Prognostic Value of Cardiopulmonary Exercise Test, Pulmonary Function Test, and Questionnaires on Mortality in Patients With Idiopathic Pulmonary Fibrosis: A Prospective Pilot Study

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Abstract

Background and Objective: Idiopathic pulmonary fibrosis (IPF) is a lung disease with a high mortality rate. Finding an effective predictor of survival is therefore important for clinicians and patients. Several parameters have been established to predict mortality, but none of these have been validated in the Asian population. In this study, we evaluated the prognostic value of the parameters of cardiopulmonary exercise test (CPET), pulmonary function test (PFT), 6-min walk test (6MWT), and certain questionnaires on mortality in Asian patients with IPF.

Methods: This prospective observational study analysed patient data, including age, gender, height, and body weight; scores of Saint George's Respiratory Questionnaire (SGRQ), Modified Medical Research Council (mMRC) for dyspnoea, and Short Form-36 (SF-36); and parameters of PFT, 6MWT, and CPET.

Results: In total, 24 patients diagnosed as having IPF were followed up for 14 months, during which 3 patients died. The nonsurvivors had significantly lower body weight; lower forced vital capacity (FVC); higher ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC); higher gender, age, and pulmonary physiology (GAP) index; shorter walk distance in 6MWT; lower end-tidal pressure of carbon dioxide (DLCO); higher functional aerobic impairment (FAI) during exercise; and higher mMRC score. FEV1/FVC, FAI, GAP index, and mMRC dyspnoea score demonstrated an area under curve (AUC) of >0.7, and the corresponding cut-off values were 89%, 54%, 7, and 3.

Conclusions: The predictive abilities of PFT, CPET, and mMRC scores were validated successfully in the study cohort of Asian patients with IPF.

Short Title: Mortality predictors in idiopathic pulmonary fibrosis

Summary at a Glance: Our study examined the survival predictive ability of parameters of cardiopulmonary exercise test, pulmonary function test, and several questionnaires in Asian patients with IPF. The ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC); functional aerobic impairment; gender, age, and pulmonary physiology (GAP) index; and Modified Medical Research Council (mMRC) dyspnoea scores demonstrated higher prognostic value.

Keywords: Area under the curve, exercise test, pulmonary fibrosis, pulmonary function tests, surveys and questionnaires

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a type of progressive interstitial lung disease characterised by increased alveolar interstitial inflammation and cell proliferation, culminating in irreversible fibrotic changes.[1] Typically, the diagnosis of IPF is established once chronic hypersensitivity pneumonitis, sarcoidosis, connective tissue diseases, and other specific types of interstitial lung diseases are ruled out.[2] Compared with common chronic pulmonary diseases, the incidence of IPF is lower in East Asia and South America.[3] However, its incidence and mortality rate are increasing steadily worldwide.[4] Despite the disease course being highly variable, the median survival period is approximately 2–3 years from the time of diagnosis.[5] Poor prognosis and the relatively short survival time have made it imperative to identify the appropriate predictors of survival for this patient population.

Tools for monitoring and evaluating the mortality risk of patients with IPF include pulmonary function test (PFT),[6, 7] cardiopulmonary exercise test (CPET),[8-11] and 6-min walk test (6MWT).[12-15] PFT measures the lung volume, capacity, rates of flow, and gas exchange.[16] In IPF, a decrease in forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) are associated with increased mortality.[17] The survival rate can also be predicted by the 6-month rate of changes in total lung capacity (TLC), FVC, forced expiratory volume in 1 s (FEV1), and DLCO.[6] A lower FEV1/FVC ratio may be significantly associated with a higher survival rate.[7] CPET can predict the mortality rate in patients with idiopathic dilated cardiomyopathy[18] and congestive heart failure,[19, 20] and it can quantify the severity of coronary artery disease.[21] CPET data have been reported to predict mortality in patients with IPF.[8-11] 6MWT is a commonly used surrogate test to predict outcomes in patients with IPF. In 6MWT, the distance walked in 6 min,[22] decrease in the distance walked at 24 weeks,[13] recovery of heart rate after 1 min of the test,[23] and oxygen desaturation[24] are associated with increased mortality in patients with IPF. Gender, age, and the two physiologic variables in PFT “FVC” and “DLCO” have been recently integrated into the gender, age and pulmonary physiology (GAP) index,[25] which can also precisely predict the survival rate in patients with IPF.[26]

For monitoring IPF, the commonly used questionnaires that evaluate the overall health impact and the degree of breathlessness include Saint George’s Respiratory Questionnaire (SGRQ), Short Form-36 (SF-36), and Modified Medical Research Council (mMRC) dyspnoea scale. SGRQ is a comprehensive questionnaire to predict mortality in patients with COPD,[27] but it has also been validated for evaluating quality of life (QoL)[28, 29] and prognosis[30] in patients with IPF. SF-36 evaluates patient QoL and can also be applied for patients with IPF,[31, 32] although few studies have used SF-36 to predict mortality in IPF. The mMRC dyspnoea scale, a straightforward questionnaire for evaluating the impact of dyspnoea in daily life, has been demonstrated to predict mortality in patients with COPD[33, 34] or IPF.[35]

Many of the aforementioned tests predict the mortality of patients with IPF, but only some of them have been validated in Asians.[7, 26, 30, 35] In this study, we aimed to determine the prognostic value of CPET, PFT, GAP index, SGRQ score, mMRC score, and SF-36 score for mortality in patients with IPF. We hypothesised that the parameters of CPET (e.g., maximal oxygen consumption) and PFT (e.g., FVC) can more effectively predict the survival rate because of their objective design.

2. Materials and Methods

2.1. Study design

This prospective observational cohort study was conducted in a tertiary medical centre in central Taiwan. Patients diagnosed as having ILD and who agreed to provide informed consent were enrolled from Dec 2018 to April 2020. The study protocol was reviewed and approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB number, CE18325B; date of approval, Dec 18, 2018).

2.2 Study population and setting

In this study, a subgroup analysis of patients with a definite diagnosis of IPF according to the criteria of the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association was conducted.[36] The parameters included patient demographic data such as age, sex, height, body weight, and occupation. The index day was defined as the day on which the patient signed the inform consent form. The participants completed SGRQ, SF-36, and mMRC dyspnoea questionnaires on the index day. Within 1 week of enrolment, the participants were administered PFT, 6MWT and CPET. The patients were followed up for 14 months to trace the major outcomes, which included acute exacerbation, hospital admission, and mortality.

2.3 Pulmonary function test

In this study, PFT included two components. First, spirometry was conducted, which involves a period of quiet breathing, followed by expiration into the sensor as quickly and as long as possible after taking the deepest inspiration. FVC and FEV1 data were obtained from the results of the spirometry. Second, the difference in the partial pressure between the inspired and expired carbon monoxide was measured. After a deep inspiration, the participants had to hold their breath for 8–12 s. The DLCO value was obtained by measuring the subsequent air expiration. Both measurements were performed in accordance with the recommendations of the American Thoracic Society.[37]

2.4 Cardiopulmonary exercise test

We performed CPET by using an electromagnetically braked cycle ergometer.

All test procedures were performed in accordance with the guidelines of the American Heart Association and comprised 3-min rest and 3-min of unloaded pedalling, pedalling with the brake gradually applied in a ramp manner up to the maximal level tolerated by the patient, and unloaded pedalling for 3 min.[38] CPET provided the following data: oxygen consumption in relation to body weight (VO2/kg), functional aerobic impairment (FAI; ratio of the difference between the observed and the predicted peak oxygen consumption to the predicted peak oxygen consumption), percentage peak oxygen consumption in relation to the heart rate (O2 pulse), end-tidal partial pressure of carbon dioxide (PETCO2) at maximal exercise, minute ventilation to carbon dioxide output (VE/VCO2) slope, heart rate recovery at 1 min after peak exercise (HR recovery), O2 desaturation, ratio of dead space to tidal volume at rest (maximal Vd/Vt), and maximal exercise (minimal Vd/Vt) and change in Vd/Vt during the test.[39]

2.5 Six-Minute Walk Test

6MWT was performed in accordance with the guidelines of the American Thoracic Society. The patients were instructed to walk as far as possible for 6 min in a corridor between the two orange traffic cones placed 30-m apart.[40] Data on oxygen saturation and the distance walked in 6 min were obtained.

2.6 Statistical analysis

All the data were analysed using IBM SPSS Statistics 23.0 (Armonk, New York, USA) software. The Shapiro–Wilk test was used to examine variables with a normal distribution. For non-normally distributed data, the Mann–Whitney U and Fisher exact tests were used to determine the presence of any significant difference between survivors and nonsurvivors. The chi-square test was used to analyse discrete variables. Cox proportional regression analysis was performed for all the parameters measured. Subsequently, receiver operating characteristic (ROC) curve analysis was performed for the parameters that were significantly different between the survivors and nonsurvivors. The parameters with areas under curve (AUCs) of >0.7 were identified, and the cut-off points were decided to maximise the sum of sensitivity and specificity values of the respective ROC curves. Furthermore, the De Long test was used to determine the differences between the AUCs of each two parameters. A p value of <0.05 was considered significant.

3. Results

In total, 24 patients with IPF were enrolled into to this study, with a follow-up duration of 14 months. Three patients died during the follow-up, with a survival duration of 44, 201, and 319 days, respectively. Patient data, including age; gender; height; body weight; mMRC, SGRQ, and SF-36 scores; and 6MWT, PFT and CPET data were collected and compared between the survivors and nonsurvivors (Table 1). We found no significant differences in age or gender between the groups, but the nonsurvivors had significantly lower body weight and body mass index (BMI; Table 1). In intergroup comparison, lower FVC and FEV1, higher FEV1/FVC, and higher GAP values were found to be significantly associated with mortality (Table 1). The survivors demonstrated significantly longer walk distance in 6MWT, higher PETCO2 and lower FAI during maximal exercise (Table 1) and significantly lower mMRC scores.

The predictors of mortality were examined through univariable Cox regression analysis, and the data are presented in Table 2. Only the distance walked in 6MWT and the GAP index demonstrated significantly higher hazards ratio (HRs) for survival (6MWT distance: HR: 1.00, 95% confidence interval [CI], 0.99–1.01, $p = 0.949$; GAP index: 2.52, 0.64–9.89, $p = 0.185$). Further analysis of the data using the multivariable Cox regression model failed to identify any further parameters with a significant p value. ROC curve analysis was performed to further identify the predictors by excluding the effect of time to mortality. As shown in Table 3, the percentage of FEV1/FVC, FAI, GAP index, and mMRC score had an AUC of >0.7, and the corresponding cut-off values were 89%, 54%, 7, and 3. The ROC curve analysis for these four parameters is presented in Figure 1. The results of the De Long test, presented in Table 4, did not demonstrate significant differences between the AUC of each two of the four parameters, including the percentage of FEV1/FVC, FAI, GAP index, and mMRC score.

4. Discussion

In this preliminary study, we established the predictive value of PFT, CPET, and mMRC dyspnoea score for mortality in an Asian cohort of patients with IPF. Although statistical significance could not be achieved in the multivariable Cox regression analysis, the four important parameters FEV1/FVC in PFT, FAI in CPET, GAP index, and mMRC dyspnoea score with a significantly large AUC in the ROC curve analysis were identified. These parameters can provide a reference to enable healthcare workers to more effectively manage Asian patients with IPF. To the best of our knowledge, this is the first study to confirm the mortality predictive role of CPET for Asian patients with IPF.

In contrast to past studies,[8, 10] which have established that the absolute value of VO2/kg can serve as a survival predictor, our study highlighted the importance of the difference between the predicted and observed oxygen consumption. Typically, the maximal oxygen consumption in a healthy person can be predicted on the basis of age, sex, body height, and body weight,[41] and older women demonstrate lower oxygen consumption and older male patients with IPF demonstrate higher mortality.[25] Therefore, using the absolute value of VO2/kg instead of FAI in female patients with IPF could have the potential hazard of overestimating mortality. For example, an 80-year-old female patient in our survivor cohort demonstrated a considerably low VO2/kg value of 13.9 mL/min/kg during CPET. However, her FAI was only 15.17%, because her oxygen consumption during exercise was not significantly lower than the predicted value. Hence, using FAI to reflect the true difference in oxygen consumption between the observed and predicted value could more effectively predict mortality theoretically, and our results support this inference. We suggest the FAI can be used to predict mortality both in normal and overweight people[42] and in patients with IPF.[11] However, these findings from the pilot study require further investigation.

IPF is a restrictive lung disease, reflected by lowered PFT FVC, which has been shown to predict mortality in patients with IPF.[6, 17] By contrast, in our study, the higher percentage of FEV1/FVC was a more favourable mortality predictor, which could be attributed to faster progression in the decrement of FVC than FEV1 in the IPF disease course. A higher percentage of FEV1/FVC may signify an advanced stage of IPF and, therefore, higher mortality. Our results are in line with those of a few earlier studies.[7, 43, 44] Nishiyama et al. suggested FEV1/FVC as a significant predictor of survival in the Asian population.[7] Furthermore, their data revealed FEV1/FVC as an independent predictor in the multivariate analysis,[7] implying that the predictive ability of higher FEV1/FVC in mortality is not completely caused by lowered FVC. Our data also suggested the same phenomenon, although the reason for this finding remains unclear.

Since 2012, the GAP index, which is derived from the patient's gender, age, FVC, and DLCO, has been used for survival prediction.[25] In addition, the index has been successfully validated in the Asian population.[45] In our study, although the AUCs of FVC and DLCO were not large enough to predict mortality, the GAP index, with an AUC as high as 0.96, is a potential predictor of survival. In contrast to the original version of GAP staging, which has two cut-off values (i.e., ≤3 and ≥6), our result demonstrated only a single cut-off value of ≥7. This could be because of the predominance of men (79.17%) and older patients (66.42 ± 10.88 years) in our study cohort, which could have elevated the cut-off value, or the small sample size.

In our study, the mMRC, a simple questionnaire, demonstrated the highest AUC of 0.98, which is in line with the study by Nishiyama et al., who validated the predictive ability of mMRC in patients with IPF.[35] In our study, a cut-off value of ≥3 had predictive mortality for patients with IPF, which is higher than the cut-off value of ≥2 for patients with COPD in an earlier study.[34]

Our study has some limitations. First, the follow-up period was shorter; thus, only a limited number of mortality cases were assessed. If any of the data of the nonsurvivors were statistical outliers, the results of our study could be significantly affected. Second, the sample size was small. This was because of the relatively low prevalence of IPF in Taiwan (2.0–4.9 cases/100,000 persons).[46] If more patients were to be included in our study, the results of the multivariate Cox regression and Kaplan–Meier curve analysis would have been more convincing. However, our study was a prospective single-centred observational study of patients with newly diagnosed IPF. These preliminary results still hold value, especially for healthcare workers managing Asian patients with IPF.

5. Conclusions

For the first time, we demonstrated the potential survival prediction value of FAI during CPET in Asian patients with IPF. Moreover, the percentage of FEV1/FVC, GAP index, and mMRC dyspnoea score were favourable predictors of mortality. In areas where facilities for PFT or CPET are unavailable, healthcare workers can include the simple questionnaire of mMRC for dyspnoea to predict survival. However, further studies with larger study cohorts and longer follow-up durations are warranted to support our findings.

Declarations

Ethics approval and consent to participate: The study protocol was reviewed and approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB number, CE18325B; date of approval, Dec 18, 2018). Patients diagnosed as having ILD and who agreed to provide informed consent were enrolled from Dec 2018 to April 2020.

Consent for publication：Not applicable

Availability of data and materials：All data generated or analysed during this study are included in this published article

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Author Contributions: Y.Y.C. and P.K.F. contributed to the research, data review and collection, and statistical analyses. Y.Y.C., S.Y.L., and S.T.C. were responsible for data collection and statistical analyses. Y.Y.C., S.Y.L., S.T.C., C.H.L., and P.K.F. were responsible for data coding and result interpretation. Y.Y.C. and P.K.F. were responsible for the study design, result interpretation, and manuscript preparation. All of the authors discussed the results and contributed to the preparation of the final manuscript. All authors read and approved the final manuscript.

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

Figure Legends

Figure 1. Curve of ROC analysis for the four parameters include FEV1/FVC, GAP score, mMRC score, and FAI (%)

Table 1. Parameters of patients with IPF stratified by survival status

	Overall (n = 24)		Survivors (n = 21; 87.5%)		Non-survivors (n = 3; 12.5%)		p value
Age (years)	66.42	±10.88	66.05	±11.60	69.00	±2.00	0.988
Sex, n (%)							1.000
Female	5	(20.83)	5	(23.81)	0	(0)	
Male	19	(79.17)	16	(76.19)	3	(100)	
Height (cm)	164.70	±9.37	164.73	±9.85	164.47	±6.24	0.870
Body weight (kg)	64.62	±14.25	66.76	±13.85	49.60	±5.74	0.030*
Body mass index (kg/m^2)	23.67	±4.12	24.44	±3.77	18.34	±1.87	0.016*
CPET data							
VO2/kg (ml/kg/min)	14.68	±3.65	14.99	±3.78	12.47	±1.46	0.278
FAI (%)	43.77	±16.69	41.42	±16.48	60.23	±4.48	0.041*
O2 pulse (%)	72.04	±20.96	74.62	±21.03	54.00	±8.66	0.061
PETCO2 (kPa)	3.69	±0.67	3.80	±0.64	2.94	±0.29	0.015*
VE/VCO2 slope	38.52	±8.30	37.36	±7.69	46.67	±9.29	0.145
HR recovery (beat)	10.04	±7.78	11.10	±7.73	2.67	±2.52	0.051
O2 desaturation (%)	6.08	±4.85	5.76	±4.44	8.33	±8.08	0.625
Maximal Vd/Vt	32.38	±11.02	31.52	±10.67	38.33	±14.05	0.397
Minimal Vd/Vt	26.92	±12.24	25.95	±11.56	33.67	±17.50	0.445
Change of Vd/Vt during CPET	5.46	±3.09	5.57	±3.08	4.67	±3.79	0.378
PFT data							
FVC (liter)	2.17	±0.76	2.31	±0.70	1.20	±0.18	0.023*
FVC (% predicted)	70.29	±23.43	74.05	±22.48	44.00	±8.72	0.030*

FEV1 (liter)	1.80	±0.53	1.90	±0.49	1.10	±0.12	0.022*
FEV1 (% predicted)	73.63	±22.40	76.81	±22.05	51.33	±7.57	0.051
FEV1/FVC (%)	85.21	±9.19	84.10	±9.16	93.00	±5.29	0.035*
DLCO (ml/min/mmHg)	11.64	±4.14	11.99	±3.93	4.93		0.100
DLCO (% predicted)	63.90	±23.78	65.63	±23.09	31.00		0.100
GAP index	3.88	±2.03	3.38	±1.63	7.33	±0.58	0.004**
6MWT data							
Resting oxygen saturation (%)	95.17	±2.01	95.38	±1.96	93.67	±2.08	0.186
Exercise oxygen saturation (%)	86.96	±5.82	87.86	±5.33	80.67	±6.11	0.050
Oxygen desaturation in 6MWT (%)	8.21	±5.34	7.52	±4.71	13.00	±8.19	0.208
Distance walked (meters)	375.25	±138.52	403.10	±110.07	180.33	±185.41	0.031*
mMRC score	1.33	±1.24	1.00	±0.89	3.67	±0.58	0.001**
SGRQ score							
Symptoms score	40.61	±21.12	38.66	±21.93	52.93	±9.62	0.129
Activity score	57.15	±24.67	54.97	±24.27	67.29	±29.24	0.451
Impacts score	37.27	±27.49	33.90	±25.70	55.22	±35.66	0.138
Total score	46.82	±23.62	44.32	±22.87	58.50	±28.55	0.362
SF-36 score							
Physical domain score	53.53	±19.91	54.82	±20.38	40.00	±3.54	0.431
Mental domain score	55.36	±22.91	56.04	±23.53	48.25	±19.09	0.565
Total score	54.45	±20.50	55.43	±21.08	44.13	±11.31	0.514

CPET, cardiopulmonary exercise test; DLCO, diffusing capacity of the lungs for carbon monoxide; FAI, Functional aerobic impairment; FVC; forced vital capacity; FEV1; forced expiratory volume in 1 s; GAP index, gender, age, and the pulmonary physiology index; HR, heart rate; IPF, idiopathic pulmonary fibrosis; mMRC, Modified Medical Research Council; PETCO2, end-tidal partial pressure of carbon dioxide; PFT, pulmonary function test; SF-36, Short Form-36; SGRQ, Saint George's Respiratory Questionnaire; Vd/Vt, ratio of dead space to tidal volume at rest; VE/VCO2, minute ventilation to carbon dioxide output; VO2/kg, oxygen consumption in relation to body weight; 6MWT, 6-min walk test.

*$p < 0.05$, **$p < 0.001$.

Table 2. Univariate analysis of the mortality predictors in patients with IPF

	Univariate model		
	HR	(95% CI)	p value
Age	1.03	(0.88– 1.20)	0.744
Gender (male vs. female)	27.15	(0.00–16694714.86)	0.627
Height	1.00	(0.87– 1.15)	0.994
Body weight	0.92	(0.84– 1.01)	0.091
Body mass index	0.72	(0.51– 1.02)	0.067
CPET data			
VO2/kg	0.83	(0.56– 1.23)	0.354
FAI (%)	1.12	(0.97– 1.28)	0.114
O2 pulse	0.94	(0.86– 1.02)	0.134
PETCO2	0.03	(0.00– 4.33)	0.164
VE/VCO2 slope	1.11	(0.97– 1.27)	0.127
Heart rate recovery	0.74	(0.49– 1.13)	0.170
O2 desaturation	1.07	(0.87– 1.33)	0.519
Maximal Vd/Vt	1.07	(0.96– 1.19)	0.201
Minimal Vd/Vt	1.08	(0.97– 1.20)	0.167
Change of Vd/Vt during CPET	0.83	(0.51– 1.35)	0.450
PFT data			
FVC	0.12	(0.01– 1.24)	0.076
FVC (% predicted)	0.94	(0.87– 1.01)	0.104
FEV1	0.06	(0.00– 1.35)	0.077
FEV1 (% predicted)	0.94	(0.86– 1.02)	0.132
FEV1/FVC (%)	1.14	(0.95– 1.37)	0.167
DLCO	0.25	(0.01– 4.61)	0.349
DLCO (% predicted)	0.78	(0.38– 1.61)	0.499
GAP index	2.60	(1.01– 6.70)	0.047*
6MWT data			
Resting oxygen saturation	0.72	(0.41– 1.27)	0.259
Exercise oxygen saturation	0.85	(0.71– 1.03)	0.101
Oxygen desaturation in 6MWT	1.13	(0.95– 1.35)	0.170
Distance walked	0.99	(0.98– 1.00)	0.034*
mMRC score	38.54	(0.13– 11427.75)	0.209
SGRQ score			
Symptoms score	1.02	(0.98– 1.07)	0.355
Activity score	1.02	(0.97– 1.08)	0.451

Impacts score	1.03	(0.98– 1.09)	0.267
Total score	1.03	(0.97– 1.09)	0.361
SF-36 score			
Physical domain score	0.96	(0.86– 1.07)	0.456
Mental domain score	0.99	(0.93– 1.06)	0.873
Total score	0.98	(0.90– 1.07)	0.653

CI, confidence interval; CPET, cardiopulmonary exercise test; DLCO, diffusing capacity of the lungs for carbon monoxide; FAI, functional aerobic impairment; FVC; forced vital capacity; FEV1; forced expiratory volume in 1 s; GAP index, gender, age, and the pulmonary physiology index; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; mMRC, Modified Medical Research Council; PETCO2, end-tidal partial pressure of carbon dioxide; PFT, pulmonary function test; SF-36, Short Form-36; SGRQ, Saint George's Respiratory Questionnaire; Vd/Vt, ratio of dead space to tidal volume at rest; VE/VCO2, minute ventilation to carbon dioxide output; VO2/kg, oxygen consumption in relation to body weight; 6MWT, 6-min walk test. *$p < 0.05$.

Table 3. ROC curve analysis of the parameters with significant differences between the survivors and nonsurvivors

	AUC	p value	Cut-off point	Sensitivity	Specificity	Accuracy	PPV	NPV
mMRC	0.98	0.008**	≥3	100	90.48	91.67	60	100
GAP index	0.96	0.011*	≥7	100	95.24	95.83	75	100
FEV1/FVC (%)	0.87	0.040*	≥89	100	76.19	79.17	37.5	100
FAI (%)	0.87	0.040*	≥54	100	80.95	83.33	42.86	100

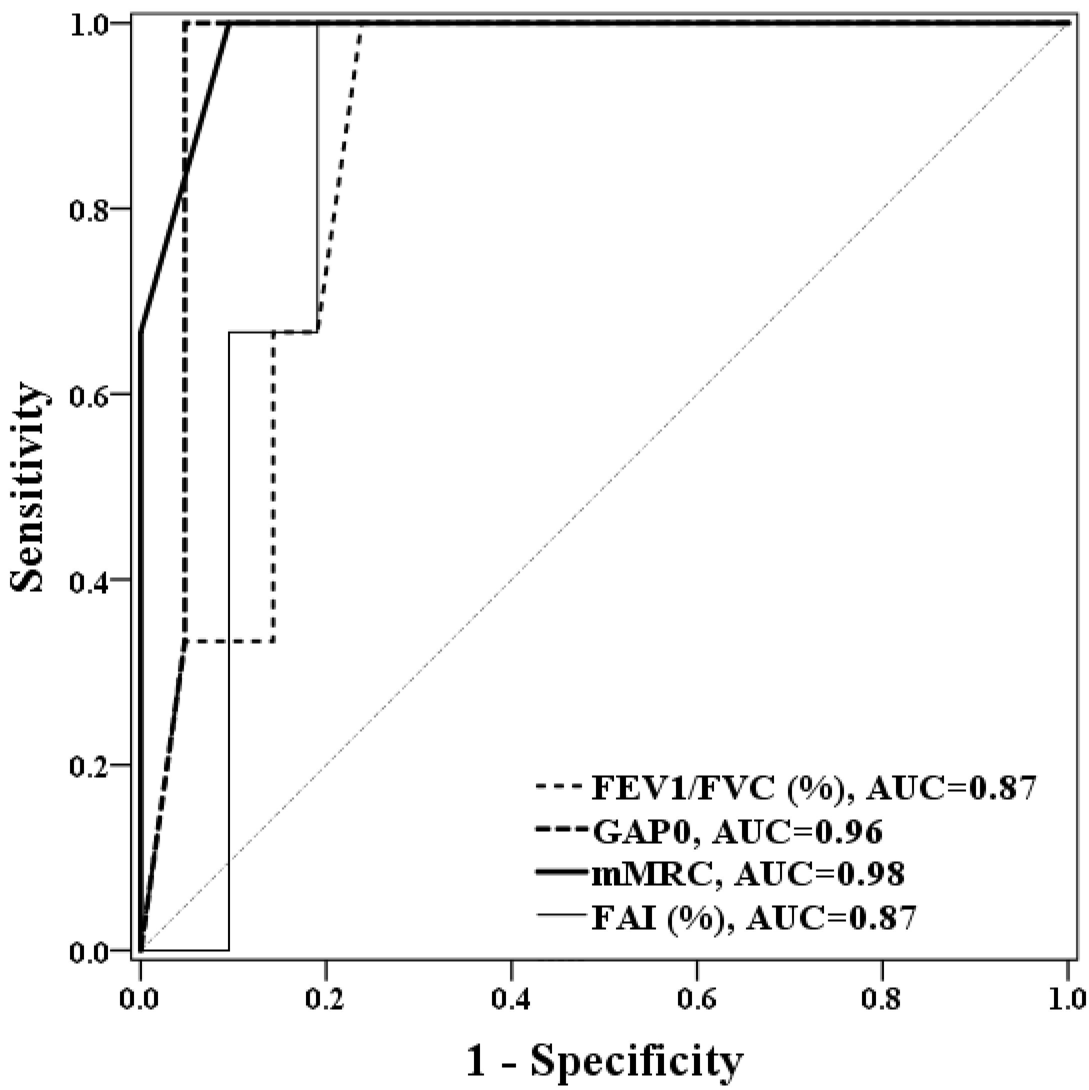
AUC, area under the curve; FAI, functional aerobic impairment; FVC; forced vital capacity; FEV1; forced expiratory volume in 1 s; GAP index, gender, age and the pulmonary physiology index; mMRC, Modified Medical Research Council; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.
*p < 0.05, **p < 0.01

Table 4. Differences in the AUC between each of the two parameters of FEV1/FVC, GAP index, FAI, and mMRC on the De Long test

		p
FEV1/FVC (%)	GAP index	0.220
	mMRC	0.135
	FAI (%)	1.000
GAP index	mMRC	0.507
	FAI (%)	0.333
mMRC	FAI (%)	0.170

Functional aerobic impairment, FVC; forced vital capacity; FEV1; forced expiratory volume in 1 s; GAP index, gender, age, and the pulmonary physiology index; mMRC, Modified Medical Research Council.

Figure 1. ROC curve analysis for the four parameters of FEV1/FVC, GAP score, mMRC score, and FAI (%)



Functional aerobic impairment, FVC; forced vital capacity: FEV1; forced expiratory volume in 1 s; GAP index, gender, age, and the pulmonary physiology index; mMRC, Modified Medical Research Council; ROC, receiver operating characteristic.

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