IPF Clinical Course, Patient Outcomes, and Healthcare Resource Utilization

Findings from recent publications based on chart reviews of patients with IPF in the United States

IPF, idiopathic pulmonary fibrosis.

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Speaker Disclosure

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Agenda

- IPF disease state overview
- Review study: Change in FVC and associated subsequent outcomes in patients with newly diagnosed IPF
- Review study: Association of early suspected acute exacerbations of IPF with subsequent clinical outcomes and HRU

FVC, forced vital capacity; HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.

IPF Overview

IPF is a rare and serious lung disease of unknown etiology\textsuperscript{1-5}*
- A type of idiopathic interstitial pneumonia, which is one form of ILD\textsuperscript{5}
- Up to 132,000 people affected in the United States\textsuperscript{2,6†}
  - Median age at diagnosis is 66 years\textsuperscript{2,7,8}

IPF is difficult to diagnose
- Average time from symptom onset to IPF diagnosis is 1-2 years\textsuperscript{7,9,10}

ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

*Rare Diseases Act of 2002: defines orphan diseases as rare diseases and disorders that affect populations smaller than 200,000 individuals in the United States.\textsuperscript{1}
†Estimated based on Raghu et al and 2010 US census data.\textsuperscript{2,6}

FVC is a pulmonary function measure used in assessing prognosis in IPF patients. IPF prognosis is poor with a 5-year survival rate of 20%-40%. Median survival time is estimated as 2-5 years from diagnosis.

Worse than many forms of cancer, including colon and kidney cancers and leukemia.

IPF survival stratified by initial FVC%

Kaplan-Meier survival estimates for change in FVC%

IPF has a highly variable and poorly predictable clinical course, whose relative frequency is unknown. The disease may be complicated by an episode of acute disease worsening of unknown cause, referred to as an "acute IPF exacerbation" if it meets clinical and radiological criteria.

**IPF Overview (cont'd)**

FVC, forced vital capacity; FVC%, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis.

Change in forced vital capacity and associated subsequent outcomes in patients with newly diagnosed idiopathic pulmonary fibrosis


Overview

Background

• Limited evidence published on the impact of lung-function loss on patient outcomes
• Key stakeholders could find such data useful for improving IPF management

Objective

• Assess the association of lung-function change with clinical outcomes and IPF-related healthcare resource utilization in patients with newly diagnosed IPF

IPF, idiopathic pulmonary fibrosis.

Methodology

Data sources, sample selection, and study period

- 168 pulmonologists in the United States conducted chart reviews
- 490 total IPF patients met the following pre-defined eligibility criteria
  - Aged ≥ 40 years with confirmed date of first IPF diagnosis with HRCT and/or lung biopsy between 1/1/2011 and 6/30/2013
  - FVC recorded at first IPF diagnosis (± 1 month) and at 6 months (± 3 months) following diagnosis
- Data were collected from the date of initial IPF diagnosis until last follow-up
  - Concurrent period: Time from initial diagnosis to the FVC measurement closest to 6 months post-diagnosis
  - Subsequent period: Available follow-up period after the concurrent period

FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis.

Reference:

Methodology (cont’d)

Main independent variable

- Relative change in FVC percent predicted (FVC%) over the concurrent period (first 6 months after diagnosis)

Patients were categorized into the following groups based on change in FVC%:

- Stable group
  - <5% decrease in FVC%
- Marginal decline group
  - ≥5% and <10% decrease in FVC%
- Significant decline group
  - ≥10% decrease in FVC%

FVC, forced vital capacity; FVC%, forced vital capacity percent predicted.

Reference:
Outcome Measures

Clinical outcomes
- Mortality (all-cause or due to IPF or suspected acute IPF exacerbation)
- Suspected acute IPF exacerbation*
- IPF progression†

Rate of IPF-related HRU in:
- Outpatient settings
- Emergency rooms
- Hospitals

DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.

*Suspected acute IPF exacerbation was defined by asking participating pulmonologists if a particular outpatient visit, emergency room visit, or hospitalization was related to an acute IPF exacerbation.

†IPF progression was based on physician reporting of emergence of any of the following since the previous visit: progressive dyspnea, increased cough, sustained reduction of forced vital capacity (FVC) and DLCO, progression of fibrosis from baseline on HRCT, acute IPF exacerbation, respiratory failure, new need for supplemental oxygen, or increase in oxygen requirements.


Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Total N=490</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.1</td>
<td>10.8</td>
</tr>
<tr>
<td>FVC at diagnosis (liters)</td>
<td>2.5</td>
<td>1.0</td>
</tr>
<tr>
<td>FVC% at diagnosis</td>
<td>60.4%</td>
<td>26.1</td>
</tr>
<tr>
<td>DLco% at diagnosis</td>
<td>51.3</td>
<td>15.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>335</td>
</tr>
<tr>
<td>White</td>
<td>369</td>
</tr>
<tr>
<td>Commercial/private plans</td>
<td>238</td>
</tr>
<tr>
<td>Medicaid</td>
<td>55</td>
</tr>
<tr>
<td>Current smokers</td>
<td>48</td>
</tr>
</tbody>
</table>

FVC% change groups

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>250</td>
</tr>
<tr>
<td>Marginal decline</td>
<td>98</td>
</tr>
<tr>
<td>Significant decline</td>
<td>142</td>
</tr>
</tbody>
</table>

DLco, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; FVC%, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.

Results: Clinical Outcomes

Clinical outcomes by FVC% change group* in the subsequent period†, unadjusted

<table>
<thead>
<tr>
<th></th>
<th>Stable (N=250)</th>
<th>Marginal decline (N=98)</th>
<th>Significant decline (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of suspected AEEx</td>
<td>19.2%</td>
<td>37.1%</td>
<td>50.9%</td>
</tr>
<tr>
<td>Risk of progression</td>
<td>62.6%</td>
<td>76.2%</td>
<td>85.6%</td>
</tr>
<tr>
<td>Mortality risk by 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to any cause</td>
<td>6.4%</td>
<td>13.1%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Death due to IPF</td>
<td>5.5%</td>
<td>10.3%</td>
<td>24.3%</td>
</tr>
<tr>
<td>Death due to AEEx</td>
<td>5.0%</td>
<td>9.3%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

AEEx, acute exacerbation; FVC%, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis.

* Lung-function change categories were defined as the relative change in FVC% from index to approximately 6 months following IPF diagnosis. “Stable” was defined as decline <5%. “Marginal” was defined as decline ≥5% and <10%, while “Significant” was defined as decline ≥10%.

† Defined as the available follow-up period after the concurrent period.


Results: Healthcare Resource Utilization

• Overall incidence rates of outpatient visits, ER visits, and hospitalization in this study cohort were 2.39, 0.43, and 0.34 per patient-year, respectively
• Overall 12-month risks of outpatient visits, ER visits, and hospitalization in this study cohort were 96.6%, 21.5% and 15.2%, respectively

HRU by FVC% change group* in the subsequent period, unadjusted

<table>
<thead>
<tr>
<th></th>
<th>Stable (N=250)</th>
<th>Marginal (N=98)</th>
<th>Significant (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month incidence rate, per patient per year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of IPF-related outpatient visits</td>
<td>2.24</td>
<td>2.57</td>
<td>2.65</td>
</tr>
<tr>
<td>Rate of IPF-related ER visits</td>
<td>0.35</td>
<td>0.54</td>
<td>0.63</td>
</tr>
<tr>
<td>Rate of IPF-related hospitalizations</td>
<td>0.24</td>
<td>0.32</td>
<td>0.61</td>
</tr>
<tr>
<td>12-month risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of having ≥1 outpatient visit</td>
<td>97.5%</td>
<td>97.3%</td>
<td>95.0%</td>
</tr>
<tr>
<td>Risk of having ≥1 ER visit</td>
<td>14.4%</td>
<td>29.4%</td>
<td>32.4%</td>
</tr>
<tr>
<td>Risk of having ≥1 hospitalizations</td>
<td>7.8%</td>
<td>19.1%</td>
<td>30.0%</td>
</tr>
</tbody>
</table>

ER, emergency room; FVC%, forced vital capacity; FVC%, forced vital capacity percent predicted; HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.

* Lung-function change categories were defined as the relative change in FVC% from index to approximately 6 months following IPF diagnosis. “Stable” was defined as decline <5%. “Marginal” was defined as decline ≥5% and <10%, while “Significant” was defined as decline ≥10%.

Results: Multivariable Analysis

<table>
<thead>
<tr>
<th>Outcomes in the subsequent period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality*</td>
</tr>
<tr>
<td>Hospitalization*</td>
</tr>
<tr>
<td>Suspected acute IPF exacerbation*</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>P-value</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>P-value</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>P-value</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-function decline group (concurrent period)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal decline vs stable</td>
<td>2.38 (1.04-5.45)</td>
<td>0.036</td>
<td>2.50 (1.06-6.91)</td>
<td>0.033</td>
<td>2.02 (1.13-3.59)</td>
<td>0.011</td>
</tr>
<tr>
<td>Significant decline vs stable</td>
<td>4.42 (2.01-9.71)</td>
<td>&lt;0.001</td>
<td>3.37 (1.62-7.00)</td>
<td>&lt;0.001</td>
<td>2.86 (1.60-4.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; GAP, gender-age-physiology; IPF, idiopathic pulmonary fibrosis.

Multivariable Cox proportional hazards regression was used to estimate the hazard ratio, 95% confidence interval, and P-value, accounting for physician clustering using generalized estimating equations. Other variables included race, body mass index, comorbidities, smoking status, use of prednisone and azathioprine in the concurrent period, symptoms at initial IPF diagnosis, physician's main practice setting, and GAP index. Suspected acute IPF exacerbation occurring in the concurrent period.


Limitations

- Findings may not be applicable to patients diagnosed with IPF outside the practice of the participating pulmonologists or outside the study period
- Potential for incomplete patient chart information and data entry errors from participating pulmonologists
- Patients who had smaller declines or improvements in FVC% within the stable group were not further stratified
- Pulmonologists likely did not adhere to the strict definition of acute IPF exacerbation established by Collard et al. in 2007 when reporting suspected acute IPF exacerbations
- Patients on both ends of the IPF severity spectrum may not have been included in the study

FVC%, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis.

Conclusions and Discussion

Greater FVC% decline in the first 6 months after the initial IPF diagnosis is associated with worse clinical outcomes and increased IPF-related HRU

- The increase in HRU after FVC% decline supports the importance of preservation of lung function

Future studies examining treatments that help slow lung function deterioration are warranted along with:

- Additional studies identifying predictors of patients at greatest risk of FVC% decline in the months following diagnosis
- Evaluating effect of lung-function change across subgroups of patients

FVC%, forced vital capacity percent predicted; HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.


Conclusions and Discussion (cont’d)

There is a need for definitions and categorization of IPF worsening that may be more relevant to IPF physicians’ daily practice and capture less severe events than those defined by the Collard et al. definition of an acute IPF exacerbation.

Management options that address FVC decline may help to improve health outcomes and reduce HRU in IPF patients.

FVC, forced vital capacity; HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.

Overview

Background
- Limited data on early acute IPF exacerbations in real-world settings and its association with clinical outcomes and IPF-related HRU
- Data on the impact of early acute IPF exacerbations on subsequent outcomes could be useful for IPF management

Objective
- Quantify the association of suspected early acute IPF exacerbations with clinical outcomes and IPF-related HRU in patients newly diagnosed with IPF

HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.

Methodology

Data sources, sample selection, and study period

• 168 pulmonologists in the United States conducted chart reviews
• 490 total IPF patients met the following pre-defined criteria
  – Aged ≥40 years with confirmed date of first IPF diagnosis with HRCT and/or lung biopsy between 1/1/2011 and 6/30/2013
  – FVC recorded at first IPF diagnosis (±1 month) and at 6 months (±3 months) following diagnosis
• Data were collected from the date of initial IPF diagnosis until last follow-up
  – Last follow-up was defined as either the last contact the pulmonologist had with the patient for those who were alive at chart abstraction, or the date of patient death


Methodology (cont’d)

Main independent variable

• Suspected acute IPF exacerbation in the first 6 months after initial IPF diagnosis was defined as early acute IPF exacerbation
  – Identified by asking participating pulmonologists if a particular outpatient visit, emergency room visit, or hospitalization was related to an acute IPF exacerbation

Study group definition (“early acute IPF exacerbation” vs “without early acute IPF exacerbation”)

• IPF patients with a suspected early acute IPF exacerbation in any setting were categorized as “early acute IPF exacerbation”
• IPF patients without a suspected early acute IPF exacerbation during the same period were categorized as “without early acute IPF exacerbation”

Outcome Measures

Clinical outcomes

• Subsequent suspected acute IPF exacerbation
• IPF progression*
• Mortality (all-cause or due to IPF or suspected acute IPF exacerbation)

Rate of IPF-related HRU in:

• Outpatient settings
• Emergency rooms
• Hospitals

DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.

*IPF progression was based on physician reporting of emergence of any of the following since the previous visit: progressive dyspnea, increased cough, sustained decrease from baseline in absolute FVC and DLCO, progression of fibrosis from baseline on HRCT, acute IPF exacerbation, respiratory failure, new need for supplemental oxygen, or increase in oxygen requirements.


Results: Patient Characteristics

~15% had a suspected early acute IPF exacerbation

DLCO, diffusing capacity of the lungs for carbon monoxide; DLCO%, diffusing capacity of the lungs for carbon monoxide percent predicted; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FVC%, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.

Results: Clinical Outcomes and HRU

Clinical outcomes and HRU assessed from 6 months post-initial IPF diagnosis until last follow-up by suspected early acute IPF exacerbation

<table>
<thead>
<tr>
<th>Early AEx-IPF (N=72)</th>
<th>Without early AEx-IPF (N=418)</th>
<th>Relative effect measure, early vs without early AEx-IPF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month risk odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of subsequent suspected AEx-IPF</td>
<td>62%</td>
<td>24.5% 5.04 (2.61-9.72)†</td>
</tr>
<tr>
<td>Risk of progression</td>
<td>79.8%</td>
<td>71.2% 1.59 (0.77-3.32)</td>
</tr>
<tr>
<td>Mortality risk by 12 months hazard ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to any cause</td>
<td>27%</td>
<td>11.5% 2.87 (1.68-4.89)†</td>
</tr>
<tr>
<td>Death due to IPF†</td>
<td>24.6%</td>
<td>9.4% 3.15 (1.72-5.77)†</td>
</tr>
<tr>
<td>Death due to AEx‡</td>
<td>15.5%</td>
<td>6.8% 3.37 (1.65-6.90)‡</td>
</tr>
<tr>
<td>12-month incidence rate incidence rate ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPF-related outpatient visits</td>
<td>3.24</td>
<td>2.22 1.46 (1.17-1.82)†</td>
</tr>
<tr>
<td>IPF-related ER visits</td>
<td>1.25</td>
<td>0.28 4.39 (2.21-8.74)†</td>
</tr>
<tr>
<td>IPF-related hospitalizations</td>
<td>1.24</td>
<td>0.16 7.96 (3.34-18.97)†</td>
</tr>
</tbody>
</table>

AEx, acute exacerbation; CI, confidence interval; HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.
†Based on development of suspected early acute IPF exacerbation as determined by pulmonologists.
‡Kaplan-Meier survival analysis was used to estimate risk of death by 12 months.
§P<0.01.

Results: Multivariable Analysis*

- Patients with suspected early acute IPF exacerbation were associated with significantly shorter:
  - Overall survival (HR=2.83, 95% CI 1.60-5.00)†
  - Time to hospitalization (HR=1.90, 95% CI 1.08-3.35)‡
  - Time to subsequent acute IPF exacerbation (HR=2.96, 95% CI 1.84-4.74)‡

CI, confidence interval; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis.
*Multivariable Cox proportional hazard regression was used to estimate the HR and 95% confidence interval accounting for physician clustering using generalized estimating equations and survey procedures. Time to first acute exacerbation was defined as time from the start of the subsequent period to the first physician-defined acute exacerbation in the subsequent period (for those with an acute exacerbation event) or last follow-up (for those that were censored).
†P<0.05.
‡P<0.01.
Limitations

- Pulmonologists likely did not adhere to the strict definition of acute IPF exacerbation established by the expert committee in 2007 when reporting suspected acute IPF exacerbations
- Findings may not be applicable to patients diagnosed with IPF outside the practice of the participating pulmonologists or outside the study period
- Potential for incomplete patient chart information from participating pulmonologists
- Patients on both ends of the IPF severity spectrum may not be included in the study

IPF, idiopathic pulmonary fibrosis.


Conclusions and Discussion

There is a substantial burden associated with early suspected acute IPF exacerbation on patients and the healthcare system. Management options that prevent or reduce the risk of acute IPF exacerbation may help to improve health outcomes and reduce HRU in IPF patients.

HRU, healthcare resource utilization; IPF, idiopathic pulmonary fibrosis.
