ORIGINAL ARTICLE

Prognostic significance of incorporating SpO2 recovery time to the 6-minute walk test protocol and to a modified GAP index risk prediction model in patients with idiopathic pulmonary fibrosis

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ABSTRACT

Background and aim: The prognostic potential of SpO2 recovery time recorded during 6-min walk test (6MWT) remains unexplored in the setting of idiopathic pulmonary fibrosis (IPF). This study aimed to investigate prognostic significance of cardiopulmonary recovery time after the 6MWT and the utility of a modified gender-age-physiology (GAP) index incorporating SpO2 recovery time instead of DLCO as a predictive model in IPF patients.

Methods: A total of 64 patients with IPF (mean±SD age: 61±10.2 years, 79.7% were males) were included in this retrospective cohort study. Cardiopulmonary recovery time (SpO2 recovery time and heart rate recovery [HRR] time in seconds), GAP index (gender, age, forced vital capacity [FVC] and diffusion capacity [DLCO]) and modified GAP index (gender, age, FVC, SpO2 recovery time) scores were recorded.

Results: SpO2 recovery time and modified GAP index predicted the increased risk of overall adverse events (OR 1.017, p=0.002 and OR 1.667, p<0.010, respectively). SpO2 recovery time at a cut-off value of >160 s (AUC: 0.813, p<0.001) and modified GAP index at a cut-off value of >3.5 (AUC: 0.762, p<0.001) were able to discriminate patients at risk of adverse clinical outcomes. Overall survival (OS) time was significantly longer in patients with SPO2 recovery time <160 s than in those with SPO2 recovery time ≥160 s (mean 24.3 vs. 8.5 months, Log-rank p value <0.001).

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Conclusions: Incorporating SpO2 recovery time to the 6MWT protocol and to a modified GAP index may improve mortality risk prognostication in IPF, supporting the utilization of continuous SpO_2 monitoring and recovery analysis during routine 6MWT.

Key words: idiopathic pulmonary fibrosis, 6-min walk test, cardiopulmonary recovery, SpO2 recovery time, GAP index, modified GAP index, adverse clinical outcomes, mortality prediction

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive chronic interstitial lung disease (ILD) which remains a fatal and incurable disease with a median survival of 3-5 years in untreated patients (1,2). Gender-age-physiology (GAP) index, based on gender, age, forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO), is as an easy-to-use risk prediction model and the first staging system for prediction of mortality in IPF (3,4). However, GAP index is of limited value in capturing decline in pulmonary function over time as it does not incorporate exercise capacity testing such as 6-min walk test (6MWT), which is considered likely to outperform the mortality predictive ability of GAP index (5-8). Recent technical advances allow for continuous SpO_2 monitoring throughout the 6MWT, allowing the detection of the lowest (nadir) SpO_2 value and the kinetics of recovery following exertion—a dynamic remains to be relatively underexplored (9,10). Although DLCO is an important parameter of GAP, DLCO testing is the difficult and cumbersome with questionable availability and feasibility in resource-limited settings, as it depends on availability of a high-end spirometry machine and technical expertise and patients' performance of breath-hold of at least 10 s (5,11). Given that lung's diffusing capacity is considered as a critical determinant of effective SpO_2 recovery, SpO_2 recovery time may also serve as an indirect measure of the extent of diffusing capacity (DLCO) (9,10,12). Hence, we proposed a modified GAP index by replacing the DLCO parameter with SpO2 recovery time as an easy to measure parameter recorded during 6MWT. Therefore, this study aimed to investigate prognostic significance of cardiopulmonary recovery time after 6MWT and the utility of a modified GAP index incorporating SpO2 recovery time as a predictive model in patients with IPF.

Methods

Study population

A total of 64 patients with IPF who presented to a tertiary care pulmonary rehabilitation outpatient clinic between 2016 and 2022 were included in this retrospective cohort study. Adult (aged 18 to 85 years) patients diagnosed with stable disease meeting the criteria for participating in a pulmonary rehabilitation program and those with available hospital records on 6MWT and pulmonary function test parameters were included in the study, while those with non-IPF ILD or incomplete hospital records were excluded. Patients who need oxygen support during 6MWT were also excluded from the study given its potential effects on SpO2 recovery time. Written informed consent was obtained from each subject. The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (Date of Approval: 02/11/2023; Protocol No: 116.2017.R-337).

Assessments

Data on patient demographics (age, gender), body mass index (BMI), disease duration, smoking status, pulmonary function parameters including

forced expiratory volume in 1 second (FEV1), FEV1% predicted, FVC, FVC% predicted, FEV1/FVC and DLCO were recorded in each patient. The disease impact parameters included Modified Medical Research Council (mMRC) Dyspnea Scale, The London Chest Activity of Daily Living (LCADL) Scale and St. George's Respiratory Questionnaire (SGRQ) scores. The 6MWT parameters involved 6-min walk distance (6MWD), pre-test and post-test values of heart rate (bpm), oxygen saturation (SpO2, %), systolic and diastolic blood pressure, Modified Borg Scale (MBS) for dyspnea and lower limb fatigue and cardiopulmonary recovery time (SpO2 recovery time and heart rate recovery [HRR] time in seconds). The GAP) index (gender, age, FVC, DLCO) and modified GAP index (gender, age, FVC, SpO2 recovery time) scores were also recorded. The potential role of 6MWD, cardiopulmonary recovery time (SpO2 recovery time and HRR time), GAP index and modified GAP index in predicting the risk of respiratory-related adverse clinical outcomes (emergency admissions, hospitalizations, mortality and overall – at least one event) within a 1-year follow up period was evaluated via multivariate logistic regression analysis. Receiver operating characteristic (ROC) curve was plotted to determine performance of SpO2 recovery time, GAP index and modified GAP index in discriminating patients at risk of adverse clinical outcomes.

6MWT

6MWT was performed on a straight 30 m corridor as supervised by physiotherapists, according to guidelines (13,14). Patients were instructed to walk at their maximal pace as far as possible for 6 min and the distance the patients could walk (6MWD) was recorded in meters.

Cardiopulmonary recovery time

Heart rate and oxygen saturation (SpO2) were recorded using a pulse oximeter at rest before the 6MWT and at the end of the 6MWT, while time (in seconds) for peak heart rate to return to resting heart rate (HRR time) and for SpO2 to return to resting SpO2 (SpO2 recovery time) after exercise cessation were recorded. MBS was also used to evaluate the self-reported dyspnea and lower limb fatigue during the same time points, based on a 0 (no appreciable dyspnea) to 10 (maximal sustainable dyspnea) rated numerical score (15). SpO2 recovery time was defined as the interval (in seconds) required for oxygen saturation to rise from the nadir at the end of the 6MWT to a value within ±2% of the resting (baseline) SpO2. The use of a ±2% threshold reflects the known measurement variability of pulse oximetry and provides a physiologically meaningful criterion for determining return to baseline without relying on an exact numerical match, which is not realistic given the device accuracy. HRR time was the time required (in seconds) for the subject's heart rate measured at the end of 6MWT to return to the resting heart rate.

GAP index and modified GAP index

The GAP index was used a staging model incorporating age, gender, FVC and DLCO to predict mortality in IPF (4). Total GAP index score was calculated using the previously described scoring criteria for gender (female: 0, male: +1), age (<60 years: 0, 60-65 years: +1, <65 years: +2), predicted FVC (>75%: 0, 50-75%: +1, <50%: +2) and predicted DLCO (>55%: 0, 36-55%: +1; ≤35%: +2; unable to perform: +3) (4). For the modified GAP index, SpO2 recovery time was used as a physiological parameter together with FVC, instead of DLCO. Hence, modified GAP parameters included age, gender, FVC and SpO2 recovery time. For SpO2 recovery time, point scores were decided based on 25 percentile (80 sec), median (113 sec), cut-off (160 sec) and 75 percentile (180 sec) values in the study population, as score 0 (SpO2 recovery time: ≤80 sec), score 1 (SpO2 recovery time: 81-113 sec) and score 2 (SpO2 recovery time: 114-160 sec) and score 3 (SpO2 recovery time: ≥160 sec). For both GAP index and modified GAP index, patients were classified as stage I (0–3 points), stage II (4–5 points), or stage III (6–8 points), based on the total point score.

LCADL

LCADL is a 15-item (four domains; personal care: 4 items, domestic: 6 items, physical: 2 items, and leisure: 3 items) tool used to assess dyspnea resulting

from ADLs. Each item is graded from 0 to 5 with higher scores indicating more difficulty in performing ADL (16). Turkish adaptation of LCADL was performed by Saka et al. (17).

SGRQ

SGRQ is a 50-item disease-specific tool to assess impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease, in three domains (symptoms, activity and impacts). Total scores range from 0 to 100, with higher scores indicating more limitations (18). Turkish adaptation of SGRQ was performed by Polatlı et al. (19).

Statistical analysis

Statistical analysis was performed using MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Normality of continuous variables was assessed using the Shapiro-Wilk test. Chi-square test (Yates continuity correction, Likelihood ratio or Fisher's exact test where available) was used for analysis of categorical variables. Mann-Whitney U test and Student t test were used to compare two independent non-normally and normally distributed numerical variables, respectively. Correlation analysis was performed using Pearson and Spearman's correlation analyses. Logistic regression analysis was conducted to examine the association between independent variables and the binary outcome variable. Both univariate and multivariate logistic regression models were employed, and results were reported as odds ratios (OR) with 95% confidence intervals (CI). ROC curve analysis was performed to evaluate the discriminative ability of the logistic regression model and individual predictors. The area under the curve (AUC) was calculated as a measure of classification performance, with values closer to 1 indicating better predictive accuracy. Sensitivity, specificity, and optimal cutoff points were determined using the Youden index. Pairwise comparison of ROC curves for the performance of GAP index and modified GAP index was also performed. Survival analysis was made via Kaplan Meier analysis and comparisons were made via Log-rank test. Data were expressed as "mean ± standard deviation (SD), median (min-max), 95% confidence interval (CI) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

Patient characteristics, pulmonary function and disease impact parameters

Mean±SD age of patients was 61±10.2 years (range, 30 to 78 years), and males comprised 79.7% of study population. Pulmonary hypertension was the most prevalent (46.9%) comorbidity (Table 1).

Pulmonary function parameters (spirometry and DLCO) and disease impact scores are summarized in Table 1.

6MWT parameters and cardiopulmonary recovery time

Median(min-max) values for 6MWD were 474.5(120-635) m, while MBS post-test scores were 3(0-5) for dyspnea and 1(0-5) for limb fatigue (Table 2).

Median(min-max) SpO2 recovery time was 113(0-1200) sec, while HRR time was 150(6-1800) sec (Table 2).

GAP index stages

Median(min-max) GAP index and modified GAP index scores were 3(1-7) and 3(0-8), respectively. Percentage of stage 1, stage 2 and stage 3 patients were 51.6%, 45.3% and 3.1% as per the GAP index and were 52.4%, 39.7% and 7.9% according to modified GAP index, respectively (Table 2).

Correlations of 6MWD and cardiopulmonary recovery parameters

6MWD was positively correlated with all spirometry parameters (more strongly with FVC, $r=0.507$, $p<0.001$) and DLCO ($r=0.400$, $p=0.09$) (Table 3).

6MWD was negatively correlated with all disease impact parameters (more strongly with SGRQ

Table 1. Patient characteristics, pulmonary function and disease impact parameters.

Patient characteristics	
Age (year)	
mean±SD	61±10.2
median(min-max)	60(30-78)
Gender, n(%)	
Female	13(20.3)
Male	51(79.7)
BMI (kg/m^2), median(min-max)	26(19.2-32.7)
Smoking status, n(%)	
Nonsmoker	2(3.1)
Former smoker	38(59.4)
Active smoker	24(37.5)
Smoking pack-years, median (min-max)	22(0-60)
Disease duration (year), median(min-max)	4(1-9)
Comorbidities, n(%)	
Diabetes	14 (21.9)
Hypertension	15 (23.4)
Coronary artery disease	10 (15.6)
Pulmonary hypertension	30 (46.9)
Any comorbidity	39 (60.9)
Pulmonary function parameters	
Spirometry	
FEV_1 (L)	1.9(0.94.2)
FEV_1% predicted	71(39105)
FVC (L)	2.1(0.95.1)
FVC % predicted	66.5(42111)
FEV_1/FVC	88(60110)
DLCO	38.5(9148)
Disease impact parameters	
mMRC dyspnea scale	2(04)
LCADL Scale	36(370)
SGRQ	
Symptoms	53.2(14.597.6)
Activity	66.5(29.8100)
Impacts	43.9(5.597.3)
Total	56.7(17.697)

Abbreviations: BMI: Body mass index; DLCO: Diffusion capacity; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; LCADL: London Chest Activity of Daily Living; mMRC: Modified Medical Research Council; SGRQ: St. George's Respiratory Questionnaire.

Table 2. 6MWT parameters, cardiopulmonary recovery time and GAP index scores.

6MWT parameters, median (min-max)	
6MWD (m)	474.5(120635)
Cardiopulmonary recovery time, median (min-max)	
SpO_2 recovery time (second)	113(01200)
Heart rate recovery time (second)	150(61800)
GAP index	3(1-7)
GAP index stage, n(%)	
Stage 1	33(51.6)
Stage 2	29 (45.3)
Stage 3	2 (3.1)
Modified GAP index stage (n=58), n(%)	3(0-8)
Stage 1	33(52.4)
Stage 2	25(39.7)
Stage 3	5(7.9)

Abbreviations: 6MWT: 6-min walk test; 6MWD: 6-min walk distance; GAP index: Gender-Age-Physiology index; MBS: Modified Borg Scale.

impact domain: r=-0.442, p=0.015 and with LCADL: r=-0.439, p=0.005), expect for SGRQ symptoms domain (Table 3). Both SPO2 recovery time (r=-0.437, p=0.011) and HRR time (r=-0.443, p=0.011) were negatively correlated with DLCO (Table 3).

Correlations of GAP index and modified GAP index

Both GAP index and modified GAP index scores were negatively correlated with 6MWD (r=-0.387, p=0.002 and r=-0.647, p<0.001). GAP index was positively correlated with SGRQ symptoms (r=0.443, p=0.014) and activity (r=0.410, p=0.025) domain scores (Table 4).

Multivariate logistic regression analysis for the determinants of adverse clinical outcomes

Increase in 6MWD predicted lower risk of emergency admissions (OR 0.994, 95% CI 0.989-0.998, p=0.009), mortality (OR 0.993, 95% CI 0.987-0.998, p=0.007) and overall events (OR 0.992, 95% CI 0.987-0.997, p<0.001) (Table 5).

Table 3. Correlations of 6MWD and cardiopulmonary recovery parameters.

	6MWD		SpO2 recovery time		Heart rate recovery time	
	r	p	r	p	r	p
Pulmonary function						
FEV1	0.495	**<0.001**	-0.223	0.141	-0.193	0.209
FVC	0.507	**<0.001**	-0.235	0.120	-0.174	0.259
FEV1%	0.488	**<0.001**	-0.282	0.064	-0.296	0.054
FVC%	0.468	**0.001**	-0.242	0.109	-0.266	0.081
FEV1/FVC	0.020	0.900	-0.026	0.865	-0.001	0.994
DLCO	0.400	**0.019**	-0.437	**0.011**	-0.443	**0.011**
Disease impact						
mMRC	-0.417	**0.004**	0.143	0.356	0.097	0.534
LCADL	-0.439	**0.005**	0.103	0.532	0.211	0.196
SGRQ- symptoms	-0.345	0.062	0.169	0.381	0.553	**0.002**
SGRQ- activity	-0.397	**0.030**	-0.078	0.689	0.373	0.046
SGRQ-impact	-0.442	**0.015**	-0.039	0.842	0.118	0.541
SGRQ- total	-0.424	**0.019**	-0.059	0.760	0.295	0.120

Abbreviations: 6MWD: 6-min walk distance; DLCO: Diffusion capacity; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; LCADL: London Chest Activity of Daily Living; mMRC: Modified Medical Research Council; SGRQ: St. George's Respiratory Questionnaire; r: correlation coefficient. Spearman correlation analysis.

Table 4. Correlations of GAP index and modified GAP index scores.

	GAP index		Modified GAP index	
	r	p	r	p
Disease impact				
LCADL	0.252	0.117	0.134	0.385
SGRQ- symptoms	0.443	**0.014**	0.179	0.276
SGRQ- activity	0.410	**0.025**	0.231	0.228
SGRQ-impact	0.182	0.337	0.233	0.224
SGRQ- total	0.333	0.072	0.115	0.553
6MWT parameters				
6MWD	-0.387	**0.002**	-0.647	**<0.001**
SpO2 recovery time	0.101	0.433	0.733	**<0.001**
Heart rate recovery time	0.219	0.087	0.220	0.085

Abbreviations: 6MWD: 6-min walk distance; DLCO: Diffusion capacity; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GAP index: Gender-Age-Physiology index; LCADL: London Chest Activity of Daily Living; SGRQ: St. George's Respiratory Questionnaire; r: correlation coefficient. Spearman analysis

Increase in SpO2 recovery time predicted the increased risk of emergency admissions (OR 1.011, 95% CI 1.001-1.021, p=0.035) and overall adverse clinical outcome events (OR 1.017, 95% CI 1.007-1.028, p=0.002). HRR time had no significant role in predicting adverse clinical outcomes (Table 5). Increase in the modified GAP index predicted the increased risk of mortality (OR 1.766, 95% CI 1.082-2.881, p=0.023)

Table 5. Multivariate logistic regression analysis for determinants of adverse clinical outcomes.

	OR	95% CI (LB-UB)	p value
6MWD			
Emergency admission	0.994	0.989-0.998	**0.009**
Hospitalization	0.996	0.990-1.001	0.994
Mortality	0.993	0.987-0.998	**0.007**
All events	0.992	0.987-0.997	**<0.001**
SpO2 recovery time			
Emergency admission	1.011	1.001-1.021	**0.035**
Hospitalization	1.001	0.997-1.005	0.588
Mortality	1.001	0.998-1.005	0.495
All events	1.017	1.007-1.028	**0.002**
Heart rate recovery time			
Emergency admission	0.999	0.996-1.002	0.999
Hospitalization	1.001	0.999-1.003	0.408
Mortality	0.998	0.994-1.003	0.480
All events	0.999	0.997-1.002	0.532
GAP index			
Emergency admission	0.860	0.522-1.417	0.554
Hospitalization	1.385	0.772-2.482	0.275
Mortality	1.213	0.701-2.101	0.490
All events	1.195	0.791-1.803	0.397
Modified GAP index			
Emergency admission	1.210	0.818-1.788	0.340
Hospitalization	1.410	0.873-2.279	0.160
Mortality	1.766	1.082-2.881	**0.023**
All events	1.667	1.132-2.455	**0.010**

Abbreviations: 6MWD: 6-minute walk distance; OR: Odds ratio; CI: Confidence interval; LB: Lower bound; UB: Upper bound

and overall events (OR 1.667, 95% CI 1.132-2.455, p<0.010). The GAP index had no significant role in predicting adverse clinical outcomes (Table 5).

ROC analysis for the performance of SpO2 recovery time, GAP and modified GAP index

ROC analysis revealed that SpO2 recovery time was able to discriminate patients at risk of adverse clinical outcomes at a cut-off value of >160 (AUC: 0.813, p<0.001) with a sensitivity of 72.22%, and specificity of 86.67% (Figure 1).

ROC analysis revealed that modified GAP index was able to discriminate patients at risk of adverse clinical outcomes at a cut-off value of >3.5 (AUC: 0.762, p<0.001) (Figure 2).

The pairwise comparison indicated superiority of modified GAP index over GAP index in discriminating patients at increased risk of adverse clinical outcomes (AUC 0.762 vs. 0.573, p=0.034) (Figure 3).

Survival outcome

Overall survival (OS) time was significantly longer in patients with SPO2 recovery time <160 s than in those with SPO2 recovery time ≥160 s (mean (SE, 95% CI) 24.3(0.9, 22.4 to 26.2) vs. 8.5(1.0, 6.4 to 10.5) months, Log-rank p value <0.001) (Figure 4).

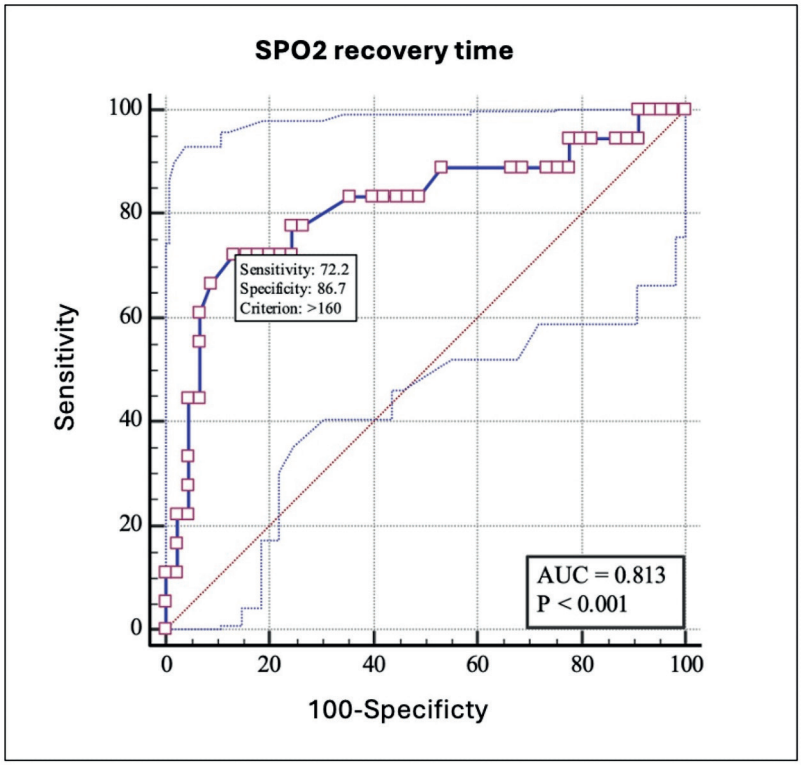
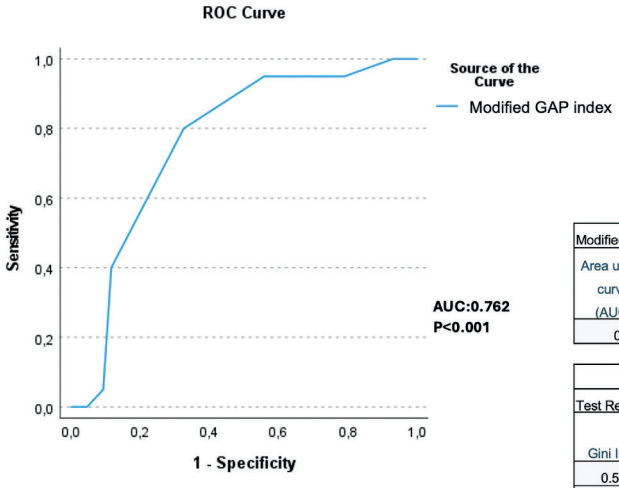


Figure 1. ROC analysis for the performance of SpO2 recovery time in discriminating patients at risk of adverse clinical outcomes AUC: Area under curve.

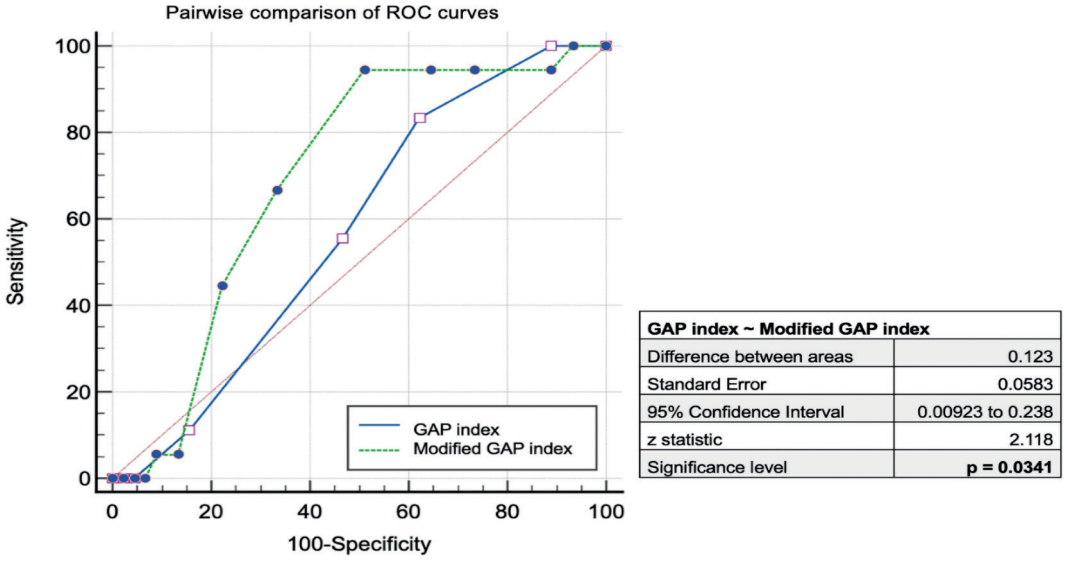


Modified GAP index				
Area under curve (AUC)	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.762	0.063	<0.001	0.639	0.885

Classifier Evaluation Metrics		
Test Result Variable(sModified GAP index		
	K-S Statistics	
Gini Index	Max K-S[a]	Cutoff[b]
0.524	0.474	3.5

a. The maximum Kolmogorov-Smirnov (K-S) metric.
b. In case of multiple cutoff values associated with Max K-S, the largest one is reported.

Figure 2. ROC analysis for the performance of modified GAP index in discriminating patients at risk of adverse clinical outcomes AUC: Area under curve.



GAP index ~ Modified GAP index	
Difference between areas	0.123
Standard Error	0.0583
95% Confidence Interval	0.00923 to 0.238
z statistic	2.118
Significance level	**p = 0.0341**

Figure 3. Pairwise comparison of ROC curves for performance of GAP index and modified GAP index in detecting patients at increased risk of adverse clinical outcomes.

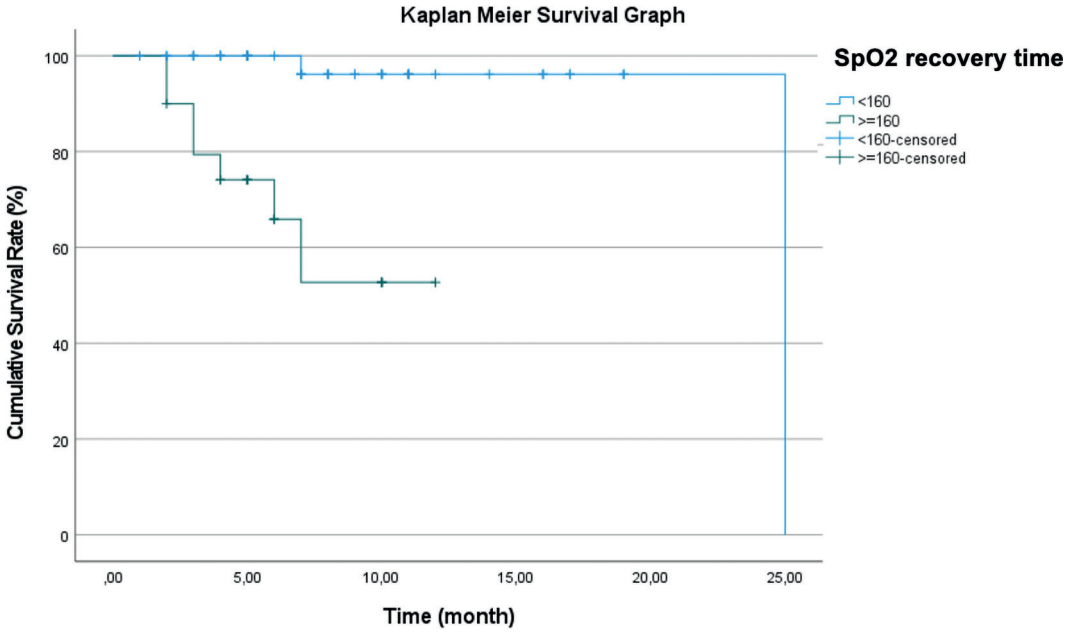


Figure 4. Kaplan-Meier analysis of overall survival (OS) time according to SPO2 recovery time cut-off value (<160 vs. ≥160 s).

No significant difference was noted between the presence and absence of any comorbidity in terms of OS time (mean (SE, 95% CI) 22.2(1.5, 19.3 to 25.1) and 16.0(1.4, 13.4 to 18.7) months, Log-rank p value: 0.278) (Figure 5).

Discussion

In this retrospective cohort of IPF patients, increase in SpO2 recovery time was found to be an independent determinant of increased risk of emergency

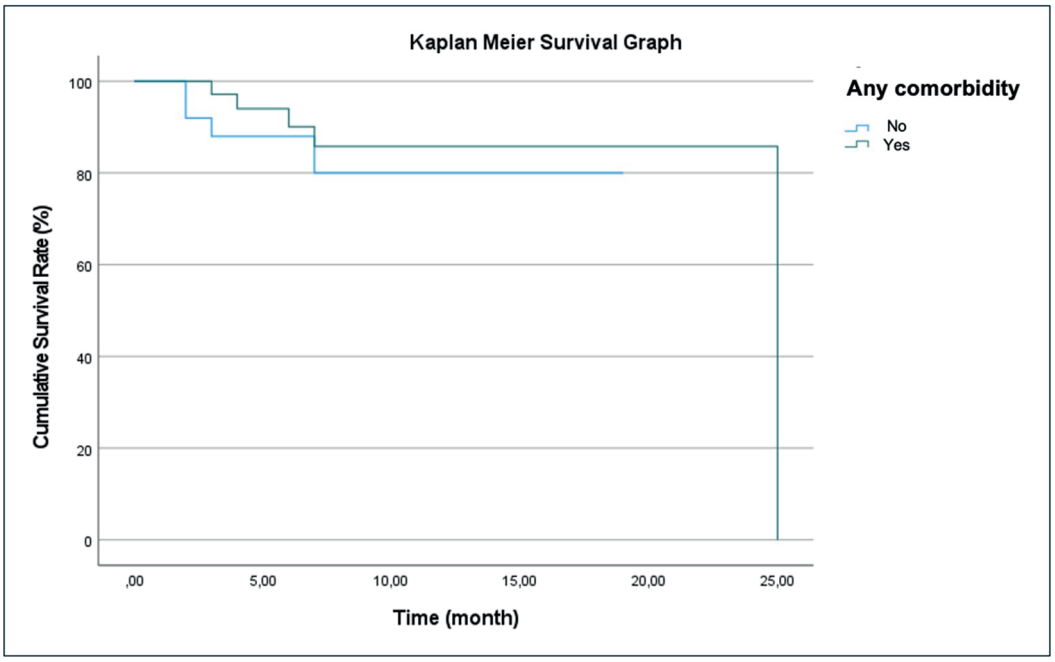


Figure 5. Kaplan-Meier analysis of overall survival (OS) time according to presence vs. absence of any comorbidity.

admissions and overall adverse clinical outcome. SpO2 recovery time was able to discriminate IPF patients at risk of adverse clinical outcomes at a cut-off value of >160 (AUC: 0.813, p<0.001) with a sensitivity of 72.22%, and specificity of 86.67%. OS time was three times greater in patients with SpO2 recovery time <160 s than in those with SPO2 recovery time ≥160 s (mean 24.3 vs. 8.5 months, Log-rank p value <0.001). These findings emphasize the likelihood of SpO2 recovery time to be used as a novel and practical marker of mortality risk prognostication in the setting of IPF, reinforcing the need for continuous SpO_2 monitoring and recovery analysis during routine 6MWT (9,12,13,20). Similarly, ΔSpO2 ≥ 10% and SpO2 recovery time ≥ 79 s were reported as the independent predictors of exacerbation and mortality in IPF patients, respectively (21). An impaired dynamic response in SpO2 and desaturation during 6MWT were associated with increased risk of exacerbation and mortality in IPF patients (22,23). A prolonged SpO2 recovery time was also associated with decreased quality of life, higher symptom rate (fatigue and dyspnea) and increased risk of pulmonary hypertension in IPF patients (20). Patients with severe ILD have marked exercise-induced hypoxemia and dyspnea due to ventilation/perfusion mismatch, oxygen diffusion impairment, and an abnormal ventilatory pattern, particularly if DLCO is < 40% (23). A critical determinant of effective SpO_2 recovery is the lung's diffusing capacity, which governs the efficiency of gas exchange. The correlation of SpO2 recovery time with DLCO in our patients is notable in this regard, emphasizing that the SpO_2 recovery time may serve as an indirect measure of the severity of diffusion impairment (9). This supports the previously reported association of post-test ΔSpO2 with ventilatory indices and DLCO in ILD patients in relation to the mechanism of respiratory physiologic changes in ILD (20,24-26). Also, it was reported that patients with lower diffusing capacity (DLCO) tend to exhibit both more pronounced desaturation during exercise and delayed recovery of oxygen saturation (10,12). The kinetics of oxygen recovery after 6MWT may reflect pathophysiological mechanisms beyond simple functional capacity, particularly in the setting of IPF. Hence, delayed SpO_2 recovery after the 6MWT is not merely a marker of transient

exercise-induced hypoxemia but a window into the patient's overall cardiopulmonary functional capacity with independent prognostic significance (9,12). Patients with more advanced pulmonary disease, compromised diffusing capacity, or concomitant cardiovascular comorbidities often display a delayed recovery, which may underlie the association between prolonged SpO_2 recovery times and adverse outcomes (9,27). Recently, in a first study to evaluate cardiopulmonary recovery time after 6MWT, comparatively in chronic obstructive pulmonary disease (COPD) and ILD patients, it was reported that although both COPD and ILD patients exhibit similar cardiopulmonary recovery times after 6MWT, only SpO_2 recovery time was a significant predictor of adverse clinical outcomes—and exclusively in the ILD group (9). In this regard, we have investigated the prognostic role of using a modified GAP index incorporating "SpO2 recovery time" instead of "DLCO" in the current cohort of IPF patients. As a result, modified GAP index was found to significantly predict adverse clinical outcomes in the multivariate analysis and was able to discriminate IPF patients at risk of adverse clinical outcomes at a cut-off value of >3.5 (AUC: 0.720, p<0.001), outperforming GAP index in this regard. Besides, while both GAP index and modified GAP index scores were negatively correlated with 6MWD, the correlation was stronger for the modified GAP index. Notably, Oğuz et al. reported the association of the desaturation during the 6MWT with an increase in GAP index in IPF patients and a longer SpO2 recovery time in patients with higher GAP index scores (20). SpO2 recovery time was also reported to be independently associated with the GAP index, the lowest oxygen saturation occurring during the 6MWT and the SGRQ score in the multiple regression analysis (20). In a study by Desai et al., a new modified GAP index (TNMC-GAP), created by replacing the DLCO parameter with the 6MWD, was tested comparatively with GAP index in IPF patients (5). Percentage of stage I, stage II, and stage III patients were 15.7%, 37.1% and 47.1% when classified as per GAP index, and were 22.9%, 35.7%, and 41.4% according to modified TNMC-GAP index, respectively (5). The replacement of the DLCO parameter with 6MWD was found to reveal concordant results in terms of 3-year mortality prediction, and thus TNMC-GAP was suggested to serve a reliable replacement for GAP in resource-limited settings (5). In our study, modified GAP index identified higher percentage of patients in the stage 3 category when compared to GAP index (3.1% vs. 7.9%), emphasizing the critical value of replacing DLCO with SpO2 recovery time in identifying more patients at risk of worse prognosis, also supporting our observations on better performance of modified GAP index in this regard. Indeed, since the introduction of the original GAP index in 2012 as the first staging system for IPF (4), a number of changes in the management of patients with IPF have occurred such as emergence of novel antifibrotic medications (pirfenidone and nintedanib) associated with reduction in the decline of lung function, reduced risk of acute deterioration and possible improved life expectancy as well as no longer recommendation of some medications (prednisone, azathioprine and N-acetylcysteine) (3,5,28,29). Accordingly, many studies investigating the performance of GAP index in their IPF cohorts have reported discrepancies regarding the discrimination of patients at mortality risk and prediction of mortality rates using GAP index stages, compared with the original cohort of validation (3,5,30,31). Notably, while modified GAP index was found to be a significant determinant of mortality and all events in our multivariate analysis, no such associations were noted for the GAP index. In a study by Chandel et al. assessing utility of the GAP index in IPF patients in the era of antifibrotic therapy, the original GAP index was not well calibrated to predict outcomes observed in their cohort (3). Hence, 6MWD and exertional hypoxia, as significant prognostic factors strongly associated with overall survival, were combined into a new model, called the distance-oxygen-GAP (DO-GAP) index (3). Addition of 6MWD and exertional hypoxia to the GAP index demonstrated improved outcome discrimination and calibration and improved survival prediction in IPF, compared with the original GAP index (3). Although some studies indicated the association of impaired HRR time after 6MWT with an increased risk of mortality in IPF patients (19,32), HRR time had no significant role in predicting adverse clinical outcomes in our patients with IPF which supports our previous observations in COPD and ILD patients (9).

Nonetheless, the significant negative correlation between HRR time and DLCO in our patients may refer to potential contribution of DLCO to HRR, as impaired gas transfer is a distinctive physiologic abnormality in IPF patients (9,32). The association of a more severe IPF (as demonstrated by lower FVC, DLCO, and 6MWD) with higher likelihood of abnormal HRR and increased risk of mortality has also been emphasized previously (32). Given the heterogenous clinical course and prognosis of IPF with a slower decline in lung function in some patients but rapid deterioration and premature mortality in others, accurate risk stratification and prognostication at the time of initial diagnosis is of critical importance (3,33). Integration of dynamic oxygenation parameters such as continuous SpO_2 monitoring into routine exercise testing protocols may provide usable information in this regard. SpO_2 recovery time, as a promising and actionable metric tool obtained easily and noninvasively using a standard pulse oximeter, may enhance risk stratification and guide management decisions and tailored rehabilitative interventions (9,10,12,34). Delayed SpO_2 recovery may serve as a red flag finding indicating closer follow-up, supplemental oxygen titration, or early referral for antifibrotic therapy in IPF patients. However, there remains several limitations in testing such as variability in test performance and reliability of recovery time measurements in the presence of supplemental oxygen administration. Therefore, further research should aim to define standardized protocols for continuous SpO_2 monitoring during and after the 6MWT, including clear definitions of the nadir SpO_2 value and the target recovery threshold to enhance the clinical applicability of this prognostic marker (9,12). Single-center retrospective design and relatively small number of patients are the main limitations of this study, limiting the generalizability of our findings. The modified GAP index was tested among IPF patients in a single tertiary care center with the possibility of referral bias, and thus performance of modified GAP index should be further evaluated in other larger and different IPF cohorts. Also, while the categorical thresholds in the original GAP index staging were maintained, it is possible that modifying one or more of the GAP index parameters could have improved its final performance. In conclusion, our findings indicate that both SpO2 recovery time (a cut-off value of >160) and modified GAP index (at a cut-off value of >3.5) were able to discriminate IPF patients at risk of adverse clinical outcomes, besides their significant role in predicting the overall adverse events. Accordingly, incorporating SpO2 recovery time to the 6MWT protocol and to a modified GAP index may improve mortality risk prognostication in IPF with its potential to unmask the hidden impairments in gas exchange and the deteriorating cardiopulmonary status, supporting the utilization of continuous SpO_2 monitoring and recovery analysis during routine 6MWT. Nonetheless, clinical relevance of modified GAP index should be further investigated in larger cohorts to determine its ability to provide an improved model discrimination and prognostication in the setting of IPF. Also, the prognostic utility of SpO_2 recovery time should also be validated in larger prospective cohorts of IPF patients, while it should also be explored whether improving SpO_2 recovery kinetics as a modifiable target would translate into better clinical outcomes.

Conflict of Interest: Each author declares that 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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