Clinical Effectiveness of the Anti-Fibrotic Medications for Idiopathic Pulmonary Fibrosis

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**Clinical impact:** This is the first real-world analysis in the United States of the clinical effectiveness of the anti-fibrotic medications pirfenidone and nintedanib. Using a large insurance database to perform a retrospective cohort analysis, we observed that the medications had an association with a reduced risk of all-cause mortality for up to two years of follow-up in patients with idiopathic pulmonary fibrosis compared to an untreated matched cohort. Due to the high mortality associated with idiopathic pulmonary fibrosis, this is a significant finding for patients with the disease and the clinicians who treat it.
“At a Glance Commentary”

Scientific Knowledge on the Subject: Idiopathic pulmonary fibrosis is a progressive lung disease with high mortality that had no effective medical treatment options until the approval of the anti-fibrotic medications pirfenidone and nintedanib in 2014. While the randomized trials leading to their approval demonstrated the medications slow the decline in lung function and may have a trend toward decreased mortality, to date there has been no analysis of their effect on clinically important outcomes such as mortality and hospitalizations in everyday clinical practice.

What This Study Adds to the Field: This is the first real-world analysis of the clinical effectiveness of pirfenidone and nintedanib. Using a large insurance database to perform a retrospective cohort analysis, it was observed that the medications had an association with a reduced risk of all-cause mortality and hospitalizations for up to two years of follow-up compared to an untreated matched cohort. There were no significant differences between the two drugs in all-cause mortality. The findings in this study support the randomized trial data suggesting these medications have an impact on clinical outcomes in patients with idiopathic pulmonary fibrosis.
ABSTRACT

Rationale: Since their approval, there has been no real-world or randomized trial evidence evaluating the effect of the anti-fibrotic medications pirfenidone and nintedanib on clinically important outcomes like mortality and hospitalizations.

Objectives: To evaluate the clinical effectiveness of the anti-fibrotic medications in patients with idiopathic pulmonary fibrosis.

Methods: Using a large United States insurance database, we identified 8098 patients with idiopathic pulmonary fibrosis between October 1, 2014 and March 1, 2018. A one-to-one propensity score matched cohort was created to compare those treated with anti-fibrotic medications (n=1255) to those not on treatment (n=1255). The primary outcome was all-cause mortality. The secondary outcome was acute hospitalizations. Subgroup analysis was performed to evaluate mortality differences by drug.

Measurements and Main Results: The use of anti-fibrotic medications was associated with a decreased risk of all-cause mortality (Hazard Ratio 0.77; 95% confidence interval, 0.62 to 0.98; p value=0.034). However, this association was present only through the first two years of treatment. There was also a decrease in acute hospitalizations in the treated cohort (Hazard Ratio 0.70; 95% confidence interval, 0.61 to 0.80; p value<0.001). There was no significant difference in all-cause mortality between patients receiving pirfenidone and those on nintedanib (Hazard Ratio 1.14; 95% CI, 0.79 to 1.65; p=0.471).

Conclusions: Among patients with idiopathic pulmonary fibrosis, anti-fibrotic agents may be associated with a lower risk of all-cause mortality and hospitalizations compared to no treatment.
Future research should test the hypothesis that these treatments reduce early but not long-term mortality as demonstrated in our study.

Abstract word count: 250

3 to 5 key words: pirfenidone; nintedanib; idiopathic pulmonary fibrosis; mortality; acute hospitalizations

Abbreviations: CI- confidence interval; FDA- Food and Drug Administration; ICD-9-International Classification of Diseases, 9th edition; ICD-10- International Classification of Diseases, 10th edition; IPF- idiopathic pulmonary fibrosis; HR- Hazard Ratio; RCT- randomized controlled trial; SD- standard deviation; US-United States
INTRODUCTION:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing lung disease with high mortality that is associated with the usual interstitial pneumonia pattern on computed tomography scan and/or biopsy.\(^1\) Over the years, several medical therapies have been tested for the treatment of patients with IPF, though they have largely failed to show benefit and some have even demonstrated harm.\(^{1-3}\) In October 2014, the anti-fibrotic medications pirfenidone and nintedanib were concurrently approved by the Food and Drug Administration (FDA) following the results of two phase III, multicenter, placebo-controlled randomized trials (ASCEND and INPULSIS 1 and 2) that demonstrated the medications slowed the decline in lung function in patients with IPF.\(^{4,5}\) There was also a non-statistically significant trend toward improved survival for both medications, though there was no change in respiratory symptoms, patient-reported outcomes, or quality of life with either treatment. This prompted a “conditional recommendation” for the use of the two medications in the 2015 American Thoracic Society IPF clinical practice guideline statement, as well as much anticipation from physicians given the belief that there were now multiple effective treatment options for patients with IPF.\(^{1,6}\)

Since approval, there have been several systematic reviews and pooled data analyses which have largely confirmed the outcomes of the randomized controlled trials (RCTs).\(^{7,8}\) There have also been network meta-analyses indirectly comparing the two medications that have suggested there were no clear outcome differences between the treatments.\(^{9-11}\) Given these comparable results in clinical trials and systematic reviews (and lack of direct comparisons), it is believed that most physicians who treat patients with IPF ultimately make the decision for therapy following a shared-decision making discussion with patients, largely based on the possible adverse effects of the chosen medication as well as out-of-pocket costs.
Despite the initial excitement surrounding the approval of the anti-fibrotics, there are several questions that remain, including whether these medications actually work in general clinical practice to improve survival and decrease hospitalizations. To date, there has been no analysis of the available real-world data of IPF patients on therapy to answer these clinically important questions. Thus, in this study, we aim to assess the treatment benefits of the medications compared to patients with IPF not receiving treatment as well as compare the effectiveness of the two medications head-to-head using individuals enrolled in United States (US) commercial and Medicare Advantage health plans. Some of the results of this study have been previously reported in the form of an abstract.12

METHODS:

Data Source: This analysis was a retrospective cohort study using de-identified administrative claims data from the OptumLabs® Data Warehouse, which includes data for commercially insured and Medicare Advantage enrollees in a large US health plan.13 The database contains claims-based information on individuals from all 50 states comprising all ages, ethnicities, and racial groups. The health plan provides comprehensive insurance coverage for physician, hospital, and outpatient prescription services. Pursuant to the Health Insurance Portability and Accountability Act, the use of de-identified data does not require Institutional Review Board Approval.

Study Populations: Two cohorts of patients with IPF were created for this study: an untreated cohort and a treated group. For the treated cohort, we identified all adult patients (≥18 years) that filled a prescription for either pirfenidone or nintedanib between October 1, 2014 and March 1, 2018. We required treated individuals to have a diagnosis of idiopathic pulmonary fibrosis using
the *International Classification of Diseases, 9th edition* (ICD-9) and *International Classification of Diseases, 10th edition* (ICD-10) billing codes for IPF (9th Edition, 516.31; 10th Edition, J84.112) in the 180 days prior to their first fill for either drug. For the untreated cohort, we identified individuals with a diagnosis of IPF (based on the above codes) who did not fill a prescription during our study period. For each patient, we defined the index date as the date of first fill for either pirfenidone or nintedanib or the first IPF encounter in the study period after patients met the 180 days enrollment requirement. We required all patients to have at least 180 days of continuous enrollment before the index date in order to have sufficient data to capture patient’s baseline medical history. For patients not receiving anti-fibrotic medications, we required patients to have an additional claim for the above codes for IPF to increase the specificity of patient identification (including those patients with a single inpatient claim or at least 2 outpatient claims on different dates).

Because there has been controversy over the specificity of billing codes used to classify the disease in prior epidemiological analyses, a local cohort validation study using chart and imaging examination by expert reviewers was performed by a separate set of clinical pulmonologists to find the most specific billing codes (unpublished data), which were found to be ICD-9 516.31 and ICD-10 J84.112. Other codes (including those used in prior studies such as post-inflammatory fibrosis [ICD-9 515, ICD-10 J84.10]) were found to be non-specific for the diagnosis of IPF and were not included in our analysis.14

**Independent Variables:** Independent variables of interest at index included age, sex, race/ethnicity, residence region, steroid use, oxygen use, health care utilization, and comorbidities (as captured by ICD-9 and ICD-10 codes on claims in any position in the 6 months before index date). Comorbidity burden was assessed using the Elixhauser sum of conditions.15
Prior hospitalizations and pulmonologist office visits in the 6-month baseline period were captured using medical claims. Prior steroid use was defined as having a filled prescription within 6 months prior to the index date. Oxygen use was identified using Healthcare Common Procedure Coding System indicating oxygen supplies during the baseline period.

**Follow-up:** Follow-up started from the index date and continued until the end of treatment, end of enrollment in health insurance plan, death, or end of study period (March 1, 2018). End of treatment was defined as discontinuation of medication (not refilling a prescription within 30 days of the end of supply).

**Study Outcomes:** The primary outcome was all-cause mortality. Mortality was identified based on the Social Security Death Master file and discharge status of the expired. The secondary outcome was all-cause hospitalizations. Subgroup analysis was performed comparing differences in all-cause mortality by drug.

**Statistical Analysis:** We used propensity score matching to balance the differences in baseline characteristics between the treated and untreated cohorts. A propensity score was estimated using logistic regression based on sociodemographic characteristics, medical history, prior steroid use, year of index, oxygen use, and utilization. Specifically, we used one-to-one nearest-neighbor caliper matching to match patients based on the logit of the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score. We evaluated the standardized difference to assess the balance of covariates after matching, and a standardized difference less than 10% was considered acceptable. Cox proportional hazards regression was then used to compare patients treated to those untreated for mortality and hospitalizations in the propensity score-matched cohort, with robust sandwich estimates to account for the clustering
within matched sets. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata version 14.1 (StataCorp).

**Sensitivity Analyses**: Subgroup analyses for mortality were performed among those treated stratified by index drug for drug-by-drug comparisons. In this analysis, if a covariate was not balanced, we examined whether including it in the regression affected results. Falsification endpoint analyses were performed to test for residual confounding; two endpoints were selected: acute myocardial infarction and fracture.

Lastly, we used inverse probability of treatment weighting instead of propensity score matching to repeat the main analyses. Specifically, we used a weight of $1/$propensity score for patients receiving a treatment and $1/ (1 − $propensity score)$ for untreated patients.

**RESULTS**

**Baseline Characteristics**

A total of 1255 treated and 6843 untreated adults with IPF were identified. The final propensity-matched cohort included 1255 matched pairs of patients with IPF treated or untreated. Baseline characteristics were well balanced between the two groups with standardized differences less than 10% as seen in Table 1. Mean duration of follow-up was 9.93 (standard deviation [SD] 9.35) months. The mean age of the treated and untreated cohorts was 72.2 and 72.4 years, respectively. The percentage of female patients was 36.9 in the untreated cohort and 37.1 in the treated group. Roughly half of patients in the untreated group (48.8 percent) received steroids in the six months prior to diagnosis compared to 49.6 percent of patients in the treated cohort, who received steroids in the six months prior to treatment initiation. Between both groups, 58.5 percent of individuals required home oxygen supplementation. The most frequent co-morbidities
by diagnostic codes in the overall cohort were hypertension (66.4 percent), other chronic pulmonary conditions (62.8 percent), and diabetes (32.9 percent).

The baseline characteristics of the subgroup analysis of patients treated with pirfenidone (n=593) compared to nintedanib (n=662) are shown in Supplementary Table E1. There were no baseline differences between patients taking the two medications in age, gender, steroid use, oxygen use, or co-morbidities even without propensity score matching. The mean duration of treatment for both medications was also similar (pirfenidone mean duration=241.32 days; nintedanib mean duration=228.86 days).

**All-Cause Mortality and Acute Hospitalizations**

For the primary outcome of all-cause mortality, there was an association with reduced all-cause mortality for those in the treated cohort compared to the untreated matched cohort (treated cohort: 13.78 per 100 person-years versus untreated cohort: 16.34 per 100 person-years; Hazard Ratio [HR] 0.77; 95% confidence interval [CI], 0.62 to 0.98; p value=0.034). This mortality benefit was only present through the first two years of follow-up as seen in Figure 1A. For the secondary outcome of acute hospitalizations, there was also a decrease in the treated cohort as seen in Figure 1B (46.70 per 100 person-years versus 62.44 per 100 person-years; HR 0.70; 95% confidence interval, 0.61 to 0.80; p value<0.001). The most common reason for hospitalization identified in this cohort was respiratory failure (Supplementary Table E2).

In subgroup analysis, we observed no significant difference in all-cause mortality between patients treated with pirfenidone and those on nintedanib as seen in Figure 2 (pirfenidone 12.83 per 100 person-years versus nintedanib 14.77 per 100 person-years; HR 1.14; 95% CI, 0.79 to 1.65; p=0.471).
All sensitivity analyses performed to confirm our primary findings showed results similar to the main analysis (Supplementary Table E3). The reasons for censoring are provided in Supplementary Table E4.

**DISCUSSION**

This is the first real-world study of the clinical effectiveness of the anti-fibrotic medications pirfenidone and nintedanib for patients with IPF since their approval in 2014. There are a number of important findings from this cohort analysis, most notably the association with an all-cause mortality benefit observed in the cohort treated with antifibrotic medications.

All-cause mortality has been proposed as the most clinically meaningful endpoint for both patients and clinicians when considering treatment of IPF.\(^{21}\) Given the relative rarity of the disease and its progressive and ultimately fatal nature, powering a trial and ensuring appropriate follow-up to demonstrate a mortality effect is incredibly difficult.\(^{22-24}\) Despite this, even before pirfenidone and nintedanib were approved, there was debate about whether the use of surrogate endpoints in the phase three trials of the drugs was appropriate.\(^{21,25}\) While the FDA ultimately deemed the primary outcome of the trials and their findings strong enough for regulatory approval, questions have remained as to whether the trial data translate into meaningful results in every day clinical practice.

In this large cohort study of privately insured and Medicare Advantage patients, we have attempted to start answering those questions by supplementing the trial data with real-world evidence. We observed that patients treated with either pirfenidone or nintedanib had an association with decreased risk of all-cause mortality and acute hospitalizations compared to a matched cohort of untreated patients. This helps complement both the initial trial data for the
medications as well as more recent studies, which have largely relied on pooled analyses of trial data.\textsuperscript{4,5,7,8,26-28} Impressively, this benefit was found in a population that was older and appeared to have more severe disease than those studied in the randomized trials, which enrolled patients with mostly mild to moderate IPF. In our cohort, more than 58 percent of patients in both the treated and non-treated groups required home oxygen supplementation. In ASCEND, the number of patients requiring oxygen was around 28 percent.\textsuperscript{4} All-cause mortality in our cohort was 14.85 percent at 52 week follow-up, while in the two trials combined all-cause mortality at one year in the placebo and treatment arms ranged from 5.6 to 6.5 percent. At least in this cohort, it would appear physicians were using pirfenidone and nintedanib in patients with more severe disease who would have been excluded from the RCTs. Despite those differences in severity, these medications are improving outcomes in patients, such as in our study.

When comparing the effectiveness of the two medications at reducing all-cause mortality, there was no difference; however, as with the published trial data, pirfenidone had a slightly more favorable trend. Comparing the demographics of patients treated with either medication (even without matching), the populations had nearly identical age, race, and co-morbidity profiles. Given these similarities, it would seem to corroborate the belief that physicians are currently deciding which medication to use based largely on shared-decision making discussions surrounding factors such as side effects and cost considerations. Due to the lack of significant clinical differences observed in this cohort, physicians should continue to solicit patient input into which medication they prefer for initial treatment while awaiting further confirmation of these results. Additional comparisons are also needed on patient-important factors such as quality of life, symptom control, medication tolerability, and exercise tolerance.
One of the more intriguing findings from this study is the decline in the benefit of therapy over
time. This is consistent with prior pooled data and survival modeling for pirfenidone suggesting
a mortality benefit for up to two years.\textsuperscript{7,26} The reason for this later decline in efficacy is
currently unclear. These medications are not curative, meaning that fibrosis continues to
accumulate over time, as do clinical events such as acute exacerbations. One hypothesis is that
as lung fibrosis progresses and vascular remodeling occurs, deposition of the drugs in the lungs
decreases.\textsuperscript{29-31} Another possibility is that acute exacerbations occur despite drug therapy, which
prior research has shown portends a worse prognosis.\textsuperscript{32,33} In pooled analyses of trial data and
indirect comparison via network meta-analysis, pirfenidone consistently has the stronger
mortality benefit, while nintedanib has a stronger impact on acute exacerbations.\textsuperscript{3,7,34} Given these
findings, it is possible that a sequential treatment model utilizing pirfenidone initially and then
switching to nintedanib following the first acute exacerbation would help prevent this decreased
efficacy over time.\textsuperscript{35} In addition, combination therapy, which has been effective in other
pulmonary diseases like asthma, emphysema, and pulmonary hypertension, may also help sustain
the mortality benefit beyond two years. Thus far, studies have shown that combination therapy
is tolerable and possibly more efficacious than single drug treatment.\textsuperscript{35-38} Further research should
aim to discover the etiology for the reduction in clinical benefit over time as well as methods to
best attenuate this finding. Given the reported cost of the medications, if combination therapy is
to be considered, studies should also focus on out-of-pocket costs to patients as well as the
overall cost effectiveness of these agents.

Despite the large cohort and key observations of this analysis, there are several important
limitations of this study to consider. First, the dataset analyzed only includes patients enrolled in
private and Medicare Advantage health plans with pharmaceutical benefits, which limits the
generalizability of this study to other groups of patients such as the uninsured or those enrolled in other government health plans such as Medicaid. These populations may have a different prevalence of risk factors as well as lower socio-economic status than individuals with private or Medicare Advantage coverage, which could lead to worse outcomes. These differences may be mitigated in our cohort by the fact that insurance coverage rates are generally higher in older Americans, the group most likely to be affected by IPF, thus making our findings largely generalizable to most patients with the disease.\textsuperscript{39} Second, despite adequate matching and adjustments across groups, confounding factors are still a distinct possibility given this study’s observational nature. Additional sensitivity tests were undertaken and demonstrated similar results to the main analysis, which further help to validate our main findings and to moderate some of the concerns over confounding factors. Third, the treated cohort was identified by date of first fill of a prescription for either anti-fibrotic medication. We acknowledge that filling a prescription does not mean that a patient actually took the medication as prescribed. However, the individuals in our cohort continued to fill their prescriptions; otherwise, they were censored. As subsequent fills were tracked, this makes significant lack of adherence unlikely. Additionally, the possibility that those in the treated cohort did not use the anti-fibrotics as intended would presumably strengthen the observations of our analysis, as we would expect the outcomes to further trend toward the treated cohort with stricter adherence.

A fourth limitation of our study is the use of the Social Security Death Master File to obtain the primary outcome of mortality. Due to various circumstances and policies, since 2011, this database has been limited in its ability to capture up to one-third of deaths.\textsuperscript{40} We attempted to minimize this gap by using discharge status (i.e. in-hospital death) to supplement the Social Security Death Master File as the majority of deaths occur in a hospital setting. Using this
approach, an additional 30 percent of deaths are typically captured in addition to those obtained through the Death Master File. While this accounts for the majority of deaths missed by the Death Master File, we acknowledge that a small proportion of patients that die outside of the hospital setting could be missing, though this number is likely not high enough to influence our overall observations.

Finally, billing codes were used to identify patients with IPF. There are a multitude of factors that make IPF a complex diagnostic decision including the need for a multidisciplinary team, the importance of considering other fibrotic interstitial lung diseases, and the ability to diagnose based solely on radiographs without tissue pathology in some cases. Such qualities make the use of billing codes prone to misidentification, something prior epidemiological studies in IPF have acknowledged. We attempted to mitigate this limitation by using a local cohort validation to identify and use only the most accurate codes for IPF (unpublished data). We also required two outpatient codes for IPF to exclude the possibility of an evolving diagnosis after the completion of further diagnostic testing. Even with these steps aimed at ensuring cohort specificity, the possibility for misdiagnosis or miscoding is still possible.

In summary, in this real-world analysis of the clinical impact of the anti-fibrotic medications pirfenidone and nintedanib, patients on treatment for idiopathic pulmonary fibrosis had an association with a reduced risk of all-cause mortality and acute hospitalizations compared to untreated matched individuals. Compared head-to-head, there was no difference in all-cause mortality between the medications. Further research is needed to test the hypothesis that these treatments reduce early but not long-term mortality as demonstrated in our study.
REFERENCES:


FIGURE LEGENDS:

Figure 1A: Mortality Cumulative Risk Percent. The cumulative risk of all-cause mortality in patients on treatment for idiopathic pulmonary fibrosis (treated) compared to an untreated IPF matched cohort (untreated) during 24-month follow-up. For the number of patients at risk during each time interval, please see Supplementary Table E5.

Figure 1B. Hospitalization Cumulative Risk Percent. The cumulative risk of acute hospitalizations in patients on treatment for idiopathic pulmonary fibrosis (treated) compared to an untreated IPF matched cohort (untreated) during 24-month follow-up. For the number of patients at risk during each time interval, please see Supplementary Table E5.

Figure 2. Comparison of Mortality Risk by Drug. The cumulative risk of all-cause mortality in patients on pirfenidone compared to those on nintedanib during 24-month follow-up. For the number of patients at risk during each time interval, please see Supplementary Table E5.
### TABLES:

Table 1. Baseline Demographics of Patients with Idiopathic Pulmonary Fibrosis Before and After Propensity Score Matching

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<tr>
<td>Steroid Use (6m baseline)</td>
<td>4589 (67.1%)</td>
<td>902 (71.9%)</td>
<td>10.4%</td>
<td>893 (71.2%)</td>
<td>902 (71.9%)</td>
<td>1.6%</td>
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<tr>
<td>Pulmonary Office Visit</td>
<td>2837 (41.5%)</td>
<td>623 (49.6%)</td>
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<td>612 (48.8%)</td>
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<tr>
<td>DME, Oxygen</td>
<td>3646 (53.3%)</td>
<td>1045 (83.3%)</td>
<td>68.1%</td>
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<tr>
<td>Conditions</td>
<td>4313 (63.0%)</td>
<td>800 (63.7%)</td>
<td>1.5%</td>
<td>778 (62.0%)</td>
<td>800 (63.7%)</td>
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<tr>
<td>Cardiac Arrhythmia</td>
<td>2241 (32.7%)</td>
<td>339 (27.0%)</td>
<td>12.5%</td>
<td>346 (27.6%)</td>
<td>339 (27.0%)</td>
<td>1.4%</td>
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<tr>
<td>Congestive Heart Failure</td>
<td>2016 (29.5%)</td>
<td>253 (20.2%)</td>
<td>21.6%</td>
<td>264 (21.0%)</td>
<td>253 (20.2%)</td>
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<tr>
<td>Chronic Pulmonary Disease</td>
<td>4313 (63.0%)</td>
<td>800 (63.7%)</td>
<td>1.5%</td>
<td>778 (62.0%)</td>
<td>800 (63.7%)</td>
<td>3.5%</td>
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<tr>
<td>Depression</td>
<td>903 (13.2%)</td>
<td>149 (11.9%)</td>
<td>3.9%</td>
<td>137 (10.9%)</td>
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<tr>
<td>Diabetes</td>
<td>2237 (32.7%)</td>
<td>412 (32.8%)</td>
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<td>415 (33.1%)</td>
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<tr>
<td>Hypertension</td>
<td>4734 (69.2%)</td>
<td>827 (65.9%)</td>
<td>7.1%</td>
<td>842 (67.1%)</td>
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<tr>
<td>Pulmonary Circulation Disor</td>
<td>1357 (19.8%)</td>
<td>261 (20.8%)</td>
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<td>Renal Failure</td>
<td>1195 (17.5%)</td>
<td>153 (12.2%)</td>
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<tr>
<td>Rheumatoid Arthritis</td>
<td>1072 (15.7%)</td>
<td>106 (8.4%)</td>
<td>22.6%</td>
<td>113 (9.0%)</td>
<td>106 (8.4%)</td>
<td>2.1%</td>
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<tr>
<td>Solid Tumor without Metastasis</td>
<td>745 (10.9%)</td>
<td>95 (7.6%)</td>
<td>11.4%</td>
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<tr>
<td>Valvular Disease</td>
<td>1370 (20.0%)</td>
<td>247 (19.7%)</td>
<td>0.8%</td>
<td>238 (19.0%)</td>
<td>247 (19.7%)</td>
<td>1.8%</td>
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</tbody>
</table>

**Elixhauser Sum of Conditions**

- **Mean (SD)**: 4.7 (2.9), 4.0 (2.5), 3.4%, 4.0 (2.5), 4.0 (2.5), 0%
- **Median**: 4, 4, 4, 4, 4
- **Smoker**: 2390 (34.9%), 534 (42.5%), 15.6%, 520 (41.4%), 534 (42.5%), 2.2%
- **Baseline hospitalizations**: 0, 4568 (66.8%), 865 (68.9%), 4.5%, 892 (71.1%), 865 (68.9%), 4.8%
<table>
<thead>
<tr>
<th></th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
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<td>1576 (23.0%)</td>
<td>295 (23.5%)</td>
<td>1.2%</td>
<td>281 (22.4%)</td>
<td>295 (23.5%)</td>
</tr>
<tr>
<td>2+</td>
<td>699 (10.2%)</td>
<td>95 (7.6%)</td>
<td>9.1%</td>
<td>82 (6.5%)</td>
<td>95 (7.6%)</td>
</tr>
</tbody>
</table>