Contemporary Hospitalization and Mortality Burden in Real-World US PAH Patients

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Background

- Pulmonary arterial hypertension (PAH) is a rare, progressive disorder defined by increased arterial pressure in the lungs.
- Despite significant therapeutic advancements over the past three decades, PAH continues to impose a substantial burden on patients in the United States (US).
- Real-world data on current morbidity and mortality rates remain limited.

Objective

- This study aimed to quantify the contemporary burden of PAH—including hospitalization, re-hospitalization, and mortality—using US real-world data.

Methods

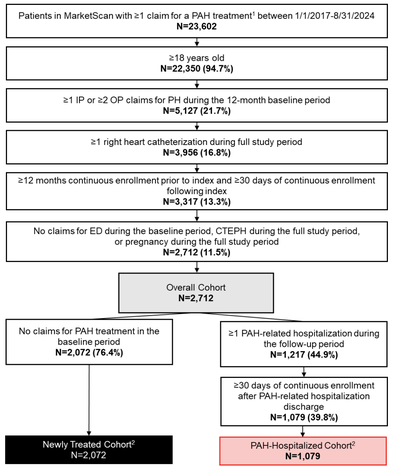
Study Design and Data Source

- This retrospective cohort study of adult treated PAH patients used data from the MarketScan Commercial and Medicare Databases between 1/1/2016 and 9/30/2024.
- PAH treatments included endothelin receptor agonists (ERAs; ambrisentan, bosentan, macitentan), phosphodiesterase-5 inhibitors (PDE-5i; sildenafil, tadalafil), soluble guanylate cyclase stimulators (sGCS; riociguat), or oral, inhaled, intravenous [IV] and subcutaneous [SC] prostacyclin pathway agents (PPAs; epoprostenol, treprostinil, iloprost, selexipag), activin signaling inhibitor (sotatercept), and macitentan/tadalafil combination pill.

Patient selection

- Patient selection criteria are shown in **Figure 1**. The index date was the first identified claim for PAH treatment.
  - Sub-cohorts of PAH-hospitalized patients and newly treated patients were also selected.
- Reporting was stratified by index treatment type (treatments in the first six months of follow-up).
  - First line therapies: PDE-5i, sGCS, ERA or any combination thereof; no PPA
  - Triple therapy: Oral/inhaled PPA, ERA, and PDE-5i/sGCS; no IV or SC PPA
  - IV/SC PPA therapy: Any regimen containing IV/SC PPA therapy, regardless of other treatments

Figure 1. Patient Attrition



CTEPH: chronic thromboembolic pulmonary hypertension; ED: erectile dysfunction; IP: inpatient; OP: outpatient; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension
[1] Includes endothelin receptor agonists (ambrisentan, bosentan, macitentan), phosphodiesterase type-5 inhibitors (sildenafil, tadalafil), prostacyclin pathway agents (epoprostenol, iloprost, selexipag, treprostinil), soluble guanylate cyclase stimulators (riociguat), sotatercept, or macitentan/tadalafil combination
[2] The newly treated cohort and the PAH-hospitalized cohort are not mutually exclusive. Some patients qualified for both of these cohorts.

Results

Patient Characteristics

- 2,712 total treated PAH patients were identified (**Figure 1**), of which 1,887 (69.6%) were treated with first-line therapies, 226 (8.3%) were treated with triple therapy and 241 (8.9%) were treated with IV/SC PPA therapy.
- Mean (SD) age of the overall patient cohort was 61.8 (13.8) years, and 68.9% were female (**Table 1**).
  - Patients with triple therapy and IV/SC PPA therapy were an average of 3.8 (mean age 58.9) and 9.2 (mean age 53.5) years younger than patients with first-line therapies (mean age 62.7).
- The mean DCI was 4.0, indicating a high comorbidity burden in PAH patients
- The most common PAH-related symptoms and comorbidities were dyspnea (81.7%), hypertension (79.9%), obesity (45.4%) and apnea (44.4%).
- Patient characteristics for the PAH-hospitalized (N=1,079, 39.8%) and newly treated (N=2,072, 76.4%) cohorts were similar to those of the overall cohort (data not shown).

All-cause utilization

- 56.2% of PAH patients had an all-cause inpatient admission in the variable-length follow-up period (**Table 2**).
  - Patients with IV/SC PPA therapy were more likely to have an inpatient visit (66.4%) but had a shorter length of stay (7.2 days IV/SC PPA cohort; 8.4 days overall cohort).
  - 54.8% of PAH patients had an all-cause ER visit, with the highest proportion among the IV/SC PPA treatment group (60.6%).
  - IV/SC PPA patients also had a highest mean number of laboratory visits, radiology visits, and other outpatient visits PPPY.

PAH-related hospitalizations

- Among all patients, 1,217 (44.9%) had at least one PAH-related hospitalization (Figure 1) during a mean 2.2 years of follow-up.
  - Patients averaged 1.5 PAH-related hospitalizations per year (data not shown).
- Of 2,551 total PAH-related hospitalizations (**Figure 2**):
  - 306 hospitalizations (12.0%) had a PH principal diagnosis.
  - 1,458 hospitalizations (57.2%) had an ICU stay.
  - The mean length of stay was 9.1 days.
  - PAH-related hospitalizations with an ICU stay were 4 days longer than those without (10.8 vs. 6.8 days).

Table 1. Baseline demographic and clinical characteristics, overall and by treatment group

	All patients N=2,712	Treatment groups[1] First-line therapies N=1,887	Triple therapy N=226	IV/SC PPA therapy N=241
Demographic Characteristics[1]				
Age, Mean (SD)	61.8 (13.8)	62.7 (13.7)	58.9 (13.2)	53.5 (13.2)
Female, N (%)	1,869 (68.9%)	1,283 (68.0%)	171 (75.7%)	192 (79.7%)
Commercially-insured, N (%)	1,571 (57.9%)	1,051 (55.7%)	157 (69.5%)	193 (80.1%)
Geographic region, N (%)[2]				
Northeast	495 (18.3%)	-	-	-
North Central	761 (28.1%)	-	-	-
South	1,126 (41.5%)	-	-	-
West	322 (11.9%)	-	-	-
Unknown	8 (0.3%)			
Length of follow-up (in years), Mean (SD)	2.2 (1.9)	2.2 (1.9)	2.5 (2.1)	2.4 (2.1)
Clinical Characteristics[1]				
Deyo-Charlson Comorbidity Index, Mean (SD)	4.0 (2.3)	4.2 (2.4)	3.5 (2.2)	3.7 (2.4)
Symptoms and comorbidities (N, %)[3]				
Apnea	1,204 (44.4%)	864 (45.8%)	98 (43.4%)	96 (39.8%)
Chronic obstructive pulmonary disease	999 (36.8%)	687 (36.4%)	79 (35.0%)	59 (24.5%)
Coronary artery disease	1,069 (39.4%)	794 (42.1%)	66 (29.2%)	59 (24.5%)
Dyspnea	2,215 (81.7%)	1,526 (80.9%)	185 (81.9%)	200 (83.0%)
Hypertension	2,167 (79.9%)	1,559 (82.6%)	166 (73.5%)	159 (66.0%)
Kidney disease	770 (28.4%)	591 (31.3%)	46 (20.4%)	49 (20.3%)
Obesity	1,232 (45.4%)	894 (47.4%)	91 (40.3%)	83 (34.4%)
Specific PAH therapies (N, %)[4]				
ERAs	414 (15.3%)	288 (18.3%)	126 (11.0%)	243 (12.9%)
PDE-5is[5]	472 (17.4%)	299 (19.0%)	173 (15.2%)	300 (15.9%)
PPAs	239 (8.8%)	167 (10.6%)	72 (6.3%)	19 (1.0%)
sGCS	67 (2.5%)	46 (2.9%)	21 (1.8%)	37 (2.0%)
Other treatments (N, %)				
Anticoagulants	838 (30.9%)	405 (25.8%)	433 (37.9%)	621 (32.9%)
Digoxin	224 (8.3%)	131 (8.3%)	93 (8.2%)	150 (7.9%)
Oral diuretics	1,944 (71.7%)	1,073 (68.3%)	871 (76.3%)	1,364 (72.3%)
Diagnostic procedures, N (%)				
CCTA	75 (2.8%)	53 (3.4%)	22 (1.9%)	59 (3.1%)
Echocardiogram	2,520 (92.9%)	1,451 (92.4%)	1,069 (93.7%)	1,753 (92.9%)
RHC	2,282 (84.1%)	1,323 (84.2%)	959 (84.0%)	1,597 (84.6%)
VQ scan	1,045 (38.5%)	622 (39.6%)	423 (37.1%)	698 (37.0%)
6-minute walk test	1,263 (46.6%)	795 (50.6%)	468 (41.0%)	793 (42.0%)

CCTA: cardiac computed tomography angiography; ERA: endothelin receptor agonist; PDE-5i: phosphodiesterase type-5 inhibitor; PPA: prostacyclin pathway agent; RHC: right heart catheterization; sGCS: soluble guanylate cyclase stimulator; VQ: ventilation-perfusion
[1] Demographic characteristics were captured on the index date; clinical characteristics were captured in the 6-month baseline period.
[2] Geographic region is masked for the subgroups due to risk of patient reidentification
[3] Symptoms and comorbidities with >25% prevalence were reported in the table. Others that were measured but not reported include: congenital heart disease, cor pulmonale, depression, idiopathic pulmonary fibrosis, inflammatory bowel disease, interstitial lung disease, left heart failure, lower respiratory disease, multiple sclerosis, pneumonia, portal hypertension, respiratory failure, right ventricular failure, sleep disorders, venous thromboembolism
[4] Includes codes for ESRD, dependence on dialysis, and kidney transplant status
[5] Use of sotatercept and macitentan/tadalafil were not observed during the baseline period, so they were excluded from the table.
[6] Because PDE-5is are also marketed under brand names that are indicated for both PAH and erectile dysfunction (ED), prescription claims for PDE5is will be required to have specific daily doses that are approved for PAH.
[7] Patients receiving an oral/inhaled PPA and ERA without evidence of PDE-5i were included in the triple therapy group under the assumption that these patients were likely getting a PDE-5i with cash payment.1 Also, treatment strata were not exhaustive (N=358 patients did not qualify for any of the treatment groups).

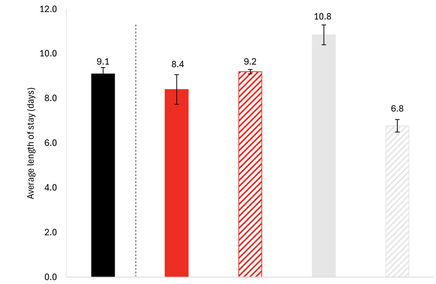
Table 2. All-cause healthcare utilization in the variable-length follow-up period, overall and by treatment group

	All patients N=2,712	Treatment groups[1] First-line therapies N=1,887	Triple therapy N=226	IV/SC PPA therapy N=241
Inpatient				
Patients with an admission	1,525 (56.2%)	1,037 (55.0%)	131 (58.0%)	160 (66.4%)
Number of inpatient admissions, PPPY	1.2 (2.1), 0.4	1.1 (2.1), 0.3	1.0 (1.7), 0.3	1.4 (1.9), 0.6
Average length of stay (in days), per admission	8.4 (12.8), 5.0	8.0 (11.1), 5.0	9.2 (16.2), 5.0	7.2 (10.0), 4.0
Outpatient				
ER visits				
Patients with an ER visit	1,487 (54.8%)	1,054 (55.9%)	124 (54.9%)	146 (60.6%)
Number of ER visits, PPPY	1.0 (1.9), 0.3	1.1 (2.0), 0.3	0.8 (1.5), 0.3	1.1 (1.5), 0.5
Outpatient office visits				
Patients with any office visit	2,660 (98.1%)	1,846 (97.8%)	223 (98.7%)	240 (99.6%)
Number of office visits, PPPY	18.1 (11.9), 15.7	18.0 (12.0), 15.9	17.1 (11.2), 15.0	17.2 (11.1), 14.0
Laboratory visits				
Patients with a laboratory visit	2,511 (92.6%)	1,746 (92.5%)	216 (95.6%)	227 (94.2%)
Number of laboratory visits, PPPY	8.9 (10.2), 6.8	8.9 (10.5), 6.8	8.2 (7.9), 6.1	9.4 (11.5), 6.8
Radiology visits				
Patients with a radiology visit	2,578 (95.1%)	1,786 (94.6%)	218 (96.5%)	232 (96.3%)
Number of radiology visits, PPPY	12.8 (14.0), 8.8	12.4 (13.2), 8.7	12.3 (11.0), 9.3	15.0 (17.9), 10.2
Other outpatient visits				
Patients with an other outpatient visit	2,690 (99.2%)	1,868 (99.0%)	226 (100.0%)	241 (100.0%)
Number of other outpatient visits	46.9 (48.2), 34.2	45.1 (49.5), 31.6	39.5 (31.8), 31.0	55.1 (52.1), 43.2
Outpatient pharmacy				
Patients with a prescription	2,710 (99.9%)	1,887 (100.0%)	226 (100.0%)	240 (99.6%)
Number of prescriptions, PPPY	67.3 (36.1), 61.7	65.8 (36.3), 60.2	77.3 (33.2), 71.5	70.3 (35.4), 64.7

Categorical variables are reported as N (%); continuous variables are reported as mean (SD), median

ER: emergency room; IV: continuous intravenous infusion; NP: nurse practitioner; PA: physician assistant; PCP: primary care provider; PPA: prostacyclin pathway agent; PPPY: per patient per year; SC: continuous subcutaneous infusion
[1] Patients receiving an oral/inhaled PPA and ERA without evidence of PDE-5i were included in the triple therapy group under the assumption that these patients were likely getting a PDE-5i with cash payment.1 Treatment strata were not exhaustive (N=358 patients did not qualify for any of the treatment groups).

Figure 2. Average length of stay among PAH-related hospitalizations (N=2,551)



ICU: intensive care unit; PAH: pulmonary arterial hypertension PH: pulmonary hypertension; PPA: prostacyclin pathway agent
PAH-related hospitalizations were identified during the variable-length post-index period. A "PAH-related" hospitalization was defined as a hospitalization with a PH diagnosis in the primary or secondary position on the claim.
Error bars represent standard error of the mean (SEM)

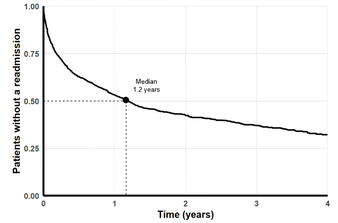
Readmissions

- Among 1,079 patients meeting the additional continuous enrollment criteria to be included in the PAH-hospitalized cohort, 58.7% had a readmission during the 1.7 years of follow-up after their initial hospitalization (**Figure 3**).
  - Median time to readmission was 1.2 years.
  - Nearly one-quarter (24.3%) had a readmission within 60 days after their initial hospitalization.

Mortality

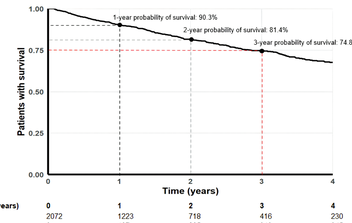
- Among newly treated patients (N=2,072), 17.9% died during the time after treatment initiation (**Figure 4**).
  - Probability of survival was 90.3% at one year after treatment initiation, 81.4% two years after, and 74.8% three years after.

Figure 3. Kaplan-Meier curve: Time to readmission among PAH-related hospitalized patients (N=1,079)



Time (years)	0	1	2	3	4
At risk	1079	471	269	162	76
Events	0	495	581	610	627

Figure 4. Kaplan-Meier curve: Time to mortality among newly treated PAH patients (N=2,072)



Time (years)	0	1	2	3	4
At risk	2072	1223	718	416	230
Events	0	167	265	313	345

Mortality analysis was conducted among newly treated patients so that time to death was evaluated from initiation of treatment, rather than at an arbitrary point during treatment.

Limitations

- This study was limited to treated PAH patients with employer-provided health coverage. Results may not be generalizable to patients with other or no health insurance.
- Clinical detail to determine PAH specifically is not available in administrative claims data, so there is potential that patients with other types of PH (e.g., Group 2, 3, 5) are included in the study population. Likewise, functional class, risk status, and other PAH etiology are not available in administrative claims data.
- Treatment groups were assigned based on drugs received in a 6-month period. It is possible that patients in the triple therapy group took the drugs sequentially rather than concurrently. Drugs administered in the inpatient setting (e.g., IV/SC PPA infusions) and drugs that may be paid for completely out of pocket (such as PDE-5i) are not captured in administrative claims.
- Deaths were identified from 1) MarketScan data contributors (e.g., inpatient death, deaths otherwise recorded by data contributors) and 2) linkage to the Social Security Administration (SSA) public death master file. It is possible that not all deaths are captured, so the true mortality rate may be underestimated.
- Requiring at least 30 days of continuous enrollment in a health insurance plan after the index date may have introduced survival bias.
- This study was descriptive in nature, and no statistical analyses were performed. All comparisons were relative and were not tested for statistical significance.

Key Takeaways

- Hospitalization burden remains high among PAH patients: 44.9% of treated US PAH patients had ≥1 PAH-related hospitalization over a mean 2.2 years of follow-up.
- Readmissions are common after a PAH-related hospitalization: 24.3% were readmitted within 60 days (median time to readmission: 1.2 years).
- Hospitalizations are frequently severe/resource intensive: 57.2% of PAH-related hospitalizations included an ICU stay; mean length of stay was 9.1 days (10.8 with ICU vs 6.8 without).
- Meaningful mortality persists among newly treated patients: 17.9% died over a mean 1.8 years after treatment initiation; survival was 90.2% at 1 year and 74.5% at 3 years.

Conclusions

- Though much improved in the 30 years since the introduction of targeted treatments, burden of disease for PAH persists, with high rates of hospitalization, re-hospitalization, and mortality.
- These findings highlight the unmet need for optimal management in PAH and the requirement to continuously monitor disease burden as progress is made with PAH therapies.

Disclosures

This study was funded by Johnson & Johnson. AR declares relationships with Johnson & Johnson (speaker and consultant), Merck (speaker), and Liquidia (speaker and consultant). AB and DL declare being employed by company Johnson & Johnson. AB also declares ownership of Johnson & Johnson stock. CRL, HV, and MJ declare being employed by Merative, which received funding from Johnson & Johnson to conduct this study. AM declares relationships with Johnson & Johnson (speaker and consultant), United Therapeutics (speaker), Merck (speaker), and Liquidia (speaker).

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