Features and predictive value of 6-min walk test outcomes in interstitial lung disease: an observation study using wearable monitors

Jiaying Li, Xiaoyan Li, Miaozhen Deng, Xinyin Liang, Huiqun Wei, Xiaobing Wu

ABSTRACT

Objectives To describe 6-min walk test (6MWT) outcomes, and to investigate their correlations with cardiopulmonary and lung function among patients with interstitial lung disease (ILD) which was not limited to idiopathic pulmonary fibrosis.

Methods We collected patients’ demographic data and obtained minute-by-minute 6MWT outcomes. Modified Borg scale was employed to assess patients’ dyspnoea, whereas New York Heart Association (NYHA) classification and pulmonary function test were used to evaluate patients’ cardiopulmonary functions.

Results Heart rate (HR) exhibited a continuous upward trend, while SpO2 exhibited an overall downward with a slight increase at the fifth minute. The SpO2 nadir for 70 patients (9.3%) was lower than 80%. Further, the SpO2 nadir for 78.27% of the participants appeared at the end of the fourth minute. The 6-min walk distance (6MWD) had the strongest correlation with NYHA classification (r=0.82, p<0.01). The ratio of 6MWD to predicted 6MWD was most correlated to forced expiratory volume in the first second (r=0.30, p<0.01) and forced vital capacity (r=0.30, p<0.01). SpO2 at 3 min had the strongest correlation to patients’ diffusion capacity of the lungs for carbon monoxide (r=0.41, p<0.01). We found significant differences in 6MWD (F=2.44, p=0.033), SpO2 change (F=2.58, p=0.025), HR at 0 min (F=2.87, p=0.014), HR at end of 6 min (F=2.58, p=0.025) and HR zenith (F=2.64, p=0.022) between the subtypes of ILD.

Conclusion This observation provided an important evidence regarding oxygen titration. It is better to maintain SpO2 above 88% for 4 min instead of 3 min. SpO2 at the third minute was the most valuable predictor of patients’ lung function. 6MWD and SpO2 changes were more discriminative in subtypes.

BACKGROUND

Interstitial lung disease (ILD) is a group of more than 200 kinds of diseases characterised by pulmonary inflammation, accompanied with or without fibrosis. Patients diagnosed with ILD mostly have dyspnoea and decreased tolerance to exercise. The 6-min walk test (6MWT) is widely used to assess patients’ performance ability with different cardiopulmonary-related diseases, which provides essential outcomes that cannot be obtained otherwise by standardised pulmonary function testing. Until, most 6MWT-related studies have focused on idiopathic pulmonary fibrosis (IPF), which is the most common type of ILD. Previous studies have investigated the outcomes of 6MWT, most of which centred on the 6-min walk distance (6MWD) and percutaneous oxygen saturation (SpO2). However, 6MWT is ideal in predicting patients’ clinical outcomes. Previous studies found that 6MWD and oxygen desaturation are associated with mortality in patients with IPF. According to a previous study, 6MWD was an independent positive factor for the physical activity of patients with IPF. In addition, 6MWD had a positive association with the subjective health-related quality of life (HRQL) and objective lung function index, which included the predicted percentage of forced vital capacity (FVC) and predicted lung diffusing capacity for carbon monoxide (DLco) as well as forced expiratory volume in the first second (FEV1) which is a negative predictor for dyspnoea. Furthermore, the occurrence of desaturation and changes in SpO2 during the test were indicators of patients’ mortality with IPF. 6MWT has multiple associated outcomes that are not restricted to 6MWD and SpO2. It comprises...
the distance walked, heart rate (HR), blood pressure, SpO2, and dyspnoea, as assessed by the Borg scale. Although the predictive value of oxygen desaturation for the clinical outcomes of the patients has been confirmed, the most predictive time point of this outcome within the 6min remains unclear. In addition, the effect of different subtypes of ILD on 6MWT outcomes has not been evaluated yet. Several studies highlighted the importance of finding the most prognostic outcome of 6MWT, and measuring SpO2 for the entire 6min duration of 6MWT is recommended by the 2014 technical standards of European Respiratory Society and American Thoracic Society. In the current study, wearable monitors were used to obtain the precise minute-by-minute data of 6MWT, which facilitated the descriptions and comparisons in detail. The comparison between subgroups of ILD will provide new insights into the distinguishing value of 6MWT outcomes.

Hence, to provide detailed features, the predictive value of 6MWT for cardiopulmonary functions, and its distinguishing value for the subtypes of ILD in the current study, we aimed to: (1) describe the detailed outcomes of 6MWT outcomes, including the HR, SpO2, blood pressure, Borg score and walking distance. (2) Identify the correlations between 6MWT outcomes and patients’ cardiopulmonary functions. (3) Investigate the effect of the differences between subclassifications of ILD on 6MWT outcomes.

**METHODS**

**Design**

This was an observational study using a wearable monitor.

**Patients**

All the patients were recruited from July 2019 to August 2020 at the Guangzhou Respiratory Health Institute, the biggest respiratory centre in China. We identified eligible patients based on the following inclusion and exclusion criteria—we included patients who were diagnosed with ILD, or whose condition was feasible to conduct 6MWT. The expert pulmonologist established the diagnosis based on patients’ symptoms, the radiologist’s opinion from the imaging tests, blood tests results, lung function tests, bronchoscopy and biopsy. We excluded patients who had walking limitations, including joint restrictions or other critical diseases and those who experienced myocardial infarction in the previous 5 days, unstable angina, syncope, symptomatic arrhythmia, severe aortic stenosis or decompensated heart failure due to another unstable medical issues. After the initial screening, we obtained informed consent from eligible participants before including them in the study.

**Measurements**

**Demographics questionnaire**

The self-designed demographic questionnaire included questions about the age, height, weight, body mass index and sex of the participants.

**NYHA functional classification**

The New York Heart Association (NYHA) classification was considered as a critical criterion for a comprehensive cardiac diagnosis. It classifies patients into four categories, based on their limitations during physical activity, which ranges from no symptoms with ordinary physical activity (class I) to symptoms at rest and increased discomfort with any physical activity (class IV).

**Borg scale**

The Borg Rating of Perceived Exertion scale was developed by Borg, which is widely used to measure patients’ effort and exertion, breathlessness and fatigue during physical work. A higher score indicated a more severe level of exertion.

**Outcomes of 6MWT**

According to Enright’s recommendations, the primary outcome in our study was 6MWD. We calculated the predicted 6MWD based on equations developed by Enright and Sherrill. For men, the predicted 6MWD=(7.57 * height-1)−(5.02 * age)-1.76 * weight−309 m. For women, the predicted 6MWD=(2.11 * height-1)−(2.29 * age)-1.76 * weight−667 m. Secondary outcomes include fatigue and dyspnoea, arterial oxygen saturation, HR and blood pressure. We measured fatigue and dyspnoea by modified Borg scale before and after 6MWT, and used wearable monitors to record patients’ arterial oxygen saturation and HR during 6MWT. We also recorded the patients’ blood pressure before and after the test, and calculate the mean arterial pressure. In this study, 6MWT was conducted without oxygen therapy support. Most of participants had received a 6MWT at the outpatient clinic before their hospital admission. In this case, the learning effect that improves the distance of second walk will be weak. Therefore, we conducted one 6MWT for each patient.

**Pulmonary function test**

Restriction of lung volumes and dysfunction of diffusion are the main functional respiratory abnormalities. An increased FEV1/FVC ratio, accompanied by a low total lung capacity, indicates restriction of lung volumes. Previous studies have proven that reduction in FVC and DLco are associated with poor survival rates and prognosis. Therefore, in this study, FVC, FEV1 and DLco were used for the respiratory function assessment.

**Subtypes of ILD**

Since ILD encompasses more than 200 parenchymal pulmonary disorders, we divided all the cases into subtypes, to facilitate the analysis. According to the classifications of Cottin et al, the subtypes contain idiopathic interstitial pneumonias, autoimmune ILDs, hypersensitivity pneumonitis, sarcoidosis and other ILDs. Because IPF is the most widely studied and the most common type of ILD, we classified it as a dependent category to make the comparisons more detailed. Therefore, we included six subtypes in total.
Data collection
We collected patients’ demographic data using a self-designed questionnaire, which was administered after 6MWT. The outcomes of the pulmonary function test and the NYHA functional classification were obtained from the patients’ medical records. The Borg scale was employed before and after walking. All the 6MWT-related outcomes were automatically collected using physiological parameters transmission management software during the 6-min module (Shenzhen zhongruiqi Electronic Technology Co.). Since the patients at the centre completed all the assessments and tests within 3 days of their admission, the outcomes of pulmonary function test, NYHA functional classification and 6MWT were obtained within the next 3 days.

Analysis
We used the statistical package for the social sciences (SPSS) software V.21.0 (IBM Corporation) for data analysis. We used descriptive statistics to summarise the participants’ demographics, 6MWT outcomes, Borg grades, NYHA functional classification and pulmonary function indexes. Specifically, we described continuous variables as mean and SD, and categorical variables as frequency. After performing a check for normality, we used the paired t-test to assess the differences in SpO2 between each end of the minute. Analysis of variance was used to assess the differences of 6MWT-related outcomes across the subtypes of ILD. We performed the Pearson correlation analysis to identify the correlations between the 6MWT outcomes and other measurements. Statistical significance was set at p<0.05.

Patient and public involvement
No patient involved.

RESULTS
Demographics and characteristics of patients
We included 954 patients with ILD from July 2019 to August 2020. The average age of participants was 55.40 (SD=12.35) years (range 14–83 years). The sample included 510 (53.50%) men (table 1).

Features of 6MWT outcomes among patients with ILD
For 750 participants with valid data, the SpO2 nadir was higher than 80%, and for 524 patients (69.9%) the SpO2 nadir was higher than 88. Other details are shown in table 2. Figure 1 shows patients’ SpO2 and HR during 6MWT. SpO2 generally showed a downward trend, but increased slightly at the end of the fifth minute, whereas HR exhibited a sharp increase in the first 2 min and reached a peak before becoming steady. Paired t-test found three significant drops in the SpO2, which occurred at the first minute (t=19.29, p<0.001), the second minute (t=25.38, p<0.001) and the third minute (t=4.75, p<0.001). This was accompanied by a slightly significant rise at the fourth minute (t=−2.06, p=0.039). Figure 2 depicts the time point when SpO2 nadir appears at the first time and the occurrence of SpO2 nadir at each end of a minute over 6 min. The SpO2 nadir of 63.87% and 78.27% of the participants’ appeared at the end of the third and the fourth minute, respectively.

Difference in 6MWT outcomes among subgroup of patients with ILD
Significant differences between the subtypes of ILD were found for 6MWD (F=2.44, p=0.033), SpO2 change (F=2.58, p=0.025), HR at 0 min (F=2.87, p=0.014), HR at end of 6 min (F=2.58, p=0.025) and HR zenith (F=2.64, p=0.022) (table 3).

Correlation between the outcomes of 6MWT and cardiopulmonary function
SpO2 was generally positively correlated to cardiopulmonary function, whereas the HR and Borg scale were negatively correlated. Specifically, the NYHA grade strongly correlated with 6MWD (r=0.82, p<0.01). The 6MWD/predicted 6MWD had the highest correlation coefficient with FVC (r=0.30, p<0.01) and FEV1 (r=0.30, p<0.01). SpO2 at the end of 3 min had the strongest correlation to DLco (r=0.41, p<0.01) (table 4).

DISCUSSION
This study described identified the correlation between 6MWT outcomes and cardiopulmonary function and compared the difference between subtypes of ILD on 6MWT outcomes. We found that the HR and SpO2 did not increase or decrease uniformly during walking. For approximately 10% of the patients, the SpO2 nadir was lower than 80%, but they completed the test. Besides, SpO2 nadir appeared at the end of the fourth minute for approximately 80% of patients. Therefore, 6MWD and SpO2 had the strongest correlation with heart function and lung function of ILD, respectively. Moreover,

Table 1 The demographic and characteristic information of patients with interstitial lung disease (ILD) (n=954)

| Variables       | Categories                 | N (%)/Mean (SD) |
|-----------------|----------------------------|-----------------|
| Height (cm)     | –                          | 161.08 (8.00)   |
| Weight (kg)     | –                          | 62.60 (10.60)   |
| BMI             | –                          | 24.07 (3.39)    |
| Subclass of ILD | Autoimmune ILDs            | 277 (29.00)     |
| IIPs            | 195 (20.40)                |
| IPF             | 171 (17.90)                |
| Sarcoidosis     | 50 (5.20)                  |
| Hypersensitivity pneumonitis | 177 (18.60) |                  |
| Others ILDs     | 37 (3.90)                  |
| Missing data    | 47 (4.90)                  |

BMI, body mass index; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis.
Table 2  The features of 6-min walk test (6MWT) outcomes among patients with interstitial lung disease

| Items                                      | N   | Minimum | Maximum | Mean (SD)          |
|--------------------------------------------|-----|---------|---------|--------------------|
| Systolic blood pressure before 6MWT (mm Hg)| 950 | 84      | 188     | 124.16 (17.26)     |
| Systolic blood pressure after 6MWT (mm Hg) | 734 | 88      | 242     | 138.46 (23.19)     |
| Diastolic blood pressure before 6MWT (mm Hg)| 950 | 50      | 128     | 77.64 (11.58)      |
| Diastolic blood pressure after 6MWT (mm Hg)| 734 | 49      | 167     | 82.45 (13.44)      |
| Mean arterial pressure before 6MWT (mm Hg) | 950 | 62.67   | 148.00  | 93.15 (12.16)      |
| Mean arterial pressure before 6MWT (mm Hg) | 734 | 66.67   | 182.00  | 101.12 (14.89)     |
| Heart rate at 0 min (times/min)           | 750 | 50      | 141     | 90.97 (14.48)      |
| Heart rate at 1 min (times/min)           | 749 | 65      | 177     | 107.69 (15.25)     |
| Heart rate at 2 min (times/min)           | 749 | 70      | 192     | 113.66 (16.33)     |
| Heart rate at 3 min (times/min)           | 749 | 68      | 199     | 115.43 (16.88)     |
| Heart rate at 4 min (times/min)           | 749 | 70      | 201     | 116.08 (17.65)     |
| Heart rate at 5 min (times/min)           | 749 | 66      | 195     | 116.49 (17.77)     |
| Heart rate at 6 min (times/min)           | 749 | 66      | 193     | 117.97 (18.00)     |
| Heart rate zenith (times/min)             | 750 | 70      | 201     | 121.38 (19.18)     |
| Heart rate change (times/min)             | 749 | −102.00 | 29.00   | −27.07 (14.45)     |
| SpO₂ at 0 min (%)                         | 750 | 82      | 100     | 95.49 (2.23)       |
| SpO₂ at 1 min (%)                         | 749 | 74      | 100     | 93.61 (3.46)       |
| SpO₂ at 2 min (%)                         | 749 | 65      | 99      | 91.03 (4.99)       |
| SpO₂ at 3 min (%)                         | 749 | 65      | 99      | 90.62 (5.82)       |
| SpO₂ at 4 min (%)                         | 749 | 58      | 99      | 90.49 (6.13)       |
| SpO₂ at 5 min (%)                         | 749 | 61      | 99      | 90.65 (6.23)       |
| SpO₂ at 6 min (%)                         | 749 | 56      | 99      | 90.54 (6.43)       |
| SpO₂ nadir (%)                            | 750 | 56.00   | 99.00   | 89.09 (6.44)       |
| SpO₂ change (%)                           | 748 | −10.00  | 33.00   | 4.96 (5.57)        |
| Distance (m)                              | 953 | 53      | 999     | 457.28 (98.40)     |
| Distance/ predicted distance (m)          | 953 | 12.49   | 175.1   | 84.74 (18.54)      |

Heart rate change and SpO₂ change were the values at the beginning minus the values at the end of 6 min respectively. SpO₂, peripheral capillary oxygen saturation.

Figure 1  Description of SpO₂ and heart rate (HR) in patients with interstitial lung disease during 6-min walk test.
group comparisons revealed that the 6MWD and SpO\textsubscript{2} change were more distinguishing for the subgroups of ILD.

Compared with previous studies, the average 6MWD in our study was 457.28 m, which was moderate.\textsuperscript{27,28} HR increased continuously and SpO\textsubscript{2} decreased, with a slight rise in the fifth minute. However, the results of a previous study showed a slight increase in the fourth minute and a sharp drop in SpO\textsubscript{2}.\textsuperscript{29} Since our study had a bigger sample size, the average 6MWD and tendency of SpO\textsubscript{2} were more representative. According to the standard, 6MWT should be terminated when SpO\textsubscript{2} falls below 80%.\textsuperscript{30} When SpO\textsubscript{2} was less than 88%, it was considered as a significant desaturation, and patients were recommended to take an oxygen supplement.\textsuperscript{31–33} Without oxygen supplements in our study, SpO\textsubscript{2} nadir were lower than 88% and 80% for 30.1% and 9.3% of the patients, respectively. They all completed 6MWT without any chest pain, leg cramps, unsteady gait, diaphoresis or a pale/ashen appearance, experiencing breathlessness, or reporting being too tired to continue. Our findings indicated that it is unwarranted to stop 6MWT when patients with ILD only experience desaturation without other indications of termination, which corroborate the findings of Afzal et al.\textsuperscript{34} The SpO\textsubscript{2} nadir is an essential outcome of 6MWT, and our research revealed that for 63.87% and 78.27% of the participants, SpO\textsubscript{2} nadir appeared at the end of the third and fourth minute respectively. Oxyhemoglobin saturation is generally performed with 6MWT to determine the oxygen flow that prevents oxygen saturation falling below 88%, measured using pulse oximetry (SpO\textsubscript{2}). According to Giovacchini et al.,\textsuperscript{35} after a certain dose of oxygen is administered, the patients’ SpO\textsubscript{2} should exceed 88% and be stable for 3 min. In our study, we found that the SpO\textsubscript{2} nadir for approximately 80% of the patients had appeared at the end of the fourth minute; hence, we strongly recommend that oxygen titration should be for 4 min.

Garin et al did not find significant differences between IPF and systemic sclerosis-associated ILD on 6MWD and dyspnoea,\textsuperscript{36} while Someya and Mugii found that patients with IPF had lower SpO\textsubscript{2} and higher Borg score than patients with dermatomyositis.\textsuperscript{37} We observed no significant differences between the subtypes for Borg score and SpO\textsubscript{2} after walking. Since previous studies merely compared two different subgroups of ILD, our results were more comprehensive and reliable. Contrary to dyspnoea and SpO\textsubscript{2} after walking, we found significant differences between groups on 6MWD and SpO\textsubscript{2} change. Therefore, 6MWD and SpO\textsubscript{2} change was the more distinguishing outcomes for subtypes of ILD. Although the HR at the 0 min, end of 6 min and HR zenith showed significant differences between the subtypes, this finding was unclear because baseline HR showed differences before walking. Therefore, future studies in another population or multicentre may reinforce the findings.

Similar to previous studies, 6MWD and SpO\textsubscript{2} positively correlated with cardiopulmonary function outcomes such as NYHA, FVC, FEV\textsubscript{1}, and DL\textsubscript{CO} \textsuperscript{5,8–10} while Borg score was negatively correlated.\textsuperscript{30} Compared with 6MWD and SpO\textsubscript{2}, the patients’ HR had a weaker positive correlation to cardiopulmonary function outcomes. Hence, SpO\textsubscript{2} and distance were more valuable than HR in predicting the patients’ cardiopulmonary function and degree of dyspnoea. In a study, 6MWD was more correlated to DL\textsubscript{CO} than SpO\textsubscript{2}; however, our result was to the contrary—lower FVC and DL\textsubscript{CO} were associated with poor prognosis and high mortality.\textsuperscript{16} 38–40 Nevertheless, the DL\textsubscript{CO} level was more valuable than FVC, as it captured the combined impact on the pulmonary reserve of IPF, emphysema and pulmonary hypertension.\textsuperscript{41} Since SpO\textsubscript{2} had the strongest correlation with DL\textsubscript{CO}, we recommend

![Figure 2](https://example.com/image2.png)
### Table 3  Difference between subgroups of interstitial lung disease (ILD) in 6-min walk test (6MWT) outcomes

| Measures                        | Categories                     | N    | Mean (SD)     | F     | P value |
|---------------------------------|--------------------------------|------|---------------|-------|---------|
| Borg score before 6MWT          | Autoimmune ILDs               | 267  | 0.25 (0.54)   | 1.59  | 0.16    |
|                                 | IIPs                           | 192  | 0.18 (0.50)   |       |         |
|                                 | IPF                            | 167  | 0.28 (0.51)   |       |         |
|                                 | Sarcoidosis                    | 49   | 0.18 (0.39)   |       |         |
|                                 | Others ILDs                    | 37   | 0.35 (0.63)   |       |         |
|                                 | Hypersensitivity pneumonitis    | 174  | 0.31 (0.59)   |       |         |
| Borg score after 6MWT           | Autoimmune ILDs               | 267  | 1.25 (1.15)   | 0.97  | 0.433   |
|                                 | IIPs                           | 192  | 1.32 (1.21)   |       |         |
|                                 | IPF                            | 167  | 1.37 (1.23)   |       |         |
|                                 | Sarcoidosis                    | 49   | 1.04 (0.98)   |       |         |
|                                 | Others ILDs                    | 36   | 1.14 (1.17)   |       |         |
|                                 | Hypersensitivity pneumonitis    | 174  | 1.38 (1.15)   |       |         |
| 6MWD (m)                        | Autoimmune ILDs               | 277  | 452.69 (96.25)| 2.44  | 0.033   |
|                                 | IIPs                           | 195  | 466.07 (96.86)|       |         |
|                                 | IPF                            | 171  | 440.70 (87.85)|       |         |
|                                 | Sarcoidosis                    | 50   | 479.36 (91.25)|       |         |
|                                 | Others ILDs                    | 37   | 482.30 (116.70)|     |         |
|                                 | Hypersensitivity pneumonitis    | 177  | 453.48 (107.31)|     |         |
| 6MWD/predicted 6MWD             | Autoimmune ILDs               | 277  | 0.84 (0.18)   | 0.84  | 0.521   |
|                                 | IIPs                           | 195  | 0.85 (0.19)   |       |         |
|                                 | IPF                            | 171  | 0.87 (0.18)   |       |         |
|                                 | Sarcoidosis                    | 50   | 0.87 (0.17)   |       |         |
|                                 | Others ILDs                    | 37   | 0.84 (0.23)   |       |         |
|                                 | Hypersensitivity pneumonitis    | 177  | 0.84 (0.19)   |       |         |
| SpO₂ at the 0 min (%)           | Autoimmune ILDs               | 219  | 95.75 (1.98)  | 2.14  | 0.059   |
|                                 | IIPs                           | 143  | 95.15 (2.53)  |       |         |
|                                 | IPF                            | 143  | 95.14 (2.33)  |       |         |
|                                 | Sarcoidosis                    | 45   | 95.40 (1.76)  |       |         |
|                                 | Others ILDs                    | 27   | 95.37 (3.12)  |       |         |
|                                 | Hypersensitivity pneumonitis    | 135  | 95.70 (2.21)  |       |         |
| SpO₂ at the end of 6 min (%)    | Autoimmune ILDs               | 218  | 90.78 (6.07)  | 2.14  | 0.059   |
|                                 | IIPs                           | 143  | 91.07 (5.74)  |       |         |
|                                 | IPF                            | 143  | 88.91 (6.49)  |       |         |
|                                 | Sarcoidosis                    | 45   | 90.89 (6.41)  |       |         |
|                                 | Others ILDs                    | 27   | 91.07 (5.86)  |       |         |
|                                 | Hypersensitivity pneumonitis    | 134  | 90.07 (7.85)  |       |         |
| SpO₂ nadir (%)                  | Autoimmune ILDs               | 219  | 89.20 (6.01)  | 1.421 | 0.215   |
|                                 | IIPs                           | 143  | 89.60 (5.52)  |       |         |
|                                 | IPF                            | 143  | 87.86 (6.56)  |       |         |
|                                 | Sarcoidosis                    | 45   | 88.89 (6.47)  |       |         |
|                                 | Others ILDs                    | 27   | 90.15 (5.82)  |       |         |
|                                 | Hypersensitivity pneumonitis    | 135  | 88.59 (8.08)  |       |         |
| SpO₂ change (%)                 | Autoimmune ILDs               | 218  | 4.98 (5.52)   | 2.58  | 0.025   |
|                                 | IIPs                           | 143  | 4.08 (5.04)   |       |         |
|                                 | IPF                            | 143  | 6.23 (5.05)   |       |         |
|                                 | Sarcoidosis                    | 45   | 4.51 (5.88)   |       |         |
|                                 | Others ILDs                    | 27   | 4.30 (3.61)   |       |         |

Continued
clinical practitioners to monitor the SpO2 of patients with ILD. Besides, the most valuable SpO2 time point remains unclear. A previous study revealed that SpO2 nadir and SpO2 change had the same degree of correlation with DLCO42, and another study also highlighted the critical predictive value of the SpO2 nadir.43 In contrast, our findings illustrated that SpO2 at the end of the third minute was more predictive than the SpO2 nadir and SpO2 change in DLCO. Although 6MWD/predicted 6MWD had a higher correlation to FEV1 and FVC than SpO2 at the end of the third minute, 6MWD was more susceptible to factors such as age, sex, shorter corridor and inappropriate walking shoes.44–46 Furthermore, DLCO was considered more critical than FEV1 and FVC for ILD. Hence, the third-minute SpO2 can be an alternative to predict lung function in patients with ILD.

Limitations and future research directions
This study had several limitations. First, we did not conduct the second 6MWT for patients, and so the measured distance might not be the longest potential distance. Second, 25% of the values regarding some non-critical variables were missing, which might introduce selection bias and affect the validity and representativeness of the results. Replication in another population or a multicentric study could reinforce the findings. Third, lack of follow-up on patients’ prognosis and mortality hindered the prediction of 6MWT outcomes on the long-term clinical outcomes. Future research is required to explore the association between the outcomes of 6MWT and long-term prognosis.

CONCLUSIONS
Despite the above limitations, this study showed that increased HR and decreased SpO2 during the 6MWT do not change uniformly. Approximately 10% of the patients, whose SpO2 was less than 80%, completed 6MWT without any discomfort indicated. Hence, it is unwarranted to halt 6MWT when patients with ILD experience only desaturation, without other indications of termination. SpO2 nadir appeared at the end of the fourth minute for approximately 80% of the patients, which provides an important

Table 3

| Measures                          | Categories                  | N     | Mean(SD)   | F    | P value |
|----------------------------------|-----------------------------|-------|------------|------|---------|
| Hypersensitivity pneumonitis     |                             | 134   | 5.63 (6.93)|      |         |
| HR at the 0min (times/min)       | Autoimmune ILDs            | 219   | 92.21 (15.09)| 2.87 | 0.014   |
| IIPs                             |                             | 143   | 91.12 (12.75)|    |         |
| IPF                              |                             | 143   | 87.15 (13.80)|    |         |
| Sarcoïdosis                      |                             | 45    | 88.44 (14.46)|    |         |
| Others ILDs                      |                             | 27    | 91.81 (13.76)|    |         |
| Hypersensitivity pneumonitis     |                             | 135   | 92.40 (15.61)|    |         |
| HR at the end of 6min (times/min)| Autoimmune ILDs            | 219   | 119.45 (17.65)| 2.58 | 0.025   |
| IIPs                             |                             | 143   | 118.76 (18.63)|    |         |
| IPF                              |                             | 143   | 113.05 (15.41)|    |         |
| Sarcoïdosis                      |                             | 45    | 118.33 (20.99)|    |         |
| Others ILDs                      |                             | 27    | 116.30 (16.22)|    |         |
| Hypersensitivity pneumonitis     |                             | 135   | 118.57 (18.77)|    |         |
| HR zenith (times/min)            | Autoimmune ILDs            | 219   | 122.29 (18.61)| 2.64 | 0.022   |
| IIPs                             |                             | 143   | 121.86 (19.58)|    |         |
| IPF                              |                             | 143   | 115.90 (15.79)|    |         |
| Sarcoïdosis                      |                             | 45    | 124.09 (23.88)|    |         |
| Others ILDs                      |                             | 27    | 122.22 (19.73)|    |         |
| Hypersensitivity pneumonitis     |                             | 135   | 122.07 (20.53)|    |         |
| HR change (times/min)            | Autoimmune ILDs            | 219   | −27.23 (14.95)| 0.8  | 0.547   |
| IIPs                             |                             | 143   | −27.64 (15.23)|    |         |
| IPF                              |                             | 143   | −25.90 (12.03)|    |         |
| Sarcoïdosis                      |                             | 45    | −29.89 (14.32)|    |         |
| Others ILDs                      |                             | 27    | −24.48 (12.92)|    |         |
| Hypersensitivity pneumonitis     |                             | 134   | −26.54 (14.52)|    |         |

HR, heart rate; IIPs, Idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis; 6MWD, 6-min walk distance; SpO2, peripheral capillary oxygen saturation.
### Table 4  Correlations between 6-min walk test (6MWT) outcomes and cardiopulmonary function

| Outcomes of 6MWT | NYHA | MAP before 6MWT | MAP after 6MWT | MAP change | FVC | FEV₁ | DL<sub>LCO</sub> |
|------------------|------|-----------------|----------------|------------|-----|------|-----------------|
| 6MWD (m)         | r    | 0.82**          | 0.07**         | 0.09*      | 0.08*| 0.24**| 0.17**          |
|                  | n    | 751             | 949            | 733        | 733 | 846   | 846             |
|                  |      | 806             |                |            |     |       |                 |
| 6MWD/predicted 6MWD | r   | 0.64**          | 0.09**         | 0.14**     | 0.09*| 0.30**| 0.30**          |
|                  | n    | 751             | 949            | 733        | 733 | 846   | 846             |
|                  |      | 806             |                |            |     |       |                 |
| SpO₂ at 0 min (%) | r    | 0.29**          | 0.03           | 0.01       | −0.02| 0.18**| 0.17**          |
|                  | n    | 750             | 746            | 732        | 732 | 644   | 644             |
|                  |      | 604             |                |            |     |       |                 |
| SpO₂ at end of 1 min (%) | r | 0.27**          | 0.02           | 0.01       | 0.01 | 0.24**| 0.21**          |
|                  | n    | 748             | 744            | 730        | 730 | 642   | 642             |
|                  |      | 602             |                |            |     |       |                 |
| SpO₂ at end of 2 min (%) | r  | 0.28**          | 0.05           | 0.03       | −0.01| 0.27**| 0.23**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| SpO₂ at end of 3 min (%) | r  | 0.29**          | 0.047          | 0.034      | 0.00 | 0.29**| 0.24**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| SpO₂ at end of 4 min (%) | r  | 0.27**          | 0.03           | 0.03       | 0.01 | 0.27**| 0.23**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| SpO₂ at end of 5 min (%) | r  | 0.27**          | 0.03           | 0.03       | 0.01 | 0.27**| 0.23**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| SpO₂ at end of 6 min (%) | r  | 0.26**          | 0.03           | 0.02       | 0.01 | 0.27**| 0.22**          |
|                  | n    | 748             | 744            | 730        | 730 | 642   | 642             |
|                  |      | 602             |                |            |     |       |                 |
| SpO₂ nadir (%)   | r    | 0.27**          | 0.05           | 0.04       | 0.01 | 0.28**| 0.24**          |
|                  | n    | 750             | 746            | 732        | 732 | 644   | 644             |
|                  |      | 604             |                |            |     |       |                 |
| SpO₂ change (%)  | r    | −0.18**         | −0.02          | −0.02      | −0.02| −0.24**| −0.19**          |
|                  | n    | 748             | 744            | 730        | 730 | 642   | 642             |
|                  |      | 602             |                |            |     |       |                 |
| Borg scale at 0 min | r  | −0.23**         | −0.02          | 0.02       | 0.05 | −0.12**| −0.06            |
|                  | n    | 727             | 926            | 714        | 714 | 829   | 829             |
|                  |      | 791             |                |            |     |       |                 |
| Borg scale at the end | r  | −0.25**         | −0.05          | 0.00       | 0.07 | −0.15**| −0.11**          |
|                  | n    | 726             | 925            | 713        | 713 | 828   | 828             |
|                  |      | 790             |                |            |     |       |                 |
| HR at 0 min (times/min) | r  | −0.02           | 0.05           | 0.03       | −0.01| −0.18**| −0.21**          |
|                  | n    | 750             | 746            | 732        | 732 | 644   | 644             |
|                  |      | 604             |                |            |     |       |                 |
| HR at end of 1 min (times/min) | r  | 0.16**          | 0.09**         | 0.106**    | 0.04 | −0.08  | −0.12**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| HR at end of 2 min (times/min) | r  | 0.18**          | 0.09*          | 0.13*      | 0.07 | −0.08  | −0.11**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| HR at end of 3 min (times/min) | r  | 0.18**          | 0.12**         | 0.16**     | 0.09*| −0.08  | −0.11**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| HR at end of 4 min (times/min) | r  | 0.19**          | 0.10**         | 0.14**     | 0.08*| −0.06  | −0.11**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| HR at end of 5 min (times/min) | r  | 0.22**          | 0.11**         | 0.16**     | 0.10**| −0.05 | −0.09*           |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| HR at end of 6 min (times/min) | r  | 0.24**          | 0.10**         | 0.16**     | 0.11**| −0.04 | −0.09*           |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |
| HR zenith (times/min) | r  | 0.19**          | 0.10**         | 0.12**     | 0.06 | −0.03  | −0.09*           |
|                  | n    | 750             | 746            | 732        | 732 | 644   | 644             |
|                  |      | 604             |                |            |     |       |                 |
| HR change (times/min) | r  | −0.32**         | −0.08*         | −0.17*     | −0.15**| −0.14**| −0.11**          |
|                  | n    | 749             | 745            | 731        | 731 | 643   | 643             |
|                  |      | 603             |                |            |     |       |                 |

*P<0.01, **P<0.05.

DL<sub>LCO</sub>, diffusing capacity of the lungs for carbon monoxide; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; HR, heart rate; MAP, mean arterial pressure; 6MWD, 6-min walk distance; NYHA, New York Heart Association; SpO₂, peripheral capillary oxygen saturation.
evidence regarding oxygen titration, that is, it is better to maintain SpO\textsubscript{2} above 88% for 4 min. Besides, the third-minute SpO\textsubscript{2} can be an alternative to predict patients’ lung function. Conclusively, 6MWD and SpO\textsubscript{2} change showed significant differences between the subtypes of ILD, which indicated that they were more distinguishing for the subtypes of ILD.

Acknowledgements The authors thank the other medical works for facilitating our data collection, they are Yann Xu, Yanfen Pan, Yanqiu Lv and Xian Li. We would also like to thank Editage (data collection, they are Yanni Xu, Yanfen Pan, Yanqiu LV and Xian Li. We would also like to thank Editage for English language editing.

Contributors JL and XW were involved in the design of the study, MD, Xiaoyan L and HW were responsible for the data collection. Xinyi L was involved in data analysis. JL drafted the manuscript. All the authors made contributions to the revision and approved the final version. XW is responsible for the overall content as guarantor.

Funding This research was supported by the First Affiliated Hospital of Guangzhou Medical University, and the funding number is ZH201822.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval Ethical principles of the Declaration of Helsinki was used for guide this study, and the research protocol has been approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University. The approval number is 2020 Nu.K-45. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data were available upon reasonable request from Xiaobing Wu (wxiaobing.gz@163.com).

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, and transform upon build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/.

ORCID iD Xiaobing Wu http://orcid.org/0000-0003-4644-2325

REFERENCES

1 Flaherty KR, Brown KK, Wells AU, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respir Res 2017;4:e000212.

2 Mikolasch TA, Porter JC. Transbronchial cryobiopsy in the diagnosis of interstitial lung disease: a cool new approach. Respiratory 2014;19:623–4.

3 Swigris JJ, Stewart AL, Gould MK, et al. Patients’ perspectives on how idiopathic pulmonary fibrosis affects the quality of their lives. Health Qual Life Outcomes 2005;3:61.

4 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.

5 Caminati A, Bianchi A, Cassandro R, et al. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Respir Med 2009;103:117–23.

6 Lancaster U. Utility of the six-minute walk test in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med 2018;13:1–7.

7 Wallaert B, Monge E, Le Rouzic O, et al. Physical activity in daily life of patients with fibrotic idiopathic interstitial pneumonia. Chest 2013;144:1652–8.

8 du Bois RM, Weycker D, Albera C, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am J Respir Crit Care Med 2011;183:1231–7.

9 Nathan SD, du Bois RM, Albera C, et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir Med 2015;109:914–22.

10 Mural M, Ferretti A, Ferro O, et al. Functional predictors of exertional dyspnea, 6-min walking distance and HRCT fibrosis score in idiopathic pulmonary fibrosis. Respiration 2006;73:495–502.

11 Kozu R, Jenkins S, Senju H. Evaluation of activity limitation in patients with idiopathic pulmonary fibrosis grouped according to medical Research Council dyspnea grade. Arch Phys Med Rehabil 2014;95:950–5.

12 Manali ED, Lyberopoulos P, Triantafillidou C, et al. MRC chronic dyspnea scale: relationships with cardiopulmonary exercise testing and 6-minute walk test in idiopathic pulmonary fibrosis patients: a prospective study. BMC Pulm Med 2010;10:32.

13 Eaton T, Young P, Milne D, et al. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005;171:1150–7.

14 Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:1084–90.

15 Przybyslawski T, Tomlaiak W, Siergiejko Z, et al. Polish respiratory Society guidelines for the methodology and interpretation of the 6-minute walk test (6MWT). Pneumonol Alergol Pol 2015;83:283–97.

16 Brown AW, Nathan SD. The value and application of the 6-minute-walk test in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2018;153:3–10.

17 Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428–46.

18 Miller-Davis C, Marden S, Leidy NK. The New York heart association classes and functional status: what are we really measuring? Heart Lung 2006;35:217–24.

19 Harvey RM. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels. J Am Med Assoc 1994;153:2054.

20 Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377–81.

21 Williams N. The Borg rating of perceived exertion (RPE) scale. Occup Med 2017;67:404–5.

22 Enright PL. The six-minute walk test. Respir Care 2003:48:783–5.

23 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158:1384–7.

24 Spencer LM, Allison JA, McKeough ZJ. Six-minute walk test as an outcome measure: are two six-minute walk tests necessary immediately after pulmonary rehabilitation and at three-month follow-up? Am J Phys Med Rehabil 2008;87:224–8.

25 Lobbard R, Johnston C. Written J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. Chest 1998;113:396–400.

26 Cottin V, Hirani NA, Hotchklin DL, et al. Presentation, diagnosis, and clinical course of the spectrum of progressive-fibrotic interstitial lung diseases. Eur Respir Rev 2018;27. doi:10.1183/16000617.0076-2018. [Epub ahead of print: 31 Dec 2018].

27 Nishiyama Y, Yamazaki R, Sano H, et al. Pulmonary hemodynamics and six-minute walk test outcomes in patients with interstitial lung disease. Can Respir J 2016;1:1–6.

28 Chetta A, Aiello M, Foresi A, et al. Relationship between outcome measures of six-minute walk test and baseline lung function in patients with interstitial lung disease. Sarcoïdosis Vasc Diffuse Lung Dis 2001;18:170–5.

29 Du Piessis JP, Fernandes S, Jamali R, et al. Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. Respirology 2018:23:392–398.

30 Holland AE, Spruit MA, Troosters T, et al. An official European respiratory Society/American thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428–46.

31 Casanova C, Cote C, Marin JM, et al. Distance and oxygen desaturation during the 6-minute walk test as predictors of long-term mortality in patients with COPD. Chest 2008;134:746–52.

32 Salzman SH. The 6-min walk test: clinical and research role, technique, coding, and reimbursement. Chest 2009;135:e52.

33 Hook JL, Arcasoy SM, Zemmel D, et al. Titrated oxygen requirement and prognostication in idiopathic pulmonary fibrosis. Eur Respir J 2012;39:359–65.

34 Afzal S, Burge AT, Lee AL, et al. Should the 6–Minute Walk Test Be Stopped If Oxygen Hemoglobin Saturation Falls Below 80%? Arch Phys Med Rehabil 2018;99:2370–2.
35 Giovacchini CX, Mathews AM, Lawlor BR, et al. Titrating oxygen requirements during exercise: evaluation of a standardized single walk test protocol. *Chest* 2018;153:922–8.

36 Garin MC, Highland KB, Silver RM, et al. Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma. *J Rheumatol* 2009;36:330–6.

37 Someya F, Mugil N. Limitations to the 6-minute walk test in dermatomyositis with interstitial lung disease in comparison with idiopathic interstitial pneumonia. *Clin Med Insights Circ Respir Pulm Med* 2013;7:CCPIM.S10764–6.

38 Holland AE, Dowman L, Fiore J, et al. Cardiorespiratory responses to 6-minute walk test in interstitial lung disease: not always a submaximal test. *BMC Pulm Med* 2014;14:136.

39 Ostojić P, Damjanov N. Different clinical features in patients with limited and diffuse cutaneous systemic sclerosis. *Clin Rheumatol* 2006;25:453–7.

40 Khanna D, Tashkin DP, Denton CP, et al. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. *Am J Respir Crit Care Med* 2020;201:650–60.

41 Wells AU. Novel exploratory data in interstitial lung disease. *Respirology* 2019;24:718–9.

42 Du Plessis JP, Fernandes S, Jamal R, et al. Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. *Respirology* 2018;23:392–8.

43 Lettieri CJ, Nathan SD, Browning RF, et al. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. *Respir Med* 2006;100:1734–41.

44 Nishiyama O, Yamazaki R, Sano H, et al. Pulmonary hemodynamics and Six-Minute walk test outcomes in patients with interstitial lung disease. *Can Respir J* 2016;2016:1–6.

45 Beekman E, Mesters I, Hendriks EJM, et al. Course length of 30 metres versus 10 metres has a significant influence on six-minute walk distance in patients with COPD: an experimental crossover study. *J Physiother* 2013;59:169–76.

46 Barrios JA, Crenshaw JR, Royer TD, et al. Walking shoes and laterally wedged orthoses in the clinical management of medial tibiofemoral osteoarthritis: a one-year prospective controlled trial. *Knee* 2009;16:136–42.