and Fisher exact test). $P < 0.05$ was considered statistically significant. Survival rate analysis was performed using the Kaplan–Meier and Cox regression analysis tests.

3. Results

3.1. Demographic characteristics and variables

Of the 158 patients enrolled in the study, 91 (57.6%) were female and 67 (42.4%) were male. The mean age was 58.9 ± 14.02 years, and the mean survival time was 42.9 ± 35.7 months. Baseline demographic characteristics and variables of the study population are shown in the Table.

The Kaplan–Meier test was used to evaluate the factors affecting the survival rate. Male and female subjects did not differ with respect to survival rate. Older patients (>65 years) survived for a significantly shorter time than did younger patients (<65 years): 98.18 months vs. 147.74 months, respectively ($P < 0.05$). An evaluation of the survival rate of patients with regard to diagnosis showed

Table. Baseline demographic characteristics and variables of study population (n =158).

Variables	Values
Age (years)	59 ± 14
Male/female	67/91 (42%/58%)
Resting cardiopulmonary parameters	
FVC% predicted	80.8 ± 24.1
FEV1% predicted	82 ± 24.3
FVC/DLCO	1.61 ± 0.6
DLCO% predicted	57.8 ± 24.7
SpO2 at rest (%)	95.1 ± 6.5
Exercise capacity, desaturation, and pulmonary hypertension	
6MWT (m)	372.5 ± 132.8
ΔSpO2 (%)	10.1 ± 5.3
sPAP (mmHg)	31.5 ± 15.9

that IPF patients' survival was significantly worse than that of patients in the other DPLD groups (P < 0.05). Most cases of death were registered in the IPF group, whereas no deaths were reported in the sarcoidosis group.

3.2. Physiological and functional parameters

Of the spirometric tests, two parameters considered valuable in the follow-up of such patients are FVC% of predicted and DLCO% of predicted. The subjects with FVC <80% of predicted survived for a shorter period of time than those with >80% predicted: 118.5 months vs. 144.19 months, respectively (P < 0.05, Figure 1a). Similarly, the subjects with lower DLCO (<80% of predicted) survived for a shorter period of time than those with higher DLCO (>80% of predicted) (P < 0.05, Figure 1b). We also investigated the effect of FVC/DLCO (≥1.4 and <1.4) on survival, but no difference was found.

Subjects with hypoxemia (<80 mmHg) have a decreased survival rate compared to normoxemic ones (>80 mmHg) (P < 0.05, Figure 1c). Different levels of PaO2 (<40 mmHg, 40–60 mmHg, 60-80 mmHg, and >80 mmHg) were also compared with respect to survival, but no significant difference was found.

The patients who walked less than 350 m in the 6MWT survived for a shorter period of time than those who walked more than 350 m: 115.7 months vs. 145.9 months, respectively (P < 0.05, Figure 1d). The desaturation level of the subjects in the 6MWT was also evaluated. Seventy-nine participants (50%) desaturated during the 6MWT. Of these, 49% desaturated by 4%–10%, and 51% desaturated

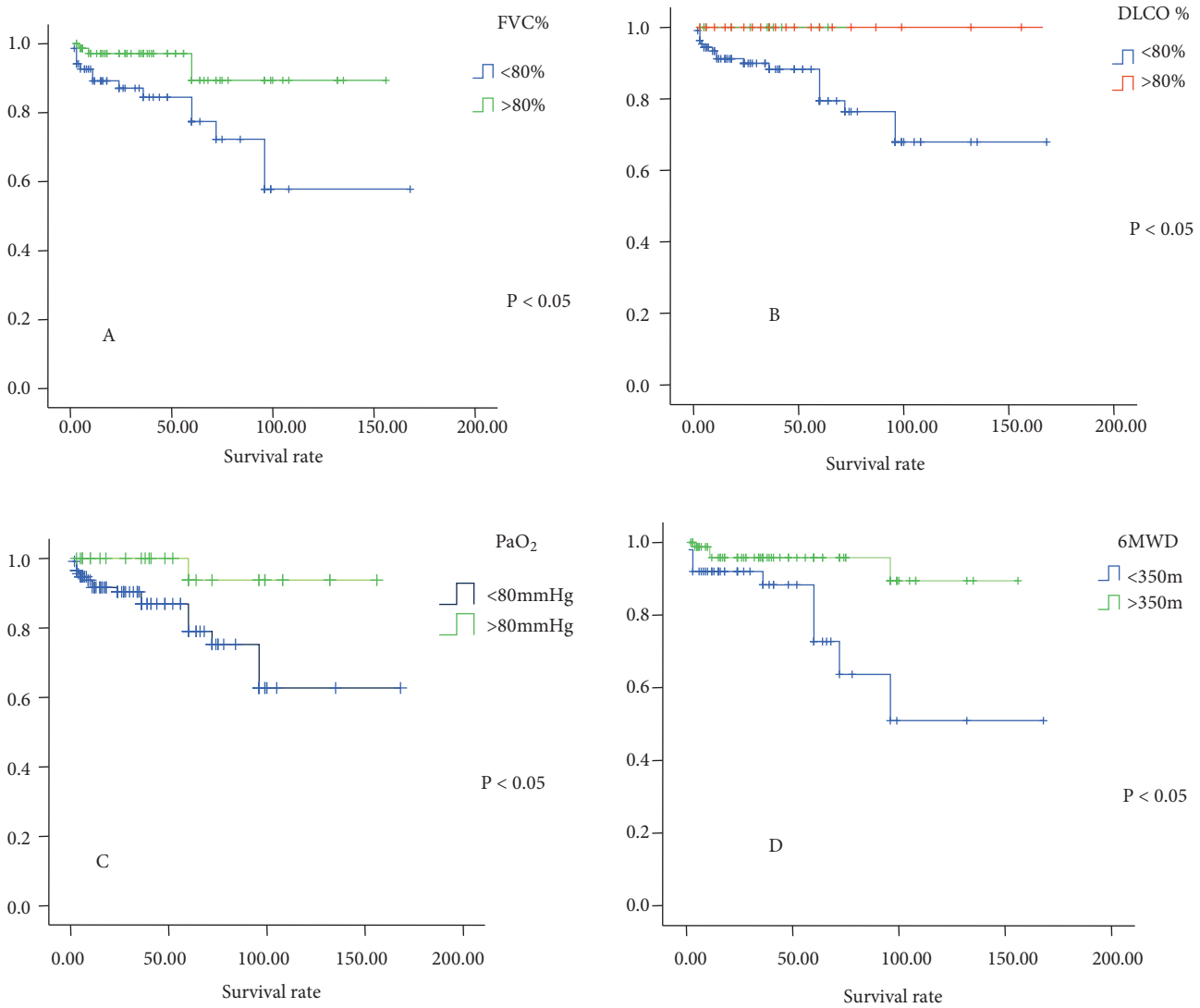

Figure 1. a) Relationship between FVC% and survival rate in all patients. b) Relationship between DLCO% and survival rate in all patients. c) Relationship between hypoxia and survival rate. d) Relationship between 6MWT and survival rate in all patients.

by >10%. The subjects with less desaturation (DeltaSat 4%–10%) and those with higher desaturation (DeltaSat >10%) differed significantly in terms of survival: 153.1 vs. 125.9 months, respectively (P < 0.01, Figure 2).

3.3. Pulmonary hypertension

The survival rate was better in subjects without PH (sPAP <35 mmHg) than in those with PH (sPAP 35–50 mmHg and >50 mmHg): 141.4 months vs. 99.96 months vs. 93.86 months, respectively (P < 0.01, Figure 3).

A strong relationship between DeltaSat and sPAP was found. Accordingly, more than 10% DeltaSat suggests PH (sPAP >50 mmHg) (Figure 4, P < 0.001).

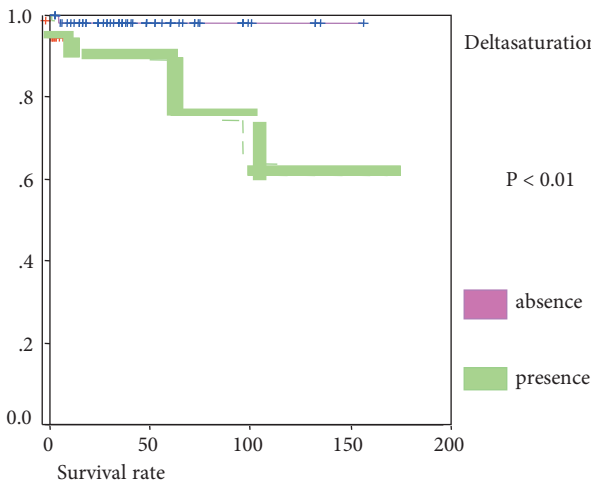

Figure 2. Relationship between the presence of DeltaSat and survival rate.

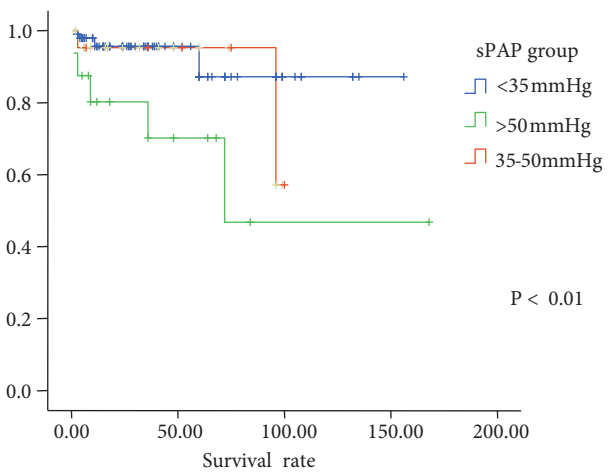

Figure 3. Relationship between sPAP values and survival rate in all patients.

All factors that we considered to have an effect on patients' survival rates, including age, sex, FVC%, DLCO%, FVC/DLCO, PaO2, 6MWT, presence of desaturation after 6MWT, and sPAP values, were evaluated using Cox regression analysis. Among all these parameters, only FVC% had an effect on survival rate (predicting factor for mortality). The most remarkable result indicated that mortality increased by a rate of 6.3% when FVC% decreased by one unit in DPLD and by 6.4% in IPF patients.

4. Discussion

This is the first and largest single-center study in Turkey addressing the effect of physiological changes on the survival of DPLD patients. One of the unique findings of this study is that a one-unit decrease in FVC% increases the mortality rate by more than 6% in DPLD and IPF patients. It is known that restrictive ventilatory defects are commonly encountered in DPLD due to fibrosis. Lung function tests are used in DPLD to identify the severity of the disease, follow up on the course of the disease, evaluate treatment responses, and predict the mortality rate of patients. There is no similar study in the literature that has established the relationship between the degree of decrease in FVC% and mortality in IIPS. Previous studies have reported only that a decrease in FVC and DLCO in patients with IIP predicts mortality (19–23). The British Thoracic Society (BTS) reported that 6–12 months of follow-up of patients with IPF demonstrated that a ≥10% decrease of FVC% or a ≥15% decrease in DLCO% led to an increase in mortality (24).

Consistent with previous findings, sex did not have any effect on survival; however, younger patients survived longer than older patients, as expected (19). The survival of IPF patients was significantly shorter than that of the other DPLD patients.

The detection of a specific threshold value that would help to differentiate the results for respiratory function is an expected factor (24). Consistent with previous studies, the current study found a low basal PaO2, FVC%, and 6MWT in patients with DLCO% <80; found that they were desaturated at the end of exercise; and found that patients with DLCO% <80 survived for shorter periods of time than those with DLCO% >80 (19,23).

Multivariate linear analysis showed that in determining the development of PH, the FVC%-to-DLCO% ratio had a positive predictive value of 71% and a negative predictive value of 81% (25); another study demonstrated that a DLCO% of <55 and a FVC%-to-DLCO% ratio of >1.4 indicated a relationship with PH (26). In light of these reports, we also investigated the FVC%-to-DLCO% ratio. Similarly, PH was more prevalent in subjects with a higher ratio in the present study. However, no relationship was found between this ratio and survival rate.

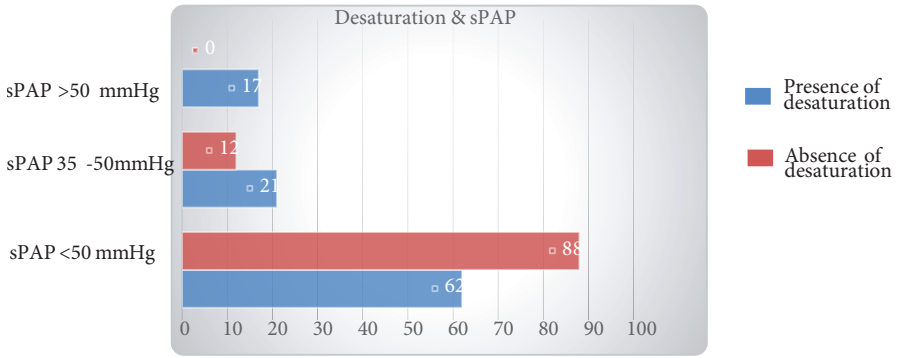

Figure 4. Relationship between DeltaSat and sPAP values.

We compared mortality rates between the patients with no desaturation and those with 4%–10% and >10% desaturation. The patients with more than 10% desaturation survived for shorter time periods than the other patients. Although arterial oxygen saturation is normal at rest in cases with interstitial lung disease (ILD), desaturation is generally observed during exercise. Desaturation is often associated with anatomical shunt development and decrease in diffusion capacity (27). In the context of DPLD, although the 6MWT is a simple test, only a few studies have shown its prognostic significance in IPF (12–14,28) and one study has done so in a mixed cohort of IPF and nonspecific interstitial pneumonia (11). None of the previous studies reported a constant threshold value for the 6MWT in meters and oxygen desaturation degree. In these studies, 350 m or 400 m for the 6MWT and >4% value for oxygen desaturation were often used (29–31). Even though different views of the relationship between 6MWT and mortality have been reported, there was a consensus that desaturation (>4%) is a strong factor in predicting mortality in IPF (12,13). Oxygen desaturation in IPF patients at baseline 6MWT was also shown to be a stronger prognostic factor compared to lung function tests in the BTS Guidelines on ILD (Evidence C) (24).

The most remarkable result of the present study is that in PH (in which sPAP was ≥50 mmHg), DeltaSat (≥10%) was more prevalent. To the best of our knowledge, this is a unique finding in English-language research. Although PH is the most well-known complication of interstitial lung disease, it has not been adequately investigated (16,17). Recent pathophysiological studies have revealed the role of PH in the course of ILD and the benefits of specific treatments. PH is most commonly observed in diseases such as IPF, CVD, and sarcoidosis. In our study, patients with sPAP >35 mmHg were also observed more commonly in the IPF and CVD groups. The development of PH increases mortality risk in DPLD (31,32). Consistent with previous studies, subjects with increased sPAP had a lower life expectancy. Additionally, in a sarcoidosis study, the authors did not find any relationship between 6MWT and increased sPAP, but desaturation in the 6MWT (DeltaSat) was reported to be an independent factor in the determination of PH (33). Furthermore, DLCO% of <35, observation of DeltaSat (>10%), and the need for oxygen supply have been demonstrated as predictive factors for PH (28,31–37). PH was suggested to have a poor prognosis, and mean life expectancy was reported to be less than 1 year in patients with sPAP >50 mmHg (32). However, no study has evaluated the relationship between PH and DeltaSat rates. This result indicates that significant DeltaSat (especially >10%) at 6MWT points to PH, thereby hindering further laboratory research and thus reducing medical expenditure.

Studies have argued for different decreased values of FVC% during a 6- or 12-month follow-up period (10% or 15%) in IIPs (22,38). In addition, some authors investigating only biopsy-proven IPF patients suggested that the presence of a honeycomb image at the end of a 3-year follow-up indicates a decrease in survival (39). Flaherty et al. showed that within a group that desaturated below 88%, serial decline in DLCO was the strongest predictor of mortality. This study also demonstrated an increased mortality risk in the group that maintained SpO2 above 88% when there was a serial decline in forced vital capacity (FVC) or increasing desaturation (13). In studies with IPF, age, male sex, low body mass index, significant increase in dyspnea, severe physiological abnormalities, high degree of fibrosis, and poor treatment response as well as frequent hospitalization and also a few biomarkers (matrix metalloproteinase-7, surfactant protein-D, Krebs von den Lungen-6, surfactant protein-A, etc.) were reported as predictive factors for a decreased survival rate (19,39–43). Consistent with the literature, in this study, older age, observation of DeltaSat, sPAP ≥35 mmHg, 6MWT <350 m, and FVC <80% were also predictive factors for a decreased survival rate.

The retrospective nature of the present study and the small number of subjects in each group of DPLD patients are this study's limitations. In conclusion, this study confirms that FVC is an important predictor of mortality. DeltaSat (>10%) is another important predictor of mortality and it is also strongly indicative of PH.

References

1. Cosgrove GP, Schwarz MI. Approach to the evaluation and diagnosis of interstitial lung disease. In: Schwarz MI, King TE, editors. Interstitial Lung Disease. 5th ed. Shelton, CT, USA: People's Medical Clearing House; 2011. pp. 3-25.
2. Antin-Ozerkis D. Interstitial lung disease: a clinical overview and general approach. In: Fishman AP, editors. Fishman's Pulmonary Diseases and Disorders. 5th ed. New York, NY, USA: McGraw-Hill; 2015. pp. 810-822.
3. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. General principles and recommendations. Am J Crit Care Med 2002; 165: 277-304.
4. Leslie KO, Trahan S, Gruden J. Pulmonary pathology of the rheumatic diseases. Semin Respir Crit Care Med 2007; 28: 369-378.
5. King TE. Connective tissue disease. In: Schwarz MI, King TE editors. Interstitial Lung Disease. 3rd ed. London, Canada: BC Decker; 1998. pp. 451-505
6. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, Eklund A, Kitaichi M, Lynch J, Rizzato G et al. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16: 73-149.
7. O'Donnell DE, Fitzpatrick MF. Physiology of interstitial lung disease. In: Schwarz MI, King TE Jr, editors. Interstitial Lung Disease. 4th ed. London, Canada: BC Decker; 2003. pp. 54-74.
8. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six minute walk test. Am J Respir Crit Care Med 2002; 166: 111-117.
9. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Sahn SA, Szwarcberg J 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: 1231-1237.
10. Eaton T, Young P, Milne D, Wells AU. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005; 171: 1150-1157.
11. Blanco I, Villaquiran C, Valera JL, Molina-Molina M, Xaubet A, Rodriguez-Roisin R, Barbera JA, Roca J. Peak oxygen uptake during the six-minute walk test in diffuse interstitial lung disease and pulmonary hypertension. Arch Bronconeumol 2010; 46: 122-128.
12. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP 3rd et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003; 168: 1084-1090.
13. Flaherty KR, Andrei AC, Murray S, Fraley C, Colby TV, Travis WD, Lama V, Kazerooni EA, Gross BH, Toews GB et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006; 174: 803-809.
14. Lettieri CJ, Nathan SD, Browning RF, Barnett SD, Ahmad S, Shorr AF. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med 2006; 100: 1734-1741.
15. Maloney JP. Advances in the treatment of secondary pulmonary hypertension. Curr Opin Pulm Med 2003; 9: 139-143.
16. Shapiro S. Management of pulmonary hypertension resulting from interstitial lung disease. Curr Opin Pulm Med 2003; 9: 426-430.
17. Strange C, Highland KB. Pulmonary hypertension in interstitial lung disease. Curr Opin Pulm Med 2005; 11: 452-455.
18. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J 2008; 31: 1357-1367.
19. du Bois R, Albera C, Bradford W, Costabel U, Hormel P, King T Jr, Noble P, Szwarcberg J, Thomeer M, Valeyre D et al. Predictors of mortality in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009; 179: A1114.
20. Hanson D, Winterbauer RH, Kirtland SH, Wu R. Changes in pulmonary function test results after 1 year therapy as predictors of survival in patients with idiopathic pulmonary fibrosis. Chest 1995; 108: 305-310.
21. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, Travis WD, Flint A, Toews GB, Lynch JP 3rd et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003; 168: 543-548.
22. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, Veeraraghavan S, Hansell DM, Wells AU. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003; 168: 531-537.
23. Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, Kim WS, Kim WD, Lee JS, Travis WD et al. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005; 171: 639-644.
24. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, Hirani N, Hubbard R, Lake F, Millar AB et al. Interstitial Lung Disease Guideline: The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008; 63 (Suppl. 5): 1-58.
25. Zisman DA, Ross DJ, Belperio JA, Saggar R, Lynch JP 3rd, Ardehali A, Karlamangla AS. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2007; 101: 2153-2159.
26. Steen VD, Graham G, Conte C, Owens G, Medsger TA Jr. Isolated diffusing capacity reduction in systemic sclerosis. Arthritis Rheum 1992; 35: 765-770.
27. Agusti AG, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. Am Rev Respir Dis 1991; 143: 219-225.

28. Hallstrand TS, Boitano LJ, Johnson WC, Spado CA, Hyes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J 2005; 25: 96-103.

29. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension in sarcoidosis. Eur Respir J 2008; 32: 296-302.

30. Villalba WO, Sampaio-Barros PD, Pereira MC, Cerqueira EMFB, Leme CA, Marques-Neto JF, Paschoal IA. Six minute walk test for evaluation of pulmonary disease severity in scleroderma patients. Chest 2007; 131: 217-222.

31. Cote CG, Casanova C, Marin JM, Lopez MV, Pinto-Plata V, de Oca MM, Dordelly LJ, Nekach H, Celli BR. Validation and comparison of reference equations fort the 6-min walk distance test. Eur Respir J 2008; 31: 571-578.

32. Lettieri C, Nathan SD, Barnett S, Ahmad S, Shorr A. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129: 746-752.

33. Shorr A, Wainright JL, Cors CS, Lettieri C, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplantation. Eur Respir J 2007; 30: 715-721.

34. Shorr A, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 2003; 124: 922-928.

35. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune I, Valeyre D, Cordier JF et al. Combined pulmonary fibrosis and emphysema: a distinct under recognised entity. Eur Respir J 2005; 26: 586-593.

36. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest 2007; 131: 657-663.

37. Collard HR, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003; 168: 538-542.

38. Gay SE, Kazerooni EA, Toews GB, Lynch JP 3rd, Gross BH, Cascade PN, Spizarny DL, Flint A, Schork MA, Whyte RI et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med 1998; 157: 1063-1072.

39. Nadraus H, Pellikka P, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, Ryu JH. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005; 128: 2393-2399.

40. Perez A, Rogers RM, Dauber JH. The prognosis of idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol 2003; 29 (Suppl. 3): 19-26.

41. Kishaba T, Nagano H, Nei Y, Yamashiro S. Body mass index—percent forced vital capacity—respiratory hospitalization: new staging for idiopathic pulmonary fibrosis patients. J Thorac Dis 2016; 8: 3596-3604.

42. Richards TJ, Kaminski N, Baribaud F, Flavin S, Brodmerkelet C, Horowitz D, Li K, Choi J, Vuga LJ, Lindell KO et al. Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012; 185: 67-76.

43. Hamai K, Iwamoto H, Ishikawa N, Horimasu Y, Masuda T, Miyamoto S, Nakashima T, Ohshimo S, Fujitaka K, Hamada H et al. Comparative study of circulating MMP-7, CCL18, KL-6, SP-A, and SP-D as disease markers of idiopathic pulmonary fibrosis. Dis Markers 2016; 2016: 4759040.