Six-minute walking test outweighs other predictors of mortality in idiopathic pulmonary fibrosis. A real-life study from the Swedish IPF registry

Ida Pesonen a, b, *, Jing Gao b, Dimitrios Kalafatis b, Lisa Carlson a, Magnus Sköld a, b, Giovanni Ferrara a, b, c

a Department of Respiratory Medicine and Allergy, New Karolinska University Hospital, Stockholm, Sweden
b Respiratory Medicine Unit, Department of Medicine, Karolinska Institutet Solna, Stockholm, Sweden
c Division of Pulmonary Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada

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ABSTRACT

Background and objective: Idiopathic pulmonary fibrosis (IPF) is a disease characterized by a progressive loss of lung function, a restrictive ventilatory impairment, and a high five-year mortality. Our aim was to characterize clinical features of IPF at baseline and to assess which of those that would predict mortality.

Methods: We used baseline data at inclusion collected from the Swedish IPF registry between January 2014 and October 2018. Patients were followed for at least six months. Demographics, lung function (forced vital capacity (FVC), total lung capacity (TLC), diffusion capacity of carbon monoxide (DLCO%), 6-min walking test (6MWT), lowest oxygen saturation during 6MWT (L-SpO2), King’s brief interstitial lung disease health status questionnaire (K-BILD) scores were collected. GAP index and Charlson Comorbidity Index (CCI) were calculated. Transplant-free survival was registered during the follow-up time.

Results: Two hundred and twenty patients were included in the study. Fifty-seven (26%) underwent lung transplant during a mean follow-up time of 24 months. Out of 220 patients, 63 patients (29%) had a FVC% equal or over 80% of predicted at baseline. Only 17 out of 155 (11%) patients had a normal TLC%. Walking distance during a 6MWT was an independent predictor of outcome death/transplant (HR 0.80, 95%CI 0.65–0.99, p = 0.037), when adjusted for TLC%, K-BILD and GAP stage in a multivariate cox regression model.

Conclusion: Our results confirm the relevance of the 6MWT as main predictor of mortality at diagnosis in IPF patients.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a prognosis worse than many forms of cancer and a median survival after diagnosis estimated between two and five years [1]. Two drugs have been approved worldwide to slow down the disease progression [2,3] and new compounds are currently under investigation in phase I-II. These drugs are expensive and all of them may have side-effects impairing quality of life (QoL).

Three potential clinical courses are described in IPF. About 20% have a slower progressive phenotype while other suffer from a rapid progressive disease [4]. Some patients have acute exacerbations but may be stable in between [5]. The disease course is not predictable, and so far, only multi-variable tools such as the GAP index have shown a predictive

Abbreviations: BMI, Body mass index; CCI, Charlson Comorbidity Index; DLCO%, Diffusing capacity of carbon monoxide, % of predicted; FEV1, Forced expiratory volume in 1 s; FEV1%, Forced expiratory volume in 1 s, % of predicted; FVC, Forced vital capacity; FVC%, Forced vital capacity, % of predicted; GAP, gender-age-physiology index for IPF; IPF, Idiopathic pulmonary fibrosis; K-BILD, King’s brief interstitial lung disease health status questionnaire; L-SpO2, Lowest oxygen saturation during a 6MWT; PFT, pulmonary function test; TLC, Total lung capacity; TLC%, Total lung capacity, % of predicted; QoL, Quality of life; 6MWD, 6-min walking distance; 6MWT, 6-min walking test.

* Corresponding author. Respiratory Medicine Unit, Department of Medicine, Karolinska Institutet Solna Department of Respiratory Medicine and Allergy, New Karolinska University Hospital Solna, SE-17176, Stockholm, Sweden.

E-mail addresses: ida.pesonen@ki.se (I. Pesonen), jing.gao@ki.se (J. Gao), dimitrios.kalafatis@ki.se (D. Kalafatis), lisa.carlson@sll.se (L. Carlson), magnus.skold@ki.se (M. Sköld), giovanni.ferrara@ki.se, ferrara@ualberta.ca (G. Ferrara).

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value for mortality at the time of diagnosis [5,6]. At the state of the art, a reduction of forced vital capacity, % of predicted, (FVC%) ≥ 10% in six months [7–9] and diffusing capacity of carbon monoxide, % of predicted (DLCO%) < 40% at diagnosis are common measurements used to predict mortality in IPF [1]. Home-daily spirometry [10] and relative change in FVC [11] have shown potential for shortening the observation time to predict mortality to three months, but they have been tested only on relatively small cohorts. Therefore, there is an urgent need for simple and easy-to-use tools to identify the patients at highest risk at the time of diagnosis.

Total lung capacity (TLC) is the lung volume measured by body plethysmography indicating restriction, and TLC, % of predicted (TLC%) is therefore an alternative to FVC% in interpreting lung function in interstitial lung diseases [12]. Often, IPF patients with a normal FVC% have already a deteriorated TLC% [12–14]. Additionally, the use of 6-min walking test (6MWT) is an established measurement on physical capacity in IPF patients at diagnosis and follow-up. In this registry-based cohort study, we tested the hypothesis that TLC% and 6MWT at baseline could be more accurate predictors of mortality compared to FVC%.

2. Materials and methods

2.1. The Swedish IPF registry

The Swedish IPF registry was launched in 2014 and includes patient data from 22 hospitals around the country [12]. All patients diagnosed with IPF according to the national and international guidelines are eligible for inclusion [15,16]. There are no specific exclusion criteria. After signing a written, informed consent, prospective data is collected. Patient data is entered in the database after each outpatient clinic visit. All visits and measurements are performed uniquely according to the patient’s standard care needs and no additional measurements or visits are required for the data collection in the Swedish IPF registry. Several measurements at the time of inclusion, e.g. pulmonary function testing (PFT), 6MWT, blood sampling and radiographic investigations, are included in the registry [12,17]. The PFT’s and 6MWT are both standardized and performed by a licenced biomedical analyst or a physiotherapist at each hospital [18,19]. Information about comorbidities, smoking habits, ongoing medications are self-reported by the patients, while health related Qol. is recorded using the King’s Interstitial Lung Disease (K-BILD) Questionnaire [20,21]. This Swedish IPF registry-based study was approved by the Stockholm’s Regional Ethical Committee (Ref No. 2014–12/01-31/4 and 2018/1449–31/1).

2.2. Study cohort

In this registry-based cohort study, patients consecutively included into the Swedish IPF registry were assessed. The study period for inclusion and follow-up was between January 1, 2014 and October 15, 2018. The inclusion criteria were: all patients diagnosed with IPF according to national and international guidelines [1,16], included in the registry with a lung function test performed six months prior to or after the consent date. Patients with a follow-up period shorter than six months were excluded, except for patients who had an outcome death or transplant within six months.

2.3. Measurements and variables

The following baseline variables collected at inclusion were extracted from the Swedish IPF registry: gender, age, smoking status (never smoker and ex/current smoker), body mass index (BMI), PFT (FVC%, TLC%, DLCO%), walking distance during a 6MWT (6MWD), lowest oxygen saturation during a 6MWT (L-\(\text{SpO}_2\)), Qol. (measured with K-BILD). The gender-age-physiology (GAP) index [6], which is a scoring system combining gender, age and lung physiology (FVC and DLCO), was extrapolated for every patient with the data available in the registry. The possible range is between zero and eight points. We divided GAP index in three stage groups (stage 1: 0–3 points, stage 2: 4–5 points and stage 3: ≥6 points) and used these groups for prediction of mortality within one, two and three years. A Charlson Comorbidity Index (CCI) was also calculated from the comorbidity data at baseline [22], with an ad hoc modified formula (coronary artery disease, other cardiovascular disease, diabetes, arterial hypertension, chronic obstructive pulmonary disease and cancer gave one point each and metabolic syndrome gave two points).

For the aims of this study, the main outcome variable was transplant-free survival, defined as the follow-up time from inclusion to death or lung transplant during the observation period. Patients who were alive at the end of the follow-up were censored and considered as survivors. The follow-up time for each patient was calculated in months to outcome or censoring. Consent date was considered as the baseline. PFTs performed within six months from the inclusion date were considered if data on PFTs were missing at the time of inclusion.

2.4. Statistical analysis

Categorical data on smoking habits and gender differences were presented as proportions and compared with Chi-squared test. Continuous data on age, BMI, PFT, 6MWD, L-\(\text{SpO}_2\), GAP index, CCI, K-BILD and follow-up time were presented as mean and standard deviation (SD) or range. Comparisons of baseline data between patients who had an outcome and those who were censored were compared with parametric and nonparametric statistical tests when appropriate.

Association between predictor variables and outcome were assessed with Cox regression analysis. Kaplan–Meier estimates and a log-rank test for mortality were performed to calculate mortality per year by GAP stages, TLC% and 6MWD. The cut off values for TLC% and 6MWD were chosen from the mean value for the patients.

The statistical software SPSS 20.0 (IBM Corp, Armonk, NY, USA) was used for the analyses.

3. Results

Two hundred and twenty patients from the Swedish IPF registry were included (Table 1). During a mean follow-up time of 24 months (range 6–48 months), 57 (26%) patients died and six (3%) underwent lung transplant. One hundred and fifty-one (69%) patients were male. Out of 220 patients, 63 patients (29%) had a FVC% equal or over 80%. Only 17 out of 155 (11%) patients had a TLC% equal or over 80% (Fig. 1). One hundred and sixty-three patients (74.1%) were treated with an anti-fibrotic drug (pirfenidone or nintedanib) for at least six months.

The GAP index could be calculated for 176 out of 220 patients. The most common reason for this loss was missing data for DLCO%. Since the reason for missing DLCO% is not shown in the registry, we were not able to consider it as a respiratory limitation. Patients who died or were transplanted had a lower TLC%, DLCO%, K-BILD and GAP index compared to survivors (Table 1).

An univariate cox regression analysis showed an association between TLC%, DLCO%, 6MWD, K-BILD, GAP stage and death or transplant (Table 2).

A cumulative rate of outcome in year one, two, three and four of 6%, 20%, 42% and 59%, respectively, is shown in the Kaplan Meier plot (Fig. 2A). There was a difference in survival between the three GAP stages (Fig. 2B). Patients with a TLC% above 66% of predicted had a better outcome-free survival compared to patients with lower TLC% (Fig. 2C). A 6MWD over 432 m was associated with a better transplant-free survival compared with a shorter walking distance (Fig. 2D).

When the above-mentioned variables were entered in a multivariate cox regression analysis, only 6MWD correlated inversely with the outcome, with higher 6MWD bearing lower risk of dying or being transplanted (Table 3).

Another model, excluding the GAP stage from the multivariate
Table 1
Baseline characteristics of the patients from the Swedish IPF Registry included in the study.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Censored</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
</tr>
<tr>
<td>Age</td>
<td>220</td>
<td>71.9 (7.5)</td>
<td>157</td>
</tr>
<tr>
<td>BMI</td>
<td>212</td>
<td>26.9 (3.9)</td>
<td>152</td>
</tr>
<tr>
<td>Gender f/m</td>
<td>69/</td>
<td>–</td>
<td>52/</td>
</tr>
<tr>
<td></td>
<td>151</td>
<td>105</td>
<td>46</td>
</tr>
<tr>
<td>Smoking status</td>
<td>58</td>
<td>–</td>
<td>39</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>138</td>
<td>–</td>
<td>98</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>9</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Missing</td>
<td>110</td>
<td>23.8 (15.3)</td>
<td>81</td>
</tr>
<tr>
<td>Pack-years (ex-smoker)</td>
<td>15</td>
<td>–</td>
<td>13</td>
</tr>
<tr>
<td>FVC %</td>
<td>220</td>
<td>72.0 (16.0)</td>
<td>157</td>
</tr>
<tr>
<td>FEV1%</td>
<td>220</td>
<td>77.8 (16.7)</td>
<td>157</td>
</tr>
<tr>
<td>TLC%</td>
<td>155</td>
<td>65.5 (12.2)</td>
<td>106</td>
</tr>
<tr>
<td>DLCO%</td>
<td>176</td>
<td>47.2 (13.5)</td>
<td>123</td>
</tr>
<tr>
<td>6MWD</td>
<td>140</td>
<td>432.2 (133.0)</td>
<td>99</td>
</tr>
<tr>
<td>L-SpO2</td>
<td>143</td>
<td>86.8 (6.3)</td>
<td>102</td>
</tr>
<tr>
<td>K-BILD</td>
<td>195</td>
<td>55.6 (10.8)</td>
<td>137</td>
</tr>
<tr>
<td>GAP index</td>
<td>176</td>
<td>4.0 (1.3)</td>
<td>123</td>
</tr>
<tr>
<td>CCI</td>
<td>148</td>
<td>4.4 (1.3)</td>
<td>101</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** Censored: patients still alive at the end of the study period; Outcome: patients who died or underwent lung transplant; BMI = body mass index; CCI = Charlson comorbidity index; DLCO = diffusion capacity of carbon monoxide; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; GAP index = gender, age, physiology – in points; K-BILD = King’s brief interstitial lung disease health status questionnaire; L-SpO2 = lowest oxygen saturation during a 6MWT; TLC = total lung capacity; 6MWD = walking distance during a 6MWT.

4. Discussion

Several randomized controlled clinical trials have used changes in FVC% and definite acute exacerbations [23] as a surrogate for mortality in IPF due to long follow-up periods and lack of events among patients with mild or moderate disease. Forced vital capacity under 80% is also used by national funding authorities as threshold for reimbursing antifibrotics, implying a risk for patients with preserved FVC to be untreated [17]. Studies have suggested that other events, such as hospitalization [24] and combination of definite and suspected acute exacerbations [23] could be used as surrogates to predict mortality.

In 2012, the GAP index combining age, gender, FVC% and DLCO% was introduced as a predictor of mortality [6]. Our study support GAP index as predictor also in Swedish IPF patients.

In our study, we were able to confirm the strong inverse predictive value of the distance walked during a 6MWT at baseline for the outcome death/transplant. Several studies using a variety of methodologies have shown similar results [25–27]. For example, a systematic review showed that a shorter 6MWD is associated with a higher mortality for patients with interstitial lung diseases with a weighted mean threshold of 254 m in four studies for predicting increased mortality [26]. A post hoc analysis by Du Bois et al. [25] suggested a threshold for a minimal clinically important difference-value as 24–45 m and a fourfold increase

Table 2
Univariate Cox regression analysis for the outcome death/transplant.

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.00–1.06</td>
<td>0.088</td>
</tr>
<tr>
<td>BMI</td>
<td>0.95</td>
<td>0.89–1.02</td>
<td>0.148</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.38</td>
<td>0.79–2.41</td>
<td>0.257</td>
</tr>
<tr>
<td>Smoking status (ex-smoker)</td>
<td>0.79</td>
<td>0.46–1.37</td>
<td>0.402</td>
</tr>
<tr>
<td>FVC %</td>
<td>0.88</td>
<td>0.74–1.04</td>
<td>0.142</td>
</tr>
<tr>
<td>DLCO%</td>
<td>0.72</td>
<td>0.57–0.90</td>
<td>0.005</td>
</tr>
<tr>
<td>6MWD%</td>
<td>0.49</td>
<td>0.39–0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>L-SpO2</td>
<td>0.73</td>
<td>0.48–1.10</td>
<td>0.134</td>
</tr>
<tr>
<td>K-BILD</td>
<td>0.70</td>
<td>0.54–1.09</td>
<td>0.004</td>
</tr>
<tr>
<td>GAP stage</td>
<td>1.86</td>
<td>1.22–3.88</td>
<td>0.004</td>
</tr>
<tr>
<td>CCI</td>
<td>1.01</td>
<td>0.80–1.27</td>
<td>0.950</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** BMI = body mass index; CCI = Charlson comorbidity index; DLCO = diffusion capacity of carbon monoxide; FVC = forced vital capacity; GAP = gender, age, physiology – in stages; K-BILD = King’s brief interstitial lung disease health status questionnaire; L-SpO2 = lowest oxygen saturation during a 6MWT; TLC = total lung capacity; 6MWD = walking distance during a 6MWT, *: every 10 unit change; #: every 50 m change.

Fig. 1. Scatter plots showing the distribution of FVC% (A) and TLC% (B) at baseline. Out of 220 patients, 63 patients (29%) had a FVC% equal or over 80% while only 17 out of 155 (11%) patients had a TLC% equal or over 80%. The limit of 80% of predicted identifying normality or abnormality is indicated.
in one year’s risk of mortality with a decline of 50 m during a period of six months compared to patients with a decline less than 25 m. A 6MWD under 250 m at baseline was associated with a two-fold risk for mortality in one year [28]. In our registry, the patients had a preserved 6MWD at inclusion. Thus, only 12 patients had a 6MWD less than 250 m. Therefore, we chose the mean value, i.e. 432 m, in order to be able to separate the patients in two groups depending on their walking distance. Further studies on relevant threshold value for Swedish IPF patients are needed in the future.

A registry based study in Australia showed that 6MWD, together with lower FVC%, desaturation during a 6MWT, a composite physiological index (CPI) and GAP stage were significant predictors of mortality [27]. Together with the Australian study, this is the first study analysing data from a real-world population highlighting the strong predictive value of 6MWD at baseline. However, in contrast to the Australian study, we analysed transplant-free survival and found that 6MWT outweighed all other variables, including GAP stage which was the strongest predictor of mortality in their study.

The 6MWT represents a valid measure of a patient’s daily physical activity and it is easy to perform without a need of expensive equipment, but it has some limitations. The 6MWD is affected by a learning effect and the technical factors used during the test. For instance, track length, walking aid, use of oxygen during the test and encouragement are factors that may influence the results. Therefore, the test should always be done under same conditions in order to be comparable with previous tests. Furthermore, patient characteristics also affect the results, where older, female, shorter and heavier patients score usually shorter distances. Many known comorbidities e.g. pulmonary hypertension and emphysema, can impact the result of the 6MWD [26,29]. Reference values for healthy persons are available; however, these are not validated for IPF patients [29,30].

The second aim of this study was to assess the predictive value of TLC % in staging IPF. As far as we know, the predictive value of TLC% is unknown. However, according to our results, 6MWD has the strongest predictive value for outcome death/transplant in IPF. Our model included other strong predictors of mortality, such as 6MWT and GAP index, therefore TLC% did not show a significant correlation with death/transplant. However, when the same multivariate analysis was performed without the GAP stage, TLC% did correlate significantly and inversely with the outcome. Furthermore, patients with TLC% > 66% of predicted had better survival; this value was chosen as cut-off for the analysis as it represented the mean value in our cohort. TLC% could be another predictor of outcome as demonstrated in a multivariate model excluding GAP index. The latter is a well-defined predictor, but it is a composite score; replacing it with a simple measure like TLC% would have clear practical advantages.

Our study is conducted with patient data from the real world, which is a strength compared to post hoc analyses of clinical trials. All outpatients are equally asked to consent in collection of patient data which guarantees the involvement of patients in every stage of the disease. Thus, it improves the generalizability of the results compared to clinical
trials, which often includes healthier patients with fewer comorbidities. The study has some limitations common for real-world data. Firstly, it was impossible to have all the measurements performed at the same time-point of inclusion. We needed to accept measurements performed within six months from the inclusion, which leads to a risk of immortality bias. There were missing data, mainly TLC%, DLCO% and 6MWD. However, this is mainly due to different local routines, thus a risk of selection bias is low.

Baseline characteristics in this study are similar to our previous reported data [12]. In comparison with other IPF registries’ baseline data, Swedish IPF patients were older than Australian (AIPFR) and German (INSIGHTS)-patients [27,31]. Swedish patients had the same FVC% as German patients but lower than Australian patients, DLCO% was slightly lower than Australian patients’ but higher than German patients’ [27,31]. Six-minute walking distance was similar in Swedish and Australian IPF patients while German IPF patients had a shorter distance [27,31].

Six-minute walking test and TLC are reported in different extent in publications from registries worldwide. As mentioned, INSIGHTS registry reports data on both 6MWT and TLC while AIPFR reports only 6MWT. All patients reported in INSIGHTS-registry performed a 6MWT, a majority of Swedish patients (64%) had a 6MWT performed while 43% of the patients in AIPFR performed a 6MWT. The national IPF-PRO registry from USA reports 6MWT but not TLC [32,33] while the Czech part of the EMPIRE registry does not report neither variable [34]. The European IPF registry (eurIPFreg) reporting data from Germany, France, Italy, Austria, Spain and Hungary, reports that both 6MWT and TLC is collected in the registry [35]. Thus, TLC is unevenly established in countries worldwide while 6MWT seems to be an important part of the clinical interpretation of IPF patients.

5. Conclusions

Six-minute walking test and TLC are used as a common baseline and follow-up measurements for IPF patients in Sweden. Our study aimed to assess the predictive value of 6MWT and TLC% in staging IPF and predicting mortality. In a cohort from the Swedish IPF registry, 6MWT outperformed other simple and composite baseline measurements as the strongest predictor of transplant-free survival.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ida Pesonen: Conceptualization, Methodology, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. Jing Gao: Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing. Dimitrios Kalafatis: Conceptualization, Methodology, Resources, Writing - review & editing. Lisa Carlson: Conceptualization, Resources, Data curation, Writing - review & editing. Magnus Sköld: Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition. Giovanni Ferrara: Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition.

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Appendix A. Supplementary data

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