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The impact of FVC/DLCO ratio on diagnosis of pulmonary hypertension and disease prognosis in idiopathic pulmonary fibrosis

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ABSTRACT

Introduction: Idiopathic pulmonary fibrosis is a chronic progressive fibrotic lung disease of unknown etiology that occurs most commonly in older adults. The presence of pulmonary hypertension in Idiopathic pulmonary fibrosis is associated with poor prognosis and mortality. Literature suggests that the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio has a positive predictive value for the diagnosis of pulmonary hypertension. Therefore, this study aimed to investigate the impact of forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio on the diagnosis of pulmonary hypertension and disease prognosis in Idiopathic pulmonary fibrosis patients.

MATERIAL AND METHOD: Forty-eight patients diagnosed with Idiopathic pulmonary fibrosis were included in the study. Patient records, echocardiographic and spirometric data were retrospectively reviewed.

Results: The average pulmonary arterial pressure was observed to be 32.8 (±9) mmHg, with the second-year follow-up pulmonary arterial pressure at 40.8 (±17.2) mmHg and the fourth-year follow-up pulmonary arterial pressure at 51 (±23.6) mmHg. In those diagnosed as pulmonary hypertension, the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio was initially 1.54 (±0.72). By the second year, it was 1.61 (±0.45), and by the fourth year, it was 1.87 (±0.8). It was found that the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio tended to increase when pulmonary artery pressure increased during the follow-up period.

Conclusion: We found that low six- minute walking test distance was an important marker for the diagnosis of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and that the presence of desaturation was also significantly associated with survival in pulmonary hypertension. Although we did not find it statistically significant, we found that both pulmonary arterial pressure and the the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio increased with progressive disease duration after diagnosis in patients with IPF. We believe that the the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio is an important marker for early detection of pulmonary hypertension and prognosis in idiopathic pulmonary fibrosis.

Keywords: Idiopathic pulmonary fibrosis, pulmonary hypertension, diffusion capacity

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic lung disease of unknown etiology that commonly occurs in older adults and is characterized by a histopathologically or radiologically typical interstitial pneumonia pattern (1). In IPF, symptoms develop over time and are usually associated with exertional dyspnea and dry cough. Progressive dyspnea is an important symptom that indicates disease progression and mortality (2).

Pulmonary function tests are essential for monitoring the clinical course of IPF. Forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) are considered the most critical parameters of pulmonary function tests (PFT) in IPF patients (3). The rate of decline of FVC has been used as a marker of disease progression because it is associated with mortality (4). Diffusion capacity of the lung for carbon monoxide measures another physiological deficiency (gas diffusion) associated with pulmonary fibrosis. It has also been reported to be associated with pulmonary hypertension

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(PH), considered a crucial concomitant disease of IPF. Forced vital capacity and DLCO may not be equally affected in pulmonary fibrosis, and pulmonary function test results may be normal in some IPF patients (3).

The presence of comorbidities in IPF patients may affect survival and quality of life and lead to disease progression. Some comorbidities, such as PH, may also be a consequence of IPF itself (5). The presence of PH in IPF is significantly associated with poor prognosis and mortality. In particular, concomitant pulmonary vascular disease in patients with advanced pulmonary parenchymal disease results in worse outcomes than a diagnosis of IPF alone (6). The overall prevalence of PH in IPF has been reported to be 36-86% and is attributed to hypoxemic vasoconstriction and destruction due to progressive fibrosis of the vascular bed (7). Presyncope or syncope, dyspnea not consistent with radiology and PFT, severely reduced diffusion capacity (DLCO < 30% predictive value), short walking distance, oxygen saturation below 85%, worsening heart rate during 6-minute walking test (6-MWT), also elevated BNP, pulmonary artery diameter/aortic diameter > 1 on thorax computed tomography (CT), increased right ventricular systolic pressure on echocardiography, enlargement of right heart chambers, and right ventricular dysfunction strongly suggest PH in a patient with IPF. However, the relationship between pulmonary artery pressure (PAP) and respiratory functions and the extent of fibrosis has not been demonstrated radiologically. Studies have shown that specific treatment is not effective in PH due to IPF and, in some cases, even leads to clinical worsening. Therefore, specific drug therapy has no place in PH due to IPF. However, it is recommended that patients with FVC greater than 70% and mean PAP > 35 mmHg measured by central cardiac catheterization should be referred to pulmonary artery hypertension (PAH) centers for treatment (8-11).

In the literature, the ratio of FVC to DLCO (FCV/DLCO) > 1.5 in patients with systemic sclerosis has been interpreted as an indicator of PH. In addition, the FVC/DLCO ratio has been shown to have a positive predictive value of 71% and a negative predictive value of 81% in determining PH development (12). Moreover, it has been shown in the literature that DLCO% < 55% and FVC/DLCO ratio > 1.4 may indicate the presence of PH (13,14). In view of this information, the aim of this study is to investigate whether FVC/DLCO ratio can be used to diagnose PH in IPF patients and what impact it has on prognosis.

MATERIAL AND METHOD

The study was carried out with the permission of Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.06.2022, Decision No: 2012-KAEK-15/2538). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was not obtained from the patients due to retrospective design.

The medical records of 72 patients who were followed up with the diagnosis of radiological and/or pathological IPF in our hospital's 8th Chest Diseases Polyclinic between January 2014 and June 2017 were retrospectively reviewed. Patients who did not have PFTs and echocardiographic examination at baseline, who were not followed up in the following 4 years, and who had comorbidities that could lead to an increase in PAP, such as heart failure, COPD, and collagen tissue disease, were excluded from the study. Thus, 48 patients could be enrolled in the study.

Data Collection

Gender, age, comorbidities, diagnosis dates, 6-MWT results at diagnosis, spirometric tests (FVC%, FEV1%, FEV1%/FVC% ratio, DLCO) and the pulmonary parenchymal findings on thorax CT at diagnosis, transthoracic echocardiography data at baseline and at the following 2 and 4 years, were retrospectively obtained from the hospital medical records system and patient files. Data were analyzed and recorded by the same researchers.

The presence of PH was determined by noninvasive transthoracic echocardiography. Transthoracic echocardiographic analysis was performed using a Philips HD 11 XE ultrasound machine with an S5-1 transducer (Koninklijke Philips N.V., Amsterdam, The Netherlands). Echocardiographic examination was done in the left lateral decubitus position. Evaluation of PAP was made by calculating the systolic transtricuspid gradient (by Bernoulli's equation using the maximum tricuspid regurgitation velocity measured by continuous wave Doppler) and adding an assumed right atrial pressure (15). A systolic PAP above 30 mmHg on echocardiography was accepted as the presence of PH.

Spirometry was performed to determine FVC, forced expiratory volume in one second (FEV1), and FEV1/FVC with a spirometer (AS-507, Minato Medical Science, Tokyo, Japan) in accordance with the American Thoracic Society-European Respiratory Society guidelines (ATS-ERS) (16). The FVC and DLCO values obtained during the spirometric tests were calculated, and their relationship with the presence of PH was investigated. The distance traveled in a straight corridor during the 6-MWT was recorded according to ATS guidelines (17). By assigning points for each variable (gender, age, FVC, DLCO) in the GAP index and staging system, a total score between 0 and 8 was obtained (18).

Statistical Analysis

Subgroups were formed for binominal regression analysis, with age cutoff at 65 years, six-minute walking test at 370 meters, and desaturation defined as saturation on room air of 88% or less. For the overall evaluation of gender, age, and lung function, the GAP index was used as an additional parameter by removing the above parameters after the initial analysis for confirmation. To evaluate the distribution of the parameters, the Kolmogorov-Smirnov test was performed. Accordingly, Pearson or Kendall's tau was used for correlation analysis. A comparison of parameters and their role in predicting PH was made by regression analysis. A p-value of less than 0.05 was accepted as statistically significant. If present, any parameter with a proportion of missing data greater than 10% of total participants should be removed from the study. The statistical analysis program used was International Business Machines (IBM) Statistical Product and Service Solutions (SPSS) Edition 23.

RESULTS

A total of 48 patients were eligible for the study. All patients were on antifibrotic treatment. The mean age of the group was 65.9 (±7.01) years, and 6.2% (n=3) of the patients were female. Most patients were diagnosed by radiological examination (81.3%, n=39), and the GAP index staging of patients was in favor of stage 1 (45%, n=22). Family history was not present in most patients (95.8%, n=46). The mean package/year smoking was 27.6 (19.6), with 68.8% (n=33) of patients being ex-smokers, 14.6% (n=7) active smokers, and the remaining 16.7% (n=8) nonsmokers. Desaturation was absent in the majority of patients, with 16 (33.3%) patients classified as moderate and severe for severity of desaturation, and the mean pulse oximeter saturation score without supplemental oxygen support was 92% (±6) (**Table 1**).

Mean pulmonary artery pressure was 32.8 (±9) mmHg and increased to 40.8 (±17.2) during the follow-up period and to 51 (±23.6) at the last examination. A greater decrease in DLCO was observed in patients diagnosed with PH than in patients without PH, with the difference increasing during the follow-up period. At baseline, patients with PH had a mean DLCO of 43.8% (±15.3), compared with 59.4 (±18.5) in patients without PH, which increased from 40.4% (±16.5) to 76.1% (±17.3) at the final examination. The FVC/DLCO ratio showed a similar pattern: in those diagnosed with PH, the ratio was first 1.54 (±0.72), then 1.61 (±0.45), and finally 1.87 (±0.8), compared with 1.28 (±0.43), 1.19 (±0.43), and 1.07 (±0.09), respectively, in patients without PH during the follow-up period (**Table 2**).

Table 1. Demographic Data, Pulmonary Fibrosis Status and History

Age (Years,SD)	65.9 (7.01)
Sex (n, %)	
Male	45 (93.8)
Female	3 (6.2)
Diagnostic Method (n,%)	
Radiologic	39 (81.3)
Pathologic	9 (18.7%)
GAP Index Stage (n,%)	
Stage 1	22 (45)
Stage 2	13 (27.1)
Stage 3	13 (27.1)
Familial History (n,%)	
No	46 (95.8)
Yes	2 (4.2)
Smoking History (n,%)	
Nonsmoker	8 (16.7)
Active Smoker	7 (14.6)
Ex Smoker	33 (68.8)
Smoking Duration (Package*Year,SD)	27.6 (19.6)
Finger Clubbing (n,%)	
Absent	28 (58.3)
Present	20 (41.7)
Six Minute Walking Test (m, SD)	414 (120)
Saturation (%, SD)	92 (6)
Desaturation Severity (n, %)	
no	6 (12.5)
mild	26 (54.2)
moderate	6 (12.5)
severe	10 (20.8)

SD:Standart Deviation,GAP Index: Scoring system for pulmonary fibrosis severity.

Table 2. Echocardiography PAP, Pulmonary Hypertension and Pulmonanry Function Test Results During Diagnosis and Follow-up

	Diagnosis	1. Follow-up	2. Follow-up
PAP (mmHg,SD)	32.8 (9)	40.8 (17.2)	51 (23.6)
FVC (%,SD)	68.8 (16.5)	68.9 (16.5)	70.9 (18.4)
PHT Presence	62.5 (16.2)	60.2 (16.5)	63 (16.7)
No PHT	68.8 (15.8)	69.6 (12.3)	81.2 (17.6)
FEV (%,SD)	73 (17.0)	72.9 (17.0)	75.9 (17.2)
PHT Presence	64.2 (14.2)	64.1 (15.7)	69.3 (13.5)
No PHT	73.8 (16.8)	74.3 (14.7)	82.8 (19.6)
FVC/DLCO (SD)	1.32 (0.49)	1.37 (0.5)	1.5 (0.65)
PHT Presence	1.54 (0.72)	1.61 (0.45)	1.87 (0.8)
No PHT	1.28 (0.43)	1.19 (0.43)	1.07 (0.09)
DLCO (%,SD)	57.4 (18.4)	55.6 (19.2)	54.9 (21)
PHT Presence	43.8 (15.3)	39.3 (11.8)	40.4 (16.5)
No PHT	59.4 (18.5)	63.33 (18.8)	76.1 (17.3)

PAP: Pulmonary Artery Pressure. SD: Standart Deviation, PHT: Pulmonary Hypertension. FEV: Forced Expiratory Flow, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of Lung for Carbon Monoxide

Binominal logistic regression was performed to evaluate the influence of age, gender, performance parameters,

and FVC/DLCO ratio on the presence of PH during the follow-up period. The logistic regression model proved not to be statistically significant ($\chi2(4)=10.427$, p=0.108) and explained (Nagelkerke R2) 30.2% of the variance in PH. Of all parameters, only 6-MWT played a role in PH, with higher walking distance reducing the likelihood that PH occurred during follow-up. No correlation was found with the FVC/DLCO ratio (p=0.407) (**Table 3**).

Table 3. Logistic Regression AnalysisRegardingParameters on Pulmonary Hypertension

	B	SE	Wald	df	p
Gender	0.194	1.605	0.015	1	0.904
Age	0.031	0.055	0.313	1	0.576
Finger Clubbing	0.132	0.776	0.029	1	0.864
Six Minute Walking Test (m)	-0.011	0.005	4.831	1	0.028
Saturation (%)	0.071	0.106	0.444	1	0.505
FVC/DLCO	0.627	0.756	0.688	1	0.407
Constant	-5.694	10.487	0.295	1	0.587

Note: Gender is for females compared to males. Saturation result was taken from finger pulse oximeter at room air.

When evaluating the parameters in the regression analysis to predict PHT for survival, only saturation was found to be statistically correlated with survival in the Kendall-Tau correlation, with a saturation value of less than 88% in room air having a negative correlation with survival (correlation coefficient -0.434, p:0.003) (**Table 4**).

Table 4. Correlation between Parameters and Survival

Correlation to Survival	Correlation Coefficient	Sig. (2-tailed)	N
Age	0.014	0.923	48
Six Minutes Walking Test	-0.205	0.160	48
Desaturation	-0.434	0.003	48
FVC/DLCO	-0.213	0.163	44
PAB	0.049	0.735	48
Gender	-0.248	0.090	48

Note: Gender is for females compared to males. Saturation result was taken from finger pulse oximeter at room air and a result below 88% was accepted as desaturation. For age, patients were divided at 65 years old cut off. 370 meters were accepted as the SMWT cut-off. A ratio of FVC/DLCO at 0.88 was defined as the cut-off for the binomial analysis.

Area under the curve (AUC) analysis for the role of the FVC/DLCO ratio in classifying the presence of PH yielded a value of 0.624 and was not considered a highly predictive model (p:0.176). An FVC/DLCO ratio greater than 0.83 had a sensitivity and specificity of 93% and 96%, respectively, whereas a higher ratio of 1.2 had a sensitivity of only 50% and a specificity of 42% for predicting PH (**Figure 1**).

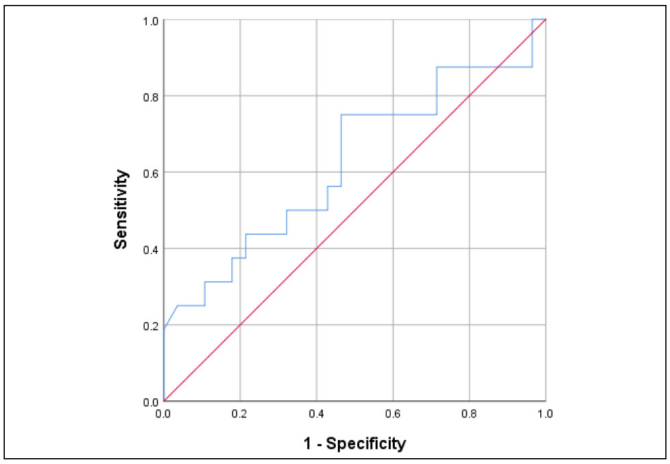

Figure 1. ROC Curve for FVC/DLCO and Pulmonary Hypertension Diagnosis During Follow-up.

DISCUSSION

The literature reports that the FCV/DLCO ratio is a useful marker for the diagnosis of PH (12,13). In our study, we investigated the usability of the FVC/DLCO ratio in IPF patients who also had PH. Consistent with the literatüre, we found that, DLCO was lower in patients with PH; and it was observed that DLCO tended to decrease as PAP increased during the follow-up. It was also observed that FVC/DLCO ratio was higher with the increase of PAP in the follow-ups; however, there was no statistical association between the presence of PH and this situation.

It has been reported that the prevalence of PH in IPF depends on the severity of IPF. In the early stages, PH affects <10% of patients. However, as IPF progresses, the prevalence of PH increases significantly (19). In the study by Teramachi et al. (18), the annual PAP change in patients with IPF was found to be 1.8 mmHg, and PAP was defined as an independent variable for mortality. Two other studies found that the frequency of PH on echocardiographic examination of patients with IPF ranged from 28 to 46% (9, 20). In our study, the frequency of PAP was lower at baseline, consistent with the literature, but increased with disease progression.

It is well known that restrictive ventilatory defects are common in IPF due to parenchymal fibrosis. Previous studies have reported that a decrease in FVC and DLCO predicts mortality in interstitial lung disease (21,22). Dyspnea, decreased DLCO, and rapid desaturation on exercise have been associated with the development of PH in IPF (20). In our study, the DLCO percentage was lower in patients with PH. It was observed that PAP tended to decrease, whereas PAP increased in periodic controls. In our study, DLCO percentage was lower in patients with PH; and it was observed that DLCO tended to decrease as PAP increased in periodic controls. In addition, we concluded that the DLCO and FVC value increased in

the patients without PH as the process progressed, while the FVC/DLCO ratio tended to decrease. Considering that all our patients received antifibrotic treatment, this result suggested that antifibrotic therapy is more effective in improving diffusion capacity in patients with IPF without PH.

In a multivariate linear analysis study, the FVC/DLCO ratio was shown to have a positive predictive value of 71% and a negative predictive value of 81% in determining the development of PH (12). Another study reported that DLCO < 55% and FVC/DLCO ratio > 1.4 were associated with PH (13). In our study, this ratio was also higher in patients with a higher PAP. It was also observed that this ratio was higher with the increase of PAP in the follow-ups; however, there was no statistical association between the presence of PH and this situation. Statistical significance could not be determined because of the small number of patients or the short follow-up period due to due to worse survival.

The study by Caminati et al. (23), showed that distance in 6-MWT was associated with mortality. A correlation between the 6-MWT and the values of PAP was also found in the literature. In addition, PH has recently been recognized as a possible complication of interstitial lung disease, particularly IPF (24,25). According to our results, lower 6-MWT distance and the presence of PH were statistically negatively correlated in patients with IPF.

Morbidity and mortality are high in IPF, and the clinical course varies widely among individuals (26). Low FVC and DLCO at baseline and a decrease in FVC or DLCO during the 6- or 12-month follow-up period predicted worse survival (27). In the study by Song et al. (28), 6-MWT distance, the presence of desaturation, and the presence of PH were associated with poor prognosis in IPF. Another study also pointed out that factors such as DLCO, presence of hypoxia, and PH had significant effects on survival (29). In our study, no significant association was found between FVC, DLCO, and 6-MWT distance and mortality. Only the presence of desaturation was associated with the survival.

This study has some limitations. First, the sample size was small. The study was retrospective. Because the included patients were those with mild-to-moderate IPF, their DLCO levels were slightly decreased, and their general condition and clinical features were mostly stable. Given the heterogeneity of IPF disease, our study group may represent only a fraction of the IPF population (especially those with preserved DLCO levels), and the result may not be valid for all patients with IPF. In addition, the fact that PAP is subjective may be limiting because it is evaluated by echocardiographic examination rather than right heart catheterization (RHC).

CONCLUSION

Because PH is a common complication of IPF and affects the clinical course of patients, it is essential to identify markers that may be useful for early diagnosis and treatment. We found that low 6-MWT distance is an important marker for the diagnosis of PH in patients with IPF, and the presence of desaturation is also significantly associated with survival in PH. Although we did not find it statistically significant, we found that PAP and the FVC/DLCO ratio increased with progressive disease duration after diagnosis in patients with IPF. We believe that the FVC/DLCO ratio is an important marker for early detection of PH and prognosis in IPF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.06.2022, Decision No: 2012-KAEK-15/2538).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Raghu G, Collard HR, Egan JJ, 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.
2. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet J Rare Dis 2008; 3: 8.
3. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic intersti tial pneumonias. Proc Am Thorac Soc 2006; 3: 315–21.
4. Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fbrosis. Eur Respir J 2010; 35: 830–6.
5. Cano-Jiménez E, Hernández González F, Peloche GB. Comorbidities and complications in ıdiopathic pulmonary fibrosis. Med Sci 2018; 6: 71.
6. Collum SD, Amione-Guerra J, Cruz-Solbes AS, et al. Pulmonary hypertension associated with ıdiopathic pulmonary fibrosis: current and future perspectives. Can Respir J 2017; 2017: 1430350.
7. Sherner J, Collen J, King CS, Nathan SD. Pulmonary hypertension in idiopathic pulmonary fibrosis: epidemiology, diagnosis, and therapeutic implications. Curr Respir Care Rep 2012; 1: 233-42.

8. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J 2008; 31: 1357-67.
9. Shorr AF, Wainright JL, Cors CS, et al. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J 2007; 30: 715-21.
10. Kimura, Taniguchi H, Kondoh Y, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. Respiration 2013; 85: 456-63.
11. Nathan SD, King CS. Treatment of pulmonary hypertension in idiopathic pulmonary fibrosis: shortfall in efficacy or trial design? Drug Des Devel Ther 2014; 8: 875-85.
12. Zisman DA, Ross DJ, Belperio JA, et al. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2007; 101: 2153-9.
13. Steen VD, Graham G, Conte C, Owens G, Medsger TA Jr. Isolated diffusing capacity reduction in systemic sclerosis. Arthritis Rheum 1992; 35: 765-70.
14. Öztürk A, Kayacan O. Rising stars of DPLD survival: FVC and exercise desaturation. Turk J Med Sci 2018; 48: 826-32.
15. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984; 70: 657–62.
16. European RS, American Thoracic Society. ATS/ ERS Statementon respiratory muscle testing. Am J Respir Crit Care Med 2002;166: 518-624.
17. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012; 156: 684–95.
18. Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan a parallel, randomized trial. Annals of Internal Medicine 2013; 158: 641-9.
19. Teramachi R, Taniguchi H, Kondoh Y, et al. Progression of mean pulmonary arterial pressure in idiopathic pulmonary fibrosis with mild to moderate restriction. Respirology 2017; 22: 986-90.
20. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129: 746-52.
21. du Bois R, Albera C, Bradford W, et al. Predictors of mortality in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009; 179: A1114.
22. 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: 305-10.
23. Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Respir Med 2009; 103: 117-23.
24. Shapiro S. Management of pulmonary hypertension resulting from interstitial lung disease. Curr Opin Pulm Med 2003; 9: 426-30.
25. Strange C, Highland KB. Pulmonary hypertension in interstitial lung disease. Curr Opin Pulm Med 2005; 11: 452-5.
26. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011; 183: 431-40.
27. Salisbury ML, Xia M, Zhou Y, et al. Idiopathic pulmonary fibrosis: gender-age-physiology ındex stage for predicting future lung function decline. Chest 2016; 149: 491-8.
28. Song H, Sun D, Ban C, et al. Independent clinical factors relevant to prognosis of patients with ıdiopathic pulmonary fibrosis. Med Sci Monit 2019; 25: 4193–201.
29. Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007; 176: 277–84.