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Predictive factors of mortality in patients with idiopathic pulmonary fibrosis treated with antifibrotics: A novel prognostic scoring system

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Abstract. *Background and aim:* There is not any available test that provides sufficient prognostic information to guide treatment decisions in idiopathic pulmonary fibrosis (IPF). The aim of our study was to determine the predictive factors of mortality in patients with IPF treated with antifibrotics. *Methods:* Patients with diagnosis of IPF who were treated with antifibrotics between 2016 – 2021 were included in the study. Demographic, clinical and laboratory characteristics of the patients was derived from hospital records retrospectively. Kaplan Meier and multivariate cox regression analysis were achieved for detection of mortality predictors. *Results:* Study population was composed of 119 IPF patients with a male predominance of 80.7% (n=96). Mean age of the patients was 67.9 ± 7.07 years. On univariate analysis, sex was not a significant predictor of mortality (HR 1.79; 95% CI: 0.87 – 3.69, p =0.11). BMI ≤ 26,6 m^2/kg, DL_{CO} ≤ 3.11 ml/mmHg/min, age over 62 years, 6MWT ≤ 382 meters, NLR ≤ 2.67 and PDW ≤ 16.7% were found to be significant for predicting mortality. On multivariate cox regression analysis four parameters remained significant for prediction of mortality: RDW > 14%, NLR ≤ 2.67, BMI ≤ 26,6 m^2/kg and DL_{CO} ≤ 3.11 ml/mmHg/min (respectively, HR: 2.0. 95% CI: 1.02 – 3.91, p=0.44; HR: 2.68. 95% CI: 1.48 – 4.85, p=0.001, HR: 2.07. 95% CI: 1.14 – 3.76, p=0.02, HR: 3.46. 95% CI: 1.85 – 6.47, p<0.001). A scoring system with these parameters discriminated patients with worse prognosis with a sensitivity of 89.1% and a specificity of 65.8% when total point was over 2 (Area under curve (AUC) 0.83, p<0.001). *Conclusions* In this study, DL_{CO}, BMI, RDW and NLR levels significantly predicted mortality in IPF patients. Along with GAP index, scoring system with these simple parameters may give information about the prognosis of an IPF patient treated with antifibrotics.

Key words: idiopathic pulmonary fibrosis, prognosis, mortality

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing disease of lungs with unknown etiology. The patients with IPF usually have poor prognosis with diminished quality of life. It is the most common and lethal type of idiopathic interstitial pneumonias (1).

Management of IPF patients should be carried out in experienced referral centers in periodic intervals. However, a single marker or test providing sufficient prognostic information to guide treatment decisions in this disease is not available (2). Comprehensive evaluation of clinical, morphological, and physiological parameters of disease is usually needed to predict outcome. Some of characteristics that predict worse prognosis in IPF patients are decline in forced vital capacity (FVC) ≥ 10% predicted or in diffusion

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capacity of lungs for carbon monoxide (DL_{CO}) ≥ 15% predicted over 6 months, worsening arterial blood gas analyses parameters, arterial saturation of oxygen (SaO_2) below 88%, progressive worsening of symptoms like dyspnea and cough, 6-minutes walking test (6-MWT) distance < 250 meters or decline in 6-MWT distance > 50 meters over 6 months, pulmonary hypertension and hospitalizations due to IPF acute exacerbation or pneumothorax (2-7).

Clinical course of IPF is heterogenous. Despite the improvements in understanding the pathogenesis of the disease, we are still unable to predict the course and treatment response reliably. Noninvasive biomarkers, especially serum biomarkers are needed for early diagnosis, differential diagnosis and prediction of prognosis and treatment response. Many molecules that have role in alveolar epithelial damage, fibroproliferation, matrix re-modelling or immunoregulation were proposed to be a potential prognostic factor for IPF. Among these molecular biomarkers, mucin 5B (MUC5B) polymorphism was found to be associated with better prognosis, whereas certain toll-interacting protein (TOLLIP) genotypes was found to be associated with higher mortality (8,9). Today, MUC5B polymorphism and matrix metalloproteinase-7 (MMP7) are considered as potential biomarkers of disease progression, but studies supporting routine clinical use of these markers lack (10,11). GAP (gender-age-physiology) model that depends on clinical and physiological parameters can be used for predicting mortality of IPF (12).

Male gender is associated with worse prognosis in IPF and non-IPF idiopathic interstitial pneumonias, with survival times significantly lower without lung transplantation. These data were confirmed with the usage of GAP score (12,13).

The aim of our study was to determine the predictive role of sex on mortality and progression of patients with IPF who were treated with antifibrotics. Secondary aim was to determine the predictive factors of mortality in patients with IPF treated with antifibrotics.

Methods

This study was conducted in a tertiary level reference hospital and received approval from local ethical board (No:73-2022/5). Patients with diagnosis of idiopathic pulmonary fibrosis who were treated with antifibrotics between 2016 – 2021 were included in the study. Diagnosis of IPF was obtained by definite high resolution computed tomography (HRCT) usual interstitial pneumonia (UIP) pattern with compatible clinical characteristics in the absence of other known causes of UIP, or by pathologically proven or probable disease in cases with probable or indeterminate HRCT UIP pattern. Patients with a diagnosis of connective tissue disease, pneumoconiosis, chronic hypersensitivity pneumonitis, and suspected drug related interstitial lung disease were excluded.

Demographic, clinical and laboratory characteristics of the patients was derived from hospital records. Age, sex, smoking status, body mass index (BMI) and comorbidity data were collected. Hemogram and basic biochemical parameters were recorded. All patients had basal spirometry for measurement of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), with diffusion capacity of lungs for carbon monoxide (DL_{CO}) and 6-minute walk test (6MWT) for estimating functional capacity. Spirometry was performed according to the ATS/ERS statement guidelines (14). For measurement of diffusion capacity of lungs, single breath carbon monoxide uptake method was used. GAP (gender-age-physiology) index for individual patient was calculated according to the method suggested by Ley et al (12).

Pulmonary parenchymal findings were evaluated by HRCT at the time of diagnosis. 64 detectors 126 slice Hitachi Supria CT device were used in scanning. Tube voltage: 120 kVp; automatic tube current modulation; tube current: 100-250 mAs; pitch: 1.0-1.2 mm; matrix: 512 × 512; slice thickness of 1.250 mm was used as scanning parameters. All images were then reconstructed with 0.625 mm with the same increment.

All patients were given antifibrotic treatment, pirfenidone or nintedanib, according to the discretion of the multidisciplinary council. Repeated measures of spirometric parameters, FEV_1 and FVC, DL_{CO} and 6MWT were performed at 12 months after the start of treatment. Side effects, compliance and any switch of treatment regimen was recorded. Survival status of the study population was noted.

Statistical analysis

Statistical analysis was achieved by SPPS (Statistical Package for Social Sciences) version 22 (SPSS Inc. Chicago, IL, USA). Normal distribution of

continuous variables was determined by Kolmogorov Smirnov test. Normally distributed variables were given as mean and standard deviation. Median follow-up time was calculated by reverse Kaplan Meier method. Analysis of predictive variables for mortality on univariate analysis was achieved by Kaplan-Meier analysis. Survival plots were constructed. Cut-off values for continuous variables that has best sensitivity and specificity values were calculated by ROC (receiver operating curve) analysis and Youden index. Variables that have $p<0.25$ on univariate analysis were included in multivariate cox-regression analysis. Changes for FVC, DL_{CO}, and 6MWT according to the sex of the participants were evaluated by repeated measures ANOVA (analysis of variances) test. $p<0.05$ was taken as the level of significance and type-1 error coefficient was determined as alpha 0.05.

Results

Study population was composed of 119 IPF patients with a male predominance of 80.7% (n=96). Mean age of the patients was 67.9 ± 7.07 years. Eighty patients (67.3%) had active or previous smoking history and 66 (55.5%) patients had at least one comorbidity. Mean body mass index of the study population was 27.9 ± 4.01 m^2/kg. Eight patients (6.7%) had a history of acute exacerbation and 20 patients (16.8%) had previous hospitalization due to IPF or acute exacerbation of IPF. Median disease duration of the study population was 42.6 months, and median follow-up time was 56.8 months.

Dyspnea (n=99, 83.2%) and cough (n=87, 73.1%) were mostly seen symptoms. Twenty-six (21.8%) of the patients had clubbing on physical examination. Mean basal FVC of the study population was 2.4 ± 0.69 l (71.0 ± 16.04%). Mean DL_{CO} was 3.95 ± 1.6 ml/mmHg/min (50.1 ± 18.32%). Mean distance of 6MWT was 376 ± 103 meters. Fifty-nine patients (49.6%) were GAP (gender-age-physiology) stage 2 and 14 patients (11.8%) were GAP stage 3.

Computed tomography findings revealed typical UIP pattern in 88 (73.9%) patients, while probable UIP pattern was present in 29 (24.4%) patients. Emphysema was co-existent in 17 (14.3%) patients. Diagnosis was obtained by lung biopsy in 28 patients (23.6%), mostly by video associated thoracic surgery (VATS). Demographic and clinical parameters of study population is seen in Table 1.

During the study period, 46 patients (38.7%) died. For Kaplan-Meier analysis of sex and other predictive factors for mortality ROC analysis revealed cut-off values with best sensitivity and specificity were as follows: age 62 years, BMI 26.6 m^2/kg, eosinophils 200/mm^3, FVC 2,39 l, GAP score 4, hemoglobin 14.7 gr/dl, hematocrit 44.4%, lymphocytes 1500/mm^3, leucocytes 7500/mm^3, mean corpuscular volume (MCV) 87 fl, mean platelet volume (MPV) 7.9 fl, neutrophil-lymphocyte ratio (NLR) 2.67, neutrophils 5000/mm^3, platelet distribution width (PDW) 16.7%, platelets 282000/mm^3, red-cell distribution width (RDW) 14%, DL_{CO} 3.11 ml/mmHg/min, and 6MWT 382 meters.

On univariate analysis, sex was not a significant predictor of mortality (HR 1.79; 95% CI: 0.87 – 3.69, p =0.11). BMI ≤ 26,6 m^2/kg, DL_{CO} ≤ 3.11 ml/mmHg/min, age over 62 years, 6MWT ≤ 382 meters, NLR ≥ 2.67 and PDW ≤ 16.7% were found to be significant for predicting mortality. On multivariate cox regression analysis four parameters remained significant for prediction of mortality: RDW > 14%, NLR ≥ 2.67, BMI ≤ 26,6 m^2/kg and DL_{CO} ≤ 3.11 ml/mmHg/min (respectively, HR: 2.0. 95% CI: 1.02 – 3.91, p=0.44; HR: 2.68. 95% CI: 1.48 – 4.85, p=0.001, HR: 2.07. 95% CI:1.14–3.76,p=0.02,HR:3.46.95%CI:1.85–6.47, p<0.001). Results of univariate and multivariate analysis are presented in Table 2. Kaplan-Meier survival curves for NLR, RDW, BMI and DL_{CO} is presented in Figure 1.

Changes of FVC, DL_{CO} and 6MWT after one year of antifibrotic treatment was analyzed according to age. Changes in these parameters in one year was similar in both sexes (respectively, p=0.92, p=0.46, p=0.60). Repeated measures ANOVA results of the parameters are presented in Table 3.

A scoring system with the parameters of NLR, RDW, DL_{CO} and BMI was evaluated for its ability to discriminate patients with worse prognosis. One point was assigned for each parameter. Association of mortality and patients scores according to the new scoring system for idiopathic pulmonary fibrosis patients is presented in Table 4. Total point ≥ 2 was found to have best sensitivity and specificity, with a sensitivity of 89.1% and a specificity of 65.8% (Area under curve (AUC) 0.83, p<0.001). ROC analysis for the scoring system is presented in Figure 2.

Table 1. Demographic and clinical characteristic of the study population.

	Study population (n=119)
Age, years, mean ± SD	67.9 ± 7.07
Sex, male, n (%)	96 (80.7)
Smoking status	
Non-smoker, n (%)	39 (32.8)
Active smoker, n (%)	14 (11.8)
Ex-smoker, n (%)	66 (55.5)
Smoking packet-years, mean ± SD	40.2 ± 35.36
BMI, m^2/kg, mean ± SD	27.9 ± 4.01
Familial history of pulmonary fibrosis, n (%)	8 (6.7)
Presence of comorbidities, n (%)	66 (55.5)
Cardiovascular disease, n (%)	37 (31.1)
Diabetes mellitus, n (%)	27 (22.7)
Hypertension, n (%)	27 (22.7)
COPD, n (%)	15 (12.6)
Hyperlipidemia, n (%)	4 (3.4)
Lung cancer, n (%)	5 (4.2)
History of IPF exacerbation, n (%)	8 (6.7)
History of hospitalization, n (%)	20 (16.8)
Symptoms	
Dyspnea, n (%)	99 (83.2)
Cough, n (%)	87 (73.1)
Sputum, n (%)	14 (11.8)
Clubbing, n (%)	26 (21.8)
Biopsy proven IPF, n (%)	28 (23.6)
Cryobiopsy, n (%)	4 (3.4)
VATS, n (%)	24 (20.2)
Computed tomography properties	
Typical UIP, n (%)	88 (73.9)
Probable UIP, n (%)	29 (24.4)
Indeterminate UIP, n (%)	2 (1.7)
Honeycomb changes, n (%)	90 (75.6)
Traction bronchiectasis, n (%)	69 (58)
Ground glass opacity, n (%)	39 (32.8)
Emphysema, n (%)	17 (14.3)
Follow-up characteristics	
Stable disease, n (%)	53 (44.5)
Symptom control, n (%)	50 (42)
Progression, n (%)	9 (7.6)
Treatment characteristics	
Nintedanib usage, n (%)	52 (43.7)
Pirfenidone usage, n (%)	67 (56.3)
Presence of side effects, n (%)	53 (44.5)
Dose reduction or interruption, n (%)	35 (29.4)
Treatment discontinuation, n (%)	22 (18.5)
Side effects, n (%)	18 (15.1)
Unresponsive, n (%)	4 (3.4)
Unwilling, n (%)	9 (7.6)
Treatment change, n (%)	14 (11.8)
Time to side effect, months, n (%)	3.65 ± 4.07
GAP stage	
Stage 1, n (%)	46 (38.7)
Stage 2, n (%)	59 (49.6)
Stage 3, n (%)	14 (11.8)
GAP Total, mean ± SD	3.81 ± 1.42
Laboratory parameters	
Hemoglobin, g/dl, mean ± SD	14.0 ± 1.93
Hematocrit, %, mean ± SD	41.8 ± 4.06
Leucocytes, /mm^3, mean ± SD	8650 ± 2130
Neutrophils, /mm^3, mean ± SD	5446 ± 1735
Eosinophils, /mm^3, mean ± SD	280 ± 175
Lymphocytes, /mm^3, mean ± SD	2224 ± 805
Platelets, /mm^3, mean ± SD	261538 ± 72429
CRP, mg/dl, mean ± SD	1.1 ± 2.62
Six minutes walking distance, m, mean ± SD	376 ± 103
Spirometry	
FVC, lt, mean ± SD	2.4 ± 0.69
FVC, %, mean ± SD	71.0 ± 16.04
FEV_1, lt, mean ± SD	2.1 ± 0.55
FEV_1, %, mean ± SD	78.4 ± 17.34
DL_{CO}, lt/mmHg/min, mean ± SD	3.95 ± 1.6
DL_{CO}, %, mean ± SD	50.1 ± 18.32
Survival, n (%)	73 (61.3)
Survival time, mean± SD	48.1 ± 25.78

Abbreviations: SD: standard deviation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis; VATS: video assisted thoracic surgery; UIP: usual interstitial pneumonia; GAP: gender-age-physiology; CRP: C- reactive protein; FVC: forced vital capacity; FEV_1: forced expiratory volume in one-second; DL_{CO}: diffusion capacity of lungs for carbon monoxide.

Table 2. Univariate and multivariate analysis of predictive factors for mortality in patients with IPF treated with antifibrotics.

	Univariate Analysis			Multivariate analysis		
	HR	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
Sex, male	1.79	0.87 – 3.69	0.11			
Age > 62 years	2.54	1.31 – 4.92	**0.006**			
Active or ex-smoker	1.76	0.97 – 3.21	0.06			
Comorbidity	1.26	0.70 – 2.26	0.44			
RDW > 14 fl	1.65	0.90 – 3.03	0.10	2.0	1.02 – 3.91	**0.04**
PDW ≤ 16.7 fl	1.88	1.05 – 3.38	**0.03**			
NLR ≥ 2.67	2.44	1.33 – 4.46	**0.004**	2.68	1.48 – 4.85	**0.001**
6MWT ≤ 382 m	2.56	1.41 – 4.65	**0.002**			
BMI ≤ 26.6 m^2/kg	2.67	1.44 – 4.96	**0.002**	2.07	1.14 – 3.76	**0.02**
FVC ≤ 2.39 l	1.54	0.86 – 2.76	0.15			
DL_{CO} ≤ 3.11 ml/mmHg/min	3.09	1.69 – 5.65	**<0.001**	3.46	1.85 – 6.47	**<0.001**
Typical UIP pattern	0.68	0.34 – 1.35	0.27			
Co-presence of emphysema	1.49	0.67 – 3.30	0.33			
Noncompliance to treatment	0.95	0.45 – 2.01	0.90			
GAP > 4	1.45	0.63 – 3.32	0.38			

Abbreviations: IPF: idiopathic pulmonary fibrosis; HR: hazard ratio; CI: confidence interval; RDW: red cell distribution width; PDW: platelet distribution width; NLR: neutrophil-lymphocyte ratio; 6MWT: Six-minute walk test; BMI: body mass index; FVC: forced vital capacity; DL_{CO}: diffusion capacity of lungs for carbon monoxide; UIP: usual interstitial pneumonia; GAP: gender-age-physiology.

Discussion

In this study, we did not find a significant predictive role of sex for determining mortality in IPF patients treated with antifibrotics, although survival tended to be lower in males. However, DL_{CO} levels below 3.11 ml/mmHg/min were associated with 3.5 times higher mortality. Other predictive factors were BMI, RDW and NLR. Scoring of these four variables, DL_{CO}, BMI, RDW and NLR, discriminated patients with poor prognosis with a sensitivity of 89.1% and specificity of 65.8%. Changes of FVC, DL_{CO} and 6MWT were similar across both sexes in the first year of antifibrotic treatment.

IPF predominantly affects males. It is not clear whether this is just a difference of occurrence or disease is dimorphic with different course, treatment response and prognosis according to gender (15). Although there was not any significant effect of gender on mortality in this study, previous studies have demonstrated that male gender was associated with higher mortality in IPF patients (16-19). In their recent study, Zaman et al. found that men had shorter transplant-free survival time compared with women, after adjustment for age and spirometric variables (17).

It should be kept in mind that, as our study population was composed of IPF patients who were treated with antifibrotics, there may be some bias of under-representation of female gender. In the study of Dempsey et al., in a retrospective cohort of about 11,000 patients, it was found that only a quarter of patients were given antifibrotic medications and patients who received antifibrotics were younger, healthier, and mostly composed of men (20). In a Korean cohort, male patients and patients with less dyspnea were significantly more received antifibrotic medications (21). These differences of IPF patients who are treated with antifibrotics may arise from the effects of worse prognostic characteristics of male gender on decision making process of the attending physicians.

Gender is one of the components of the gender-age-physiology (GAP) system which is a simple tool validated for predicting survival in IPF (12). This staging system was also evaluated in IPF patients receiving antifibrotic therapy with favorable results (22,23). In our study population, GAP system also

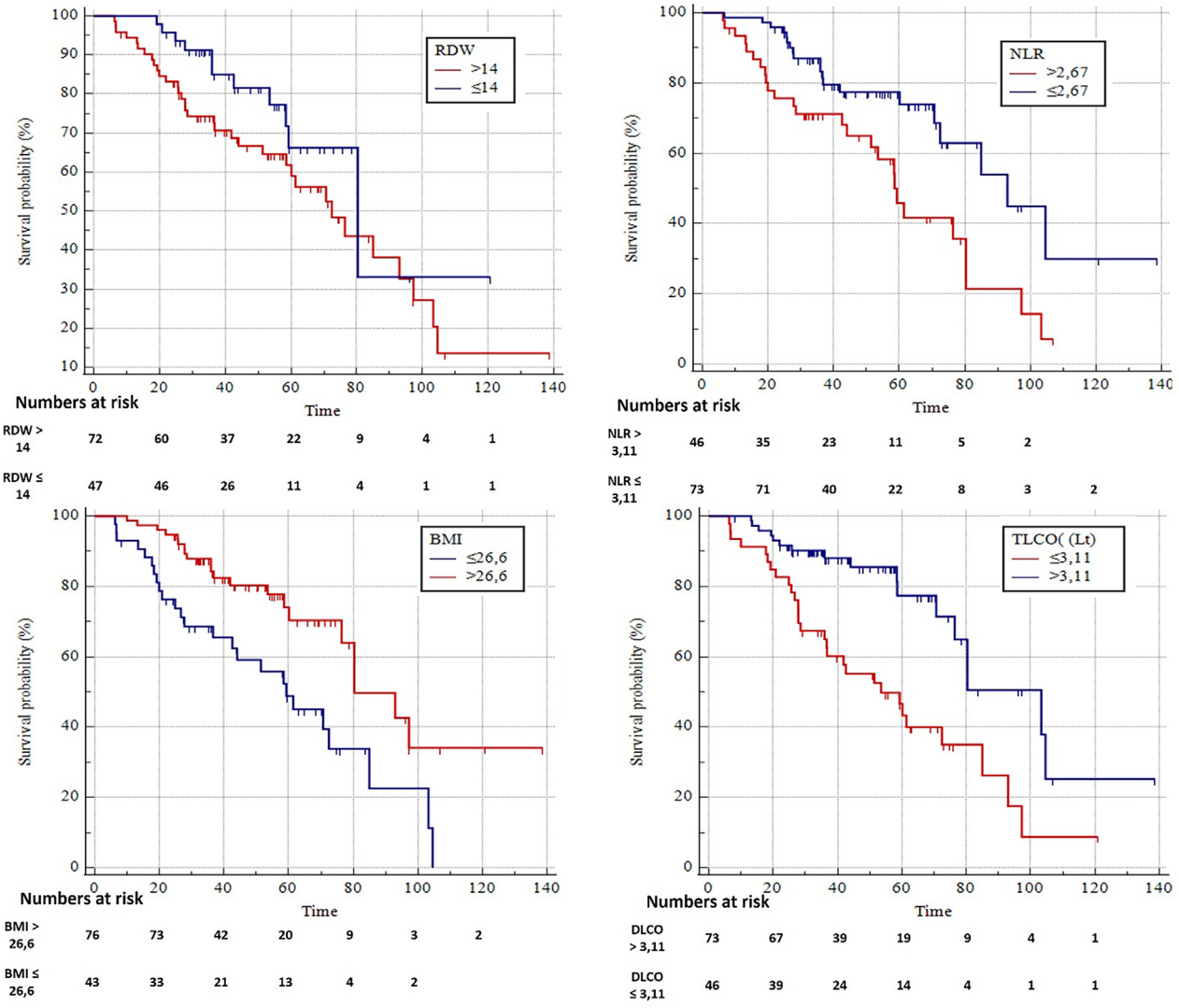

Figure 1. Kaplan Meier curves for red cell distribution width (RDW), neutrophil-lymphocyte ratio (NLR), body mass index (BMI) and DL_{CO} (diffusion capacity of lungs for carbon monoxide).

Table 3. Changes in physiological parameters at the end of first year of antifibrotic treatment initiation in patients with IPF.

	Males		Females		
	Basal values	**Follow-up values**	**Basal values**	**Follow-up values**	**P value**
FVC, l	2.70 ± 0.66	2.59 ± 0.64	1.77 ± 0.41	166 ± 0.40	0.92
DL_{CO}, ml/mmHg/min	4.22 ± 1.53	4.08 ± 1.64	3.19 ± 1.13	3.24 ± 1.06	0.46
6MWT, m	420.4 ± 107.6	404.5± 102.87	353 ± 82.19	324.8 ± 95.36	0.60

Abbreviations: IPF: idiopathic pulmonary fibrosis; 6MWT: Six-minute walk test; FVC: forced vital capacity; DL_{CO}: diffusion capacity of lungs for carbon monoxide.

Table 4. Association of mortality and patients scores according to the new scoring system for idiopathic pulmonary fibrosis patients.

Total point of scores	Survived (n=73)	Exitus (n=46)
0, n (%)	11 (15.1)	1 (2.2)
1, n (%)	37 (50.7)	4 (8.7)
2, n (%)	20 (27.4)	18 (39.1)
3, n (%)	5 (6.8)	18 (39.1)
4, n (%)	0	5 (10.9)

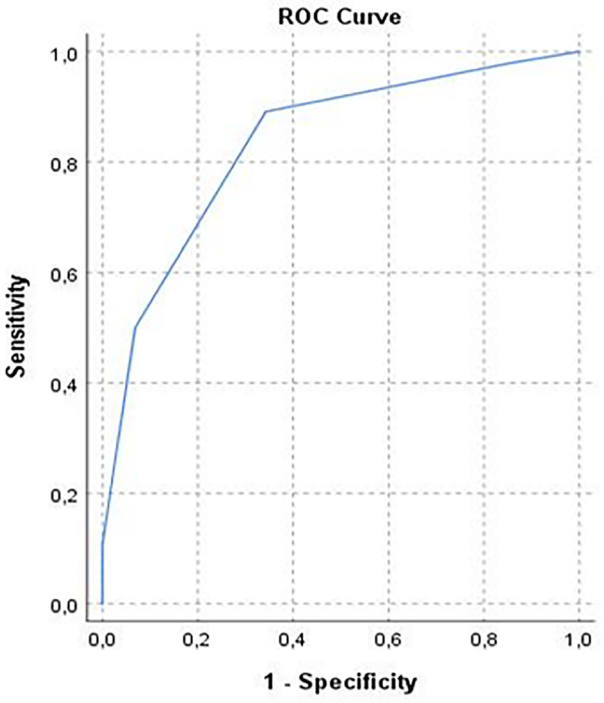

Figure 2. ROC curve for the new scoring system for idiopathic pulmonary fibrosis.

revealed significant mortality differences among stages. However, gender and age were not significant parameters on multivariate analysis. Among functional evaluation decrement in DL_{CO} was significantly associated with mortality. Similar to our findings, in the cohorts of the study of Suzuki et al. FVC and DL_{CO} levels significant predictive factors of mortality on multivariate analysis, while gender and age were nonsignificant (24). DL_{CO} is one of the important predictive variables of mortality in IPF, and in most studies significant results are obtained, although accurate measurement of this component is less reliable in hypoxemic patients (16,25).

We also found that baseline BMI is a significant prognostic factor for IPF. There are reports that link low baseline BMI to higher mortality of IPF or higher in-hospital mortality of acute exacerbation of IPF (26,27). However, most studies confirm association of mortality with BMI loss overtime (28-30). In their recent study, Suzuki et al. proposed usage of BMI as a composite index with GAP model to better discrimination of mortality prediction in IPF patients (24).

Computed tomography characteristics of the disease, such as honeycombing and concomitant emphysema, are also proposed predictors of mortality in IPF patients (31). Some studies failed to show any survival difference between patients with different initial HRCT findings (32). Our results did not support predictive role of HRCT features, neither definite UIP pattern nor presence of emphysema was not associated with mortality in our study population.

Hemogram parameters like NLR and PLR are inexpensive and easily performed tests. They are considered as biomarkers of inflammation and oxidative stress. Several studies evaluated prognostic role of NLR and PLR in IPF. Chen Y et al, reported worse prognosis with elevated NLR levels in IPF patients, independent of GAP scores (33). In the study of Nathan et al., beside baseline levels of NLR and PLR, their change in twelve months was also associated with poor outcomes, more significantly for NLR (34). NLR in bronchoalveolar lavage samples were also found to be correlated with spirometric findings and composite pulmonary index score (35). RDW is also another hemogram parameter evaluated for its prognostic significance in IPF. Some reports support the predictive role of RDW for survival in IPF (36). However, in a recent study by Karampitsakos et al., although high RDW levels were associated with severe disease, it was not significant for predicting mortality (37).

Recently, more promising biomarkers in blood are evaluated to discriminate progressive disease, either with ELISA or proteomic analysis (38). However, these parameters are not readily available and feasible in most centers and further validation studies are needed.

We consider our results important as our study population represents data of IPF patients in the antifibrotic era. However, this study is a retrospective study with limited number of patients. Similar to exclusion criteria of major antifibrotic trials, patients

with low FVC or low DLCO were not represented in our study population, as general health insurance system covers antifibrotics in patients with FVC over 50%. As stated previously, patients on antifibrotics may represent younger and less symptomatic patients with differing gender distributions. These may cause a selection bias and prevent generalization of results to all IPF patients.

We assigned 1 point for each variable in our scoring system. This may be regarded as a methodological flaw. Weighting variables according to the regression coefficients is another option for implementing scoring system. However, our analysis did not reveal major advantage of weighted scoring system, in terms of sensitivity and specificity, so we decided to assign equal weights to each variable to have a feasible and simple score.

Comorbidities are one of the important prognostic factors of IPF which may also interfere with treatment and clinical course of disease (39). However, we did not find any significant effect of comorbidities on mortality. Due to retrospective nature of our study some important comorbidities of IPF, like pulmonary hypertension and gastroesophageal reflux disease may not be fully evaluated. We considered it as another limitation of our study.

In this subpopulation of IPF patients, scoring system with these simple parameters may give information about the prognosis of an IPF patient treated with antifibrotics, in conjunction with or as an alternative to GAP index. Further studies are needed to validate and compare predictive value of this scoring system with GAP index. However, there is still need for validated markers for IPF to predict survival, treatment response and course of the disease.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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