Pulmonary Arterial Hypertension (PAH) Episodes of Care: Survival Analysis of PAH Patients Based on World Health Organization (WHO) Functional Class (FC)

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Background

PAH is a rare disease in which patients experience increased pulmonary vascular resistance and arterial pressure that may result in remodeling of the pulmonary vasculature and heart potentially leading to right heart failure and death.[1] The prevalence is 10.6 cases per million people in the US.[2] The incidence of PAH in the US is 2.0 cases per million people annually.[2] The WHO pulmonary hypertension classification system categorizes PAH by increasing disease severity into 4 Functional Classes (FC); FC I – FC IV. Progression along the FC hierarchy is correlated with reduced functionality and increased medical costs.[4] FC improvement is possible[3,5] and achieving at least FC II is a treatment goal. Previous research has examined the effect of FC changes on survival outcomes of PAH patients.[3]

Objective

To examine the survival rates of PAH patients and how various factors (e.g., FC, age, comorbidity index) influence patients' 2-year survival.

Methods

- **Data Source:** Humana Research Database (Humana, Louisville, KY, USA), a limited dataset which includes data from geographically dispersed US commercial and Medicare health plans, providing coverage for approximately 19 million members. The data set consists of integrated medical, pharmacy, laboratory claims and eligibility files. Additionally, prior authorization records for PAH therapies were used to obtain provider-reported Functional Class.
- **Inclusion and Exclusion Criteria:**
  - Enrolled Medicare Advantage or commercial member at index (first claim for a FDA approved treatment for PAH during study time period).
  - Pharmacy or medical claim during the identification period for an FDA approved treatment for PAH: oral endothelin-receptor antagonist (ERA), oral phosphodiesterase type 5 inhibitor (PDE5i) or an inhaled prostacyclin.
  - A medical claim with an ICD-9 CM diagnosis code of Primary Pulmonary Hypertension (416.0), Other Pulmonary heart diseases (416.8), or Chronic pulmonary heart disease, unspecified (416.9).
- **Outcomes:** Adjusted Hazard Ratio (HR) for 2-year survival rates were computed.
  - The index date consisted of the fill date for a PAH-treatment.
  - Deceased dates, any cause, were identified and time to death was computed.
  - Proportion of deceased patients by Functional Class.
- **Statistical Analyses:** Multivariable Cox Proportional Hazard model was used to examine the relationship between FC and survival.
  - Age, gender, race, geographical region, Elixhauser Comorbidity Index and initial PAH Treatment type were also included in the model
  - 95% Confidence Intervals were computed for each FC pairwise contrasts.
  - Frequencies were tested using Chi-square tests.
- **Study Period:** 1/1/2009 – 6/30/2014.

Results

Table 1. Baseline Demographics

Main demographic and clinical characteristics of the PAH patients in the sample for the baseline period of 3 months pre-index.

	PAH Functional Class			
Measure	**FC II**	**FC III**	**FC IV**	***P* value**
N	99	282	56	-
Age, mean (SD)				
Age	67.0 (13.6)	67.9 (10.8)	66.3 (9.9)	0.54
Gender, %				
Female	67.7%	69.5%	71.4%	0.88
Race, %				
White	70.6%	78.5%	70.9%	0.23
Geographic Region, %				
South	68.7%	65.6%	64.3%	0.98
Midwest	23.2%	24.5%	23.2%	
Index Therapy, %				
ERA	57.6%	55.3%	37.5%	0.11
PDE5i	36.4%	39.4%	51.8%	
Prostacyclin	6.1%	5.3%	10.7%	
Patients adding 2nd Therapy, %				
Additional Therapy	17.2%	28.7%	37.5%	0.02
Elixhauser Comorbidity Index, mean (SD)				
ECI	6.5 (4.1)	7.3 (3.8)	7.1 (4.2)	0.2

There is no statistical differences between the 3 sub-cohort on the demographic characteristics as measured by Chi-Square tests.

The use of PDE5i is more frequent than the use of ERA for FC IV patients .
The use of ERA is more frequent than the use of PDE5i for FCII patients.
The use of Prostacyclin is most frequent in FC IV patients.
However, these contrasts are not statistically significant.

FC IV patients are more likely to add a second PAH therapy than the other two groups.

Table 2. Adjusted Hazard Ratio for Factors Influencing Survival

	Measure	
Factors	**Adjusted HR Time to Death**	**Risk Interpretation**
FC II	0.298*	FC II patients are 70.2% less likely to die during the 2-year post-index period than FC IV patients
FC III	0.479*	FC III patients are 52.1% less likely to die during the 2-year post-index period than FC IV patients
Age	1.022*	A one-year age increase decreases survival by 2.2%. Hence a 5-year age increase results in a 11.0% decrease in survival rate.
Gender	0.612*	Being a woman reduces risk of dying during the 2-year post-index period by 44.2%
Race	2.016*	Being white decreases the survival rate during the 2-year post-index period by 101.6%
Elixhauser Comorbidity Index	1.066*	Each 1-point increase in ECI decreases the survival rate during the 2-year post-index period by 6.6%

* P < 0.05 by Chi-Square tests

Table 3. Adjusted Hazard Ratio Functional Class Effect

Measure	**FC II v. FC III**	**FC III v. FC IV**	**FC II v. FC IV**
Adjusted HR Time to Death	0.621	0.479	0.298
Adjusted HR 95% Confidence Interval	0.34 - 1.14	0.29 - 0.79	0.15 - 0.60
Adjusted HR converted into % less likely to die	37.9%	52.1%	70.2%

Figure 1. Two-Year Survival Rates for the Overall PAH Cohort (N=437) across Functional Class

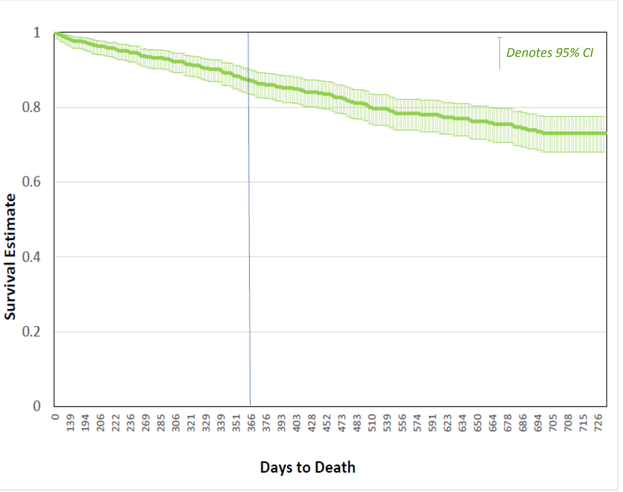

Figure 2. Two-Year Survival Rates by Functional Class (FCII-FCIV) for the PAH Cohort

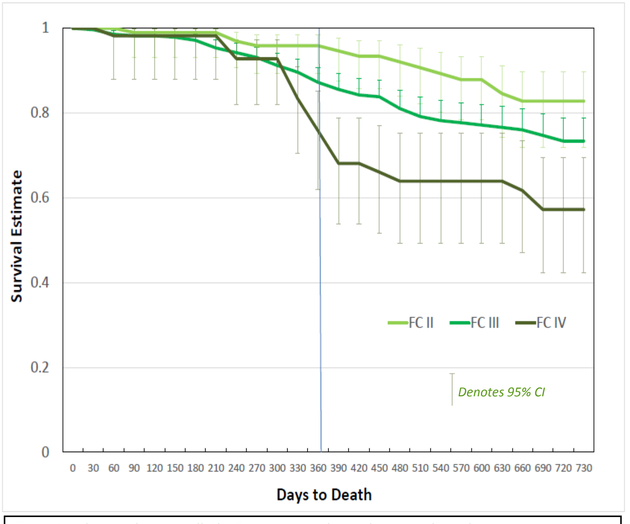

Figure 1 indicates that overall, the 2-year survival rate decreases linearly.
Figure 2 indicates FC IV patients have a more pronounced decrease in survival rate than FC II or FC III patients. That decrease begins around the 9th month observed.

Conclusions

- FC II PAH patients had higher survival rates than patients from either FC III or FC IV, though the comparison of FC II vs. FC III is not statistically significant. This replicates previous findings.[3,5,6]
- The results from this retrospective study reinforce that aggressive treatment is important in achieving treatment goals, such as improving to FC II per the guidelines generated by the WHO World Symposium on Pulmonary Hypertension (PH) and the Joint Task Force for the Diagnosis and Treatment of PH of the European Society of Cardiology (ESC) and of the European Respiratory Society (ERS). [7]

Limitations

- Limitations common to studies using administrative claims data apply to this study. These include lack of certain information in the database (e.g., some lab results, weight, and health behavior information) and error in claims coding.
- There is no specific ICD-9 codes for PAH and claims data do not clearly indicate patient severity.
- No causal inference can be ascertained from this study, as it is an observational study using retrospective claims data.
- Because this study uses data from Humana members only, the results may not be generalized to the general population. However, Humana is a large national health plan with members residing in a broad array of geographic regions.
- The reliability of clinical information obtained from prior authorization documentation has yet to be fully vetted.

Reference

1. Badesch, DB et al (2010). Pulmonary arterial hypertension: Baseline characteristics from REVEAL registry. Chest: 137(2), 376-387.

2. McGoon, MD et al (2013). Pulmonary Arterial Hypertension: Epidemiology and Registries. Journal of the American College of Cardiology: 62(25), Supplement D51-D59.

3. Barst , RJ et al (2013). Functional class improvement and 3-year survival in patients with pulmonary arterial hypertension in the REVEAL Registry. Chest: 144 (1), 160-168.

4. Dufour, R, Pruett, J et al (2015, November). Pulmonary Arterial (PAH): Real-World Treatment Patterns , Outcomes and Costs Based on the World Health Organization (WHO) Functional Class (FC). Poster presented at the International Society of Pharmacoeconomics and Outcomes Research 18th Annual European Congress, Milan, Italy.

5. Pulido, T et al (2013). Macitentan and morbidity and mortality in pulmonary hypertension. N Engl J Med: 369(9):809-818.

6. Nickel, N et al (2012). The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Resp J : 39(3):589-596.

7. Galié, N, Humbert, M et al (2015). 2015 ESC/ECR guidelines for the diagnosis and treatment of Pulmonary Hypertension-Web Addenda. Eur Heart J:doi:10.1093/eurheartj/ehv317.

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