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RESEARCH ARTICLE

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Excess healthcare resource utilization and costs for commercially insured patients with pulmonary arterial hypertension: A real-world data analysis

Tracey Weiss[1] | **Dena R. Ramey**[1] | **Ngan Pham**[2] | **Nazneen Fatima Shaikh**[2] | **Dajun Tian**[2] | **Xiaohui Zhao**[2] | **Aimee M. Near**[2] | **Dominik Lautsch**[1] | **Steven D. Nathan**[3]

[1]Merck & Co., Inc., Rahway, New Jersey, USA

[2]IQVIA Inc., Durham, North Carolina, USA

[3]Inova Fairfax Hospital, Falls Church, Virginia, USA

Correspondence
Tracey Weiss, 351 N Sumneytown Pike, North Wales, PA 19454, USA.
Email: Tracey.Weiss@merck.com

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Abstract

This retrospective study was conducted to evaluate all-cause healthcare resource utilization (HCRU) and costs in commercially insured patients living with pulmonary arterial hypertension (PAH) and explore end-of-life (EOL)-related HCRU and costs. Data from the IQVIA PharMetrics® Plus database (October 2014 to May 2020) were analyzed to identify adults (≥18 years) with PAH (PAH cohort) and those without PH (non-PH cohort). Patients were required to have data for ≥12 months before (baseline) and ≥6 months after (follow-up) the first observed PH diagnosis (index date) for PAH cohort or pseudo index date for non-PH cohort. A PAH EOL cohort was similarly constructed using a broader data window (October 2014 to March 2022) and ≥1 month of follow-up. Annualized all-cause HCRU and costs during follow-up were compared between PAH and non-PH cohorts after 1:1 matching on propensity scores derived from patient characteristics. EOL-related HCRU and costs were explored within 30 days and 6 months before the death date and estimated by a claims-based algorithm in PAH EOL cohort. The annual all-cause total ($183,616 vs. $20,212) and pharmacy ($115,926 vs. $7862; both $p < 0.001$) costs were 8 and 14 times higher, respectively, in the PAH cohort versus matched non-PH cohort ($N = 386$ for each). In PAH EOL cohort ($N = 28$), the mean EOL-related costs were $48,846 and $167,524 per patient within 30 days and 6 months before the estimated death, respectively. Hospitalizations contributed 58.8%–70.8% of the EOL-related costs. The study findings indicate substantial HCRU and costs for PAH. While pharmacy costs were one of the major sources, hospitalization was the primary driver for EOL-related costs.

KEYWORDS
end-of-life care, healthcare costs, healthcare resource utilization, mortality, pulmonary artery hypertension (PAH)

INTRODUCTION

Pulmonary arterial hypertension (PAH), or group 1 pulmonary hypertension (PH) is characterized by constriction of pulmonary blood vessels, increased pulmonary vascular resistance, and eventually right-sided ventricular failure that can lead to death.[1] PAH is a rare disease, with an estimated prevalence of 109 per million for adults 19–64 years of age and 451 per million for adults ≥65 years of age in the United States.[2] The disease burden of PAH can be substantial. One systematic review reported that the direct healthcare costs of patients with PAH varied from $2476 to $11,875 per patient per month (PPPM) in 2014 US dollars.[3]

Pharmacological treatments approved in the United States include phosphodiesterase 5 (PDE-5) inhibitors, a soluble guanylate cyclase (sGC) stimulator, endothelin receptor antagonists (ERA), a prostacyclin receptor agonist (PRA), and prostacyclin analogues (PCAs).[1,4] While the knowledge of and pharmacological options for PAH have expanded in the past decade, the long-term prognosis for patients with PAH remains poor, with a mortality rate of nearly 50% over 5 years.[5] Delayed diagnosis and initiation of therapy leads to a poor prognosis,[6] which could lead to a significant economic burden for PAH patients. Published studies have estimated healthcare resource utilization (HCRU) and associated costs among patients with PAH[7–9]; however, there are few studies estimating the excess burden of PAH relative to patients without PH. For example, a recent study reported the direct healthcare costs (2018 USD) were $9915 PPPM for 1293 commercially insured patients with prevalent PAH as compared to $359 for demographically (age, sex, region) matched non-PAH patients.[10] To obtain a contemporary estimation of the real-world burden of PAH, this study compared all-cause HCRU and associated costs of commercially insured patients with PAH to patients without PH and explored EOL-related HCRU and costs among patients with PAH.

METHODS

Study design and patient population

This retrospective study analyzed data from the IQVIA PharMetrics® Plus (P+) patient-level claims database, a longitudinal health plan database of commercially insured patients in the United States. Adult (≥18 years) patients with PAH (i.e., PAH cohort) and patients without PH (i.e., non-PH cohort; patients without any form of PH [groups 1–5]) were identified between October 1, 2014 and May 31, 2020 (study period). Patients were selected into the PAH cohort if they had ≥1 inpatient or ≥2 outpatient diagnoses for PAH (International Classification of Diseases, Tenth Revision of Clinical Modification [ICD-10-CM] codes of I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83) that were ≥30 days apart between October 1, 2015 and November 30, 2019 (selection window), Figure 1. The date of the first observed PAH diagnosis code was the index date. Patients were required to have ≥12 months of continuous enrollment before (baseline) and ≥6 months of continuous enrollment after (follow-up) the index date. Patients were also required to have ≥1 FDA-approved medication indicated for PAH any time on or after the PAH index date and any of the following: ≥1 right heart catheterization (RHC) procedure any time during the study period or ≥2 PAH medications in different classes (PDE-5 inhibitors, sGC stimulators, ERAs, and PRA/PCAs) on or after the index date. Patients were excluded if there was any diagnosis of chronic obstructive pulmonary disease (COPD), chronic thromboembolic pulmonary hypertension (CTEPH), pulmonary fibrosis, interstitial lung disease, or idiopathic interstitial pneumonia, PH due to left heart disease (PH-LHD), left-sided heart failure, and any pulmonary endarterectomy or balloon pulmonary angioplasty (BPA) procedure during the study period. Patients who had a lung transplant surgery during the 12 months before the index date or had any data quality issues were also excluded. A non-PH cohort was similarly constructed to include patients without diagnosis of PH during the study period, Figure 2. Index date was randomly assigned to replicate the distribution of index dates in the PAH cohort. As the non-PH cohort included a large number of patients, a 25% random sample of patients without PH who had data activity during the selection window was selected for the non-PH cohort. Patients with any FDA-approved medications indicated for PAH during the study period were excluded from the non-PH cohort.

To explore the EOL-related HCRU and costs, a PAH EOL cohort was constructed using the same selection criteria for the PAH cohort, with three modifications: (1) a broader time frame (October 1, 2014 through March 31, 2022) was used as more recent data were available at time of EOL analysis; (2) a minimum of 1 month of follow-up was required in the PAH EOL cohort to reduce immortal time bias; and (3) a claims-based algorithm[11] was employed to identify patients with evidence of death, Figure A1. For the claims-based mortality algorithm, clinical codes indicating potentially fatal events were identified from published literature and expert opinion.[11–14] Among patients with any fatal event codes (Table A1), the time from the last fatal event code observed (A) to the last medical claim in the

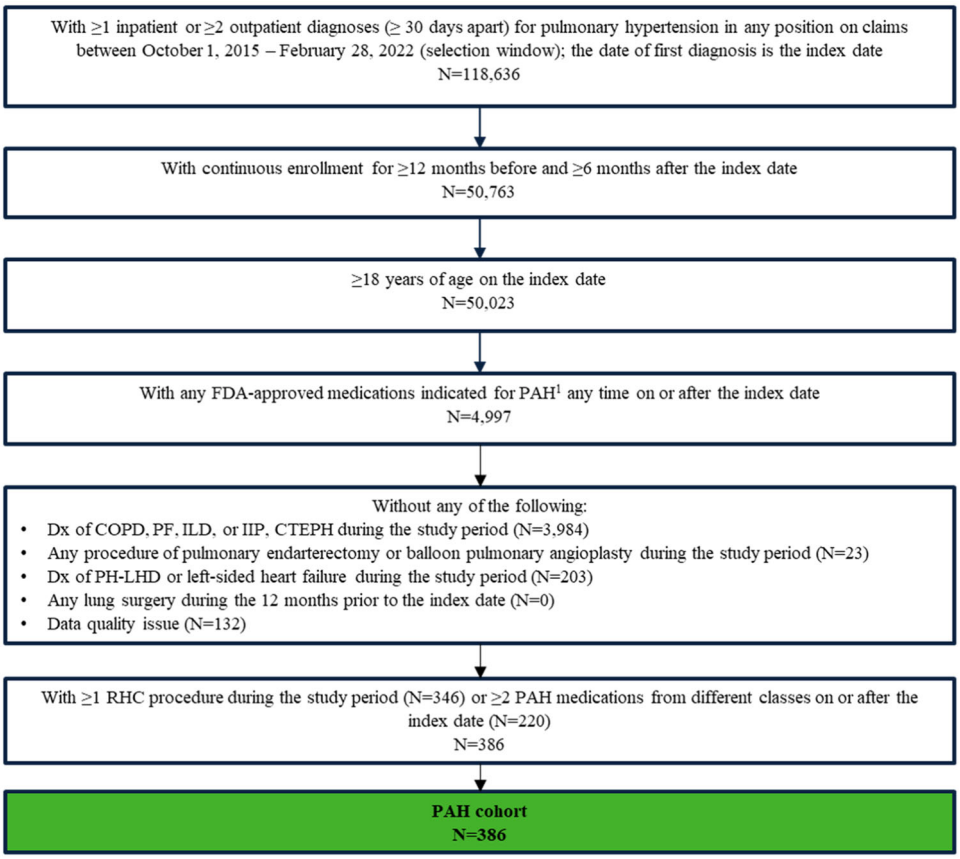

FIGURE 1 Patient selection of the PAH cohort. [1]Medications approved for PAH included phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin receptor agonists, and prostacyclin analogues. CTEPH, chronic thromboembolic pulmonary hypertension; Dx, diagnosis; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; PAH, pulmonary artery hypertension; PF, pulmonary fibrosis; PH-LHD, PH due to left heart disease; RHC, right heart catheterization.

data (B) and from the last medical claim (B) to the end of insurance eligibility (C) or end of the study period (D) were determined, Figure 3. A flag indicating possible death was assigned to patients with ≥30 days of follow-up after A (i.e., A to C) and ≤30 days between A and B. For patients who had <30 days of follow-up after A and the end of insurance eligibility before the study end (i.e., C to D ≥1 day), a flag indicating possible death was assigned upon review of medical claims with the fatal events and the final medical claims by a clinical expert. The date of the last claim was considered as the estimated death date among patients with a flag indicating possible death.

Study measures

Annualized all-cause, PH-related HCRU and associated costs were evaluated during the minimum 6-month follow-up period in the PAH and non-PH cohorts by multiplying the monthly estimates from the data by 12. The risk of medical service encounters was quantified by the number of patients with a specific outcome divided by total patient-years followed and reported as the number of patients with ≥1 outcome of interest per 100 patient-years. Total patient-years followed were evaluated as the time from the index date to the earliest of the patient's first event of interest, the end of continuous enrollment, or the end of the study period. PH-related medical service use and associated costs were examined in the PAH cohort and defined by a primary diagnosis with I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 on the claim or a primary diagnosis with Q21.1 or Q20.0 accompanied with a diagnosis of I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 in any position of the same claim. EOL-related HCRU and associated costs were examined during the 30-day and 6-month before the estimated death date in the PAH EOL cohort. The total healthcare costs and cost associated with each type of HCRU were measured by the contracted reimbursable amount of the covered care and reported in 2022 US dollars using the Consumer Price Index of Medical care for all Urban Consumers.[15]

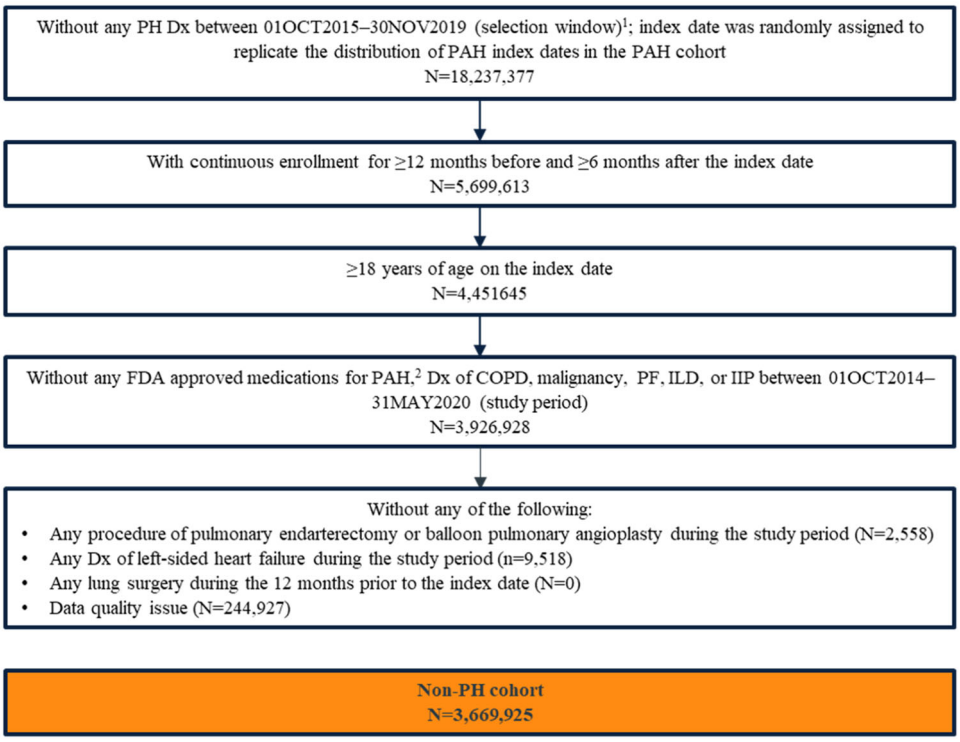

FIGURE 2 Patient selection of the non-PH cohort. [1]A 25% random sample of selected individuals without any PH diagnosis who had ≥1 medical or pharmacy claim and ≥1 month of continuous enrollment during the selection window was selected to improve analysis efficiency; [2]Medications approved for PAH included phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin receptor agonists, and prostacyclin analogues. CTEPH, chronic thromboembolic pulmonary hypertension; Dx, diagnosis; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; PAH, pulmonary artery hypertension; PF, pulmonary fibrosis.

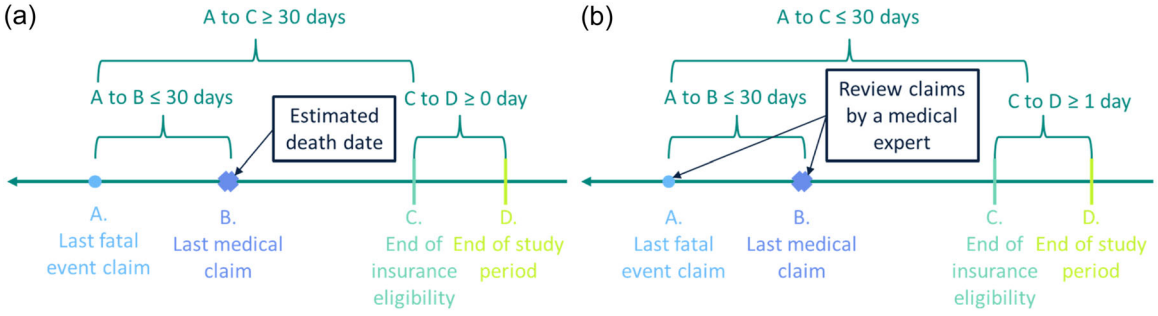

FIGURE 3 Claims-based mortality algorithm for the PAH EOL cohort. A flag indicating possible death was assigned to patients with ≥30 days of follow-up after A (i.e., A to C) and ≤30 days between A and B (a) and was assigned to patients who had <30 days of follow-up after A and the end of insurance eligibility before the study end (i.e., C to D ≥1 day) upon review of medical claims with the fatal events and the final medical claims by a clinical expert (b).

Patient demographics and clinical characteristics, including comorbidities (Charlson Comorbidity Index [CCI] excluding chronic pulmonary disease[16] and the presence/absence of individual comorbid conditions), and total all-cause healthcare costs were assessed in the ≥12-month baseline period for the PAH and non-PH cohorts. The presence of a comorbidity/symptom was defined by ≥1 relevant diagnosis code.

Statistical analysis

Patients in the PAH cohort were 1:1 matched to patients in the non-PH cohort based on propensity scores derived from baseline patient characteristics (index year, continuous age, gender, continuous length of baseline, US census region, payer type, plan type, continuous CCI score, the presence of sleep apnea, atrial fibrillation,

cardiovascular disease [CVD], diabetes, hypertension, heart failure, kidney disease, obesity, asthma, pneumonia, connective tissue disease, dyslipidemia, liver disease, and systemic autoimmune disease). Matching was performed using the greedy nearest neighbor approach without replacement based on a caliper width of 0.01 (i.e., 0.2 of the standard deviation of the logit of the propensity score).[17] Baseline patient demographic and clinical characteristics were described and compared for the PAH cohort and non-PH cohort before and after matching. Covariates were deemed balanced after matching if the standardized mean difference (SMD) was ≤10%. Annualized all-cause HCRU and associated costs (per-patient-per-year [PPPY]) during the ≥6 months of follow-up were compared between the PAH cohort and non-PH cohort after matching, using the McNemar's test for proportions and paired t test for means. For all analyses, a two-tailed test of significance was assumed, and the α level was set a priori at 0.05. All data management and analyses were performed with SAS version 9.4 (SAS Inc.).

RESULTS

Description of the study cohorts

There were 386 patients in the PAH cohort and 3,669,925 patients in the non-PH cohort. Before matching, the PAH cohort and non-PH cohort were different in several demographic and baseline clinical characteristics (Table 1). The PAH patients were, on average, 8 years older than the non-PH cohort (mean ± standard deviation [SD] age: 50.9 [±11.4] vs. 42.5 [±14.0 years], SMD = 0.65), with a higher proportion of females (59.1% vs. 53.0%, SMD = 0.12). The PAH cohort had a longer baseline period as compared to the non-PH cohort (median [interquartile range, IQR] duration: 22.9 [16.0–32.1] vs. 19.2 [14.9–26.6] months, SMD = 0.36). During the baseline period, compared to the non-PH cohort, the PAH cohort had a higher CCI score (mean [±SD]: 1.9 [±2.3] vs. 0.3 [±0.9], SMD = 0.92) and a higher proportion of patients with a CCI ≥ 3 (29.0% vs. 2.7%, SMD = 0.77). Furthermore, most respiratory comorbidities examined occurred more frequently in the PAH cohort versus non-PH cohort, with the largest difference seen for pneumonia/acute bronchitis/bronchiolitis (25.9% vs. 9.1%, SMD = 0.45). All nonrespiratory comorbidities were more frequently observed in the PAH cohort versus non-PH cohort as well. The PAH cohort also had significantly higher mean all-cause healthcare costs PPPM during baseline (mean [±SD]: $2914 [±6355] vs. $297 [±1102], SMD = 0.57).

After 1:1 matching on propensity scores, there were 386 patients in the PAH and non-PH cohorts, with no loss of patients from the PAH cohort during the matching process. The demographic characteristics and most baseline clinical characteristics were well balanced (SMD ≤ 10%) after matching. As expected, dyspnea, a hallmark symptom of PAH, remained more prevalent in the PAH cohort compared to the matched non-PH cohort (67.6% vs. 22.5%, SMD = 1.02). In addition, the PAH cohort had higher prevalence of pulmonary edema (4.9% vs. 2.1%, SMD = 0.16), coronary heart disease (21.2% vs. 16.1%, SMD = 0.13), and alcohol-related disorders (6.0% vs. 2.1%, SMD = 0.20) but lower prevalence of hypertension (59.1% vs. 65.5%, SMD = 0.13) and obesity (71.2% vs. 80.4%, SMD = 0.22) as compared to the matched non-PH cohort. The baseline healthcare costs remained higher in the PAH cohort as compared to the matched non-PH cohort (mean [±SD]: $3069 [±6694] vs. $1571 [±6027], SMD = 0.24).

Follow-up all-cause and PH-related HCRU

The median (IQR) follow-up was 22.9 (14.0–36.6) months for the PAH cohort and 21.5 (13.3–35.5) months for the matched non-PH cohort. During the follow-up period, the PAH cohort had high rates of PH-related medical service use (e.g., hospitalization, ED visit, outpatient/physician visit). On average, about 18% in the PAH cohort had ≥1 PH-related hospitalization during a year (18.2 per 100 patient-years). PH-related outpatient and other medical services visits were also commonly observed (112.3 and 131.0 per 100 patient-years, respectively), Figure 4. For PAH medications, PDE-5 inhibitor (82.5%) was the most commonly used treatment class, followed by ERAs (47.1%), PRA/PCAs (16.2%), and sGC stimulator (4.1%). Among patients with ≥1 fill of the respective medication class, the median (IQR) number of fills PPPY was 9.7 (5.9–11.5) for ERAs, 8.6 (3.8–12.8) for PRA/PCAs, 7.6 (2.4–11.3) for PDE-5 inhibitors, and 7.4 (3.9–11.2) for sGC stimulators.

The PAH cohort had higher all-cause HCRU compared to the non-PH cohort across all care settings, with the largest difference observed for hospitalizations, Figure 5. The risk of all-cause hospitalization was almost seven times higher in the PAH cohort versus the non-PH cohort (47.1 vs. 7.2 per 100 patient-years, both $p < 0.001$). Among patients with ≥1 hospitalization, the PAH cohort also had significantly longer cumulative hospital stays PPPY as compared to the non-PH cohort (median [IQR]: 6.7 [2.4–12.8] vs. 2.4 [1.2–7.4] days, $p = 0.009$).

TABLE 1 Patient demographic and baseline clinical characteristics of the PAH and non-PH cohorts, before and after PS-matching.

	Prematching ($N = 3,670,311$)			Postmatching ($N = 722$)		
Patient characteristics	**PAH ($N = 386$)**	**Non-PH ($N = 3,669,925$)**	**SMD**	**PAH ($N = 386$)**	**Non-PH ($N = 386$)**	**SMD**
Index year (*n*, %)						
2015	52 (13.5%)	760,475 (20.7%)	0.476	52 (13.5%)	51 (13.2%)	0.133
2016	135 (35.0%)	1,726,857 (47.1%)		135 (35.0%)	117 (30.3%)	
2017	103 (26.7%)	842,663 (23.0%)		103 (26.7%)	101 (26.2%)	
2018	61 (15.8%)	218,110 (5.9%)		61 (15.8%)	75 (19.4%)	
2019	35 (9.1%)	121,820 (3.3%)		35 (9.1%)	42 (10.9%)	
Age at index (years)						
Mean (SD)	50.9 (11.4)	42.5 (14.0)	0.654	50.9 (11.4)	51.8 (11.7)	0.086
Median (IQR)	53.0 (43.0–60.0)	43.0 (31.0–54.0)		53.0 (43.0–60.0)	54.0 (45.0–60.0)	
Age group (*n*, %), years						
18–39	64 (16.6%)	1,550,214 (42.2%)	0.607	64 (16.6%)	60 (15.5%)	0.107
40–54	160 (41.5%)	1,236,560 (33.7%)		160 (41.5%)	144 (37.3%)	
55–64	150 (38.9%)	824,536 (22.5%)		150 (38.9%)	170 (44.0%)	
65+	12 (3.1%)	58,615 (1.6%)		12 (3.1%)	12 (3.1%)	
Female (*n*, %)	228 (59.1%)	1,946,231 (53.0%)	0.122	228 (59.1%)	230 (59.6%)	0.011
Census region (*n*, %)						
Northeast	61 (15.8%)	658,581 (17.9%)	0.065	61 (15.8%)	60 (15.5%)	0.084
Midwest	99 (25.6%)	963,410 (26.3%)		99 (25.6%)	113 (29.3%)	
South	156 (40.4%)	1,404,831 (38.3%)		156 (40.4%)	145 (37.6%)	
West	70 (18.1%)	643,103 (17.5%)		70 (18.1%)	68 (17.6%)	
Unknown/missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Payer type (*n*, %)						
Private insurance	239 (61.9%)	2,302,617 (62.7%)	0.123	239 (61.9%)	226 (58.5%)	0.074
Commercial Medicare	14 (3.6%)	66,899 (1.8%)		14 (3.6%)	14 (3.6%)	
Commercial Medicaid	21 (5.4%)	164,485 (4.5%)		21 (5.4%)	25 (6.5%)	
Other[a]	112 (29.0%)	1,135,924 (31.0%)		112 (29.0%)	121 (31.3%)	
Plan type (*n*, %)						
HMO	71 (18.4%)	543,463 (14.8%)	0.103	71 (18.4%)	67 (17.4%)	0.038
PPO	288 (74.6%)	2,827,673 (77.0%)		288 (74.6%)	289 (74.9%)	
POS	15 (3.9%)	156,689 (4.3%)		15 (3.9%)	17 (4.4%)	
Other/unknown	12 (3.1%)	142,100 (3.9%)		12 (3.1%)	13 (3.4%)	
Length of all available baseline period, months						
Mean (SD)	25.7 (11.9)	21.9 (9.1)	0.363	25.7 (11.9)	26.4 (11.8)	0.062
Median (IQR)	22.9 (16.0–32.1)	19.2 (14.9–26.6)		22.9 (16.0–32.1)	24.3 (16.7–32.5)	
Charlson Comorbidity Index (CCI)[b]						
Mean (SD)	1.9 (2.3)	0.3 (0.9)	0.929	1.9 (2.3)	1.8 (2.4)	0.064
Median (IQR)	1 (0.0–3.0)	0.0 (0.0–2.0)		1.0 (0.0–3.0)	1.0 (0.0–3.0)	

TABLE 1 (Continued)

Patient characteristics	Prematching ($N = 3,670,311$)			Postmatching ($N = 722$)		
	PAH ($N = 386$)	Non-PH ($N = 3,669,925$)	SMD	PAH ($N = 386$)	Non-PH ($N = 386$)	SMD
Categories (n, %)						
0	141 (36.5%)	3,095,621 (84.4%)	1.121	141 (36.5%)	174 (45.1%)	0.175
1	75 (19.4%)	318,851 (8.7%)	0.313	75 (19.4%)	65 (16.8%)	0.067
2	58 (15.0%)	156,928 (4.3%)	0.370	58 (15.0%)	43 (11.1%)	0.115
≥3	112 (29.0%)	98,525 (2.7%)	0.773	112 (29.0%)	104 (26.9%)	0.046
Comorbidities of interest (n, %)						
Respiratory						
Asthma	57 (14.8%)	199,825 (5.4%)	0.313	57 (14.8%)	65 (16.8%)	0.057
Allergic rhinitis or atopy	47 (12.2%)	380,643 (10.4%)	0.057	47 (12.2%)	57 (14.8%)	0.076
Chronic rhinitis	7 (1.8%)	47,814 (1.3%)	0.041	7 (1.8%)	11 (2.8%)	0.069
Dyspnea	261 (67.6%)	208,280 (5.7%)	1.678	261 (67.6%)	87 (22.5%)	1.016
Pneumonia/acute bronchitis/bronchiolitis	100 (25.9%)	334,565 (9.1%)	0.453	100 (25.9%)	105 (27.2%)	0.029
Pulmonary edema	19 (4.9%)	3728 (0.1%)	0.312	19 (4.9%)	8 (2.1%)	0.156
Sinusitis	90 (23.3%)	610,445 (16.6%)	0.168	90 (23.3%)	99 (25.6%)	0.054
Tuberculosis	1 (0.3%)	1771 (0.0%)	0.054	1 (0.3%)	(0.0%)	0.072
Sleep apnea	70 (18.1%)	137,061 (3.7%)	0.474	70 (18.1%)	67 (17.4%)	0.020
Nonrespiratory						
Alcohol-related disorder	23 (6.0%)	52,250 (1.4%)	0.242	23 (6.0%)	8 (2.1%)	0.199
Anxiety/depression	103 (26.7%)	663,423 (18.1%)	0.208	103 (26.7%)	108 (28.0%)	0.029
Atrial fibrillation	47 (12.2%)	31,072 (0.8%)	0.472	47 (12.2%)	36 (9.3%)	0.092
Cardiovascular disease	98 (25.4%)	121,410 (3.3%)	0.664	98 (25.4%)	89 (23.1%)	0.054
Connective tissue disease	44 (11.4%)	15,363 (0.4%)	0.479	44 (11.4%)	47 (12.2%)	0.024
Diabetes	80 (20.7%)	270,706 (7.4%)	0.391	80 (20.7%)	78 (20.2%)	0.013
Dyslipidemia	168 (43.5%)	833,059 (22.7%)	0.454	168 (43.5%)	164 (42.5%)	0.021
Hypertension	228 (59.1%)	768,162 (20.9%)	0.845	228 (59.1%)	253 (65.5%)	0.134
Heart failure	103 (26.7%)	28,399 (0.8%)	0.813	103 (26.7%)	88 (22.8%)	0.090
Kidney disease	68 (17.6%)	56,226 (1.5%)	0.568	68 (17.6%)	62 (16.1%)	0.042
Liver disease	77 (19.9%)	108,475 (3.0%)	0.554	77 (19.9%)	67 (17.4%)	0.067
Metabolic syndrome	7 (1.8%)	22,707 (0.6%)	0.109	7 (1.8%)	7 (1.8%)	0.000
Osteoporosis	15 (3.9%)	49,285 (1.3%)	0.160	15 (3.9%)	14 (3.6%)	0.014
Peptic ulcer/GERD	7 (1.8%)	9677 (0.3%)	0.153	7 (1.8%)	4 (1.0%)	0.066
Systemic autoimmune disease[c]	47 (12.2%)	71,331 (1.9%)	0.408	47 (12.2%)	47 (12.2%)	0.000
Nonmissing BMI[d]	111 (28.8%)	431,889 (11.8%)	0.433	11 (28.8%)	107 (27.7%)	0.023
Underweight/normal weight	11 (9.9%)	92,865 (21.5%)	0.323	11 (9.9%)	7 (6.5%)	0.123
Overweight	21 (18.9%)	119,585 (27.7%)	0.209	21 (18.9%)	14 (13.1%)	0.160

(Continues)

TABLE 1 (Continued)

Patient characteristics	Prematching ($N = 3,670,311$)			Postmatching ($N = 722$)		
	PAH ($N = 386$)	Non-PH ($N = 3,669,925$)	SMD	PAH ($N = 386$)	Non-PH ($N = 386$)	SMD
Obese	79 (71.2%)	219,219 (50.8%)	0.427	79 (71.2%)	86 (80.4%)	0.216
With smoking cessation therapies (n, %)[e]	6 (1.6%)	31,487 (0.9%)	0.064	6 (1.6%)	8 (2.1%)	0.039
Total all-cause healthcare costs PPPM (2020 USD)[e]						
Mean (SD)	$2913.6 ($6355.4)	$296.8 ($1102.0)	0.574	$2913.6 ($6355.4)	$1491.0 ($5721.7)	0.235
Median (IQR)	$679.9 ($254.9–$2292.7)	$66.6 ($16.3–$223.5)		$679.9 ($254.9–$2292.7)	$202.6 ($56.4–$699.3)	

Abbreviations: BMI, body mass index; GERD, gastroesophageal reflux disease; HMO, health maintenance organization; IQR, interquartile range; POS, point-of-service; PPO, preferred provider organization; PPPM/Y, per patient per month/year; SD, standard deviation; SMD, standardized mean difference.

[a]Other payers included self-pay insurance and unknown payer type.

[b]CCI was calculated using Quan's adaptation, excluding chronic pulmonary disease.

[c]Autoimmune diseases included graft-vs.-host disease, inflammatory bowel disease, rheumatoid arthritis, Scleroderma, Sjogren's disease, and valvular heart disease.

[d]BMI was identified by ICD-9 or ICD-10 diagnosis codes and were expected to be underreported.

[e]Somking cessation therapy and baseline total healthcare costs were examined in the 12-month baseline period.

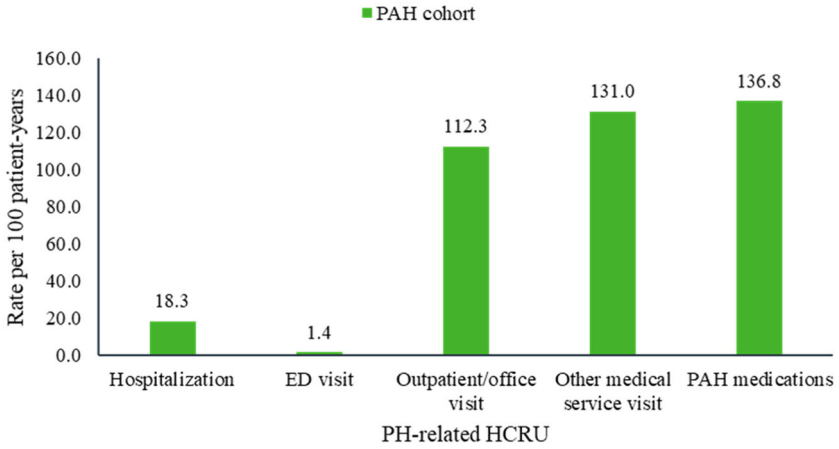

FIGURE 4 PH-related HCRU during the follow-up period of the PAH cohort. Other medical service included laboratory and pathology test, radiology, surgery, medical procedures/supplies/products during office visits, and other ancillary services. PH-related medical services (hospitalization, ED visit, outpatient/office visit, other medical service visit) were defined by a primary diagnosis with I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 on the claim or a primary diagnosis with Q21.1 or Q20.0 accompanied with a diagnosis of I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 in any position of the same claim. PAH Medications included phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin receptor agonists, and prostacyclin analogues. ED, emergency department; HCRU, healthcare resource utilization.

Follow-up all-cause and PH-related healthcare costs

The total all-cause healthcare costs were $163,404 higher in the PAH cohort than the matched non-PH cohort ($183,616 [±$191,045] and $20,212 [±$54,799] PPPY, $p < 0.001$). Pharmacy and hospitalizations were the leading cost drivers, accounting for 63.1% and 20.0% of the total all-cause costs in the PAH cohort, respectively, as well as 66.1% and 19.6% of the excess costs, respectively, when comparing the PAH cohort to the non-PH cohort, Figure 6a. The total PH-related costs in the PAH cohort were $107,311 (±$125,916) PPPY, with >90% of the costs attributable to FDA-approved medications for PAH. The total PH-related costs for medical services were $10,625 (±$24,950), Figure 6b.

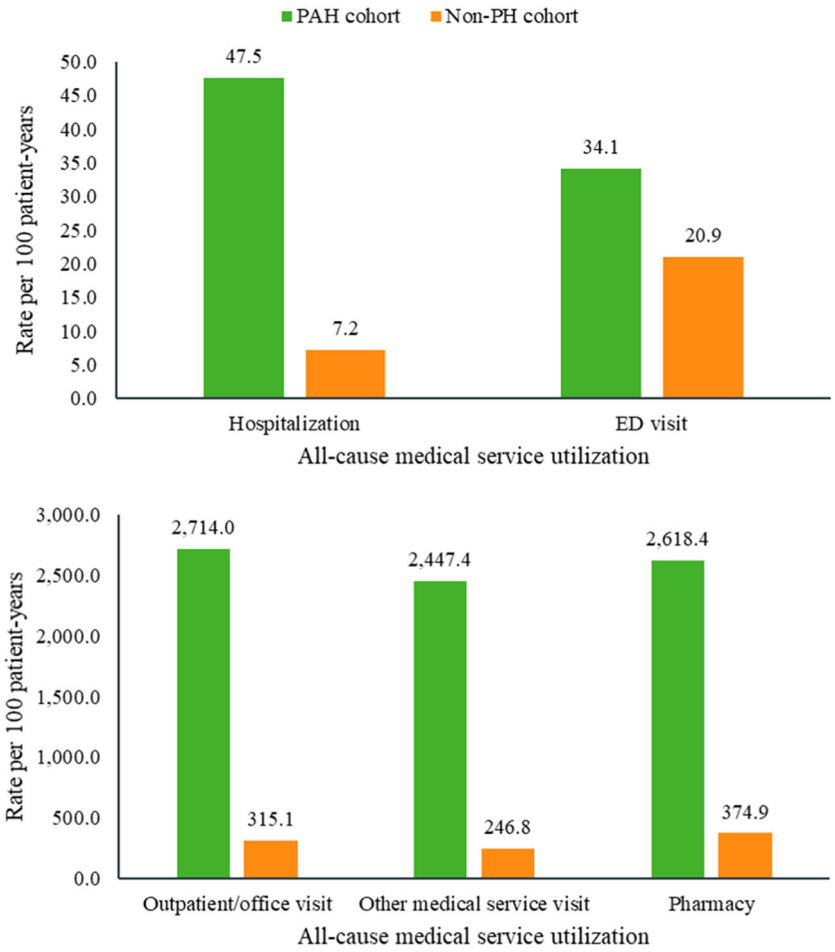

FIGURE 5 All-cause HCRU during the follow-up period of the matched PAH and non-PH cohort. Other medical service included laboratory and pathology test, radiology, surgery, medical procedures/supplies/products during office visits, and other ancillary services. ED, emergency department.

Follow-up EOL-related HCRU and associated costs

A total of 28 patients with evidence of death were identified and included in the PAH EOL cohort based on the claims-based algorithm. Within 30 days before the estimated death date, 60.7% of the patients had ≥1 hospitalization with a median (IQR) total length of stay of 8.0 (4.0–16.0) days. Approximately one-third (32.1%) of patients had ≥1 ED visit. Most patients had ≥1 outpatient/office visit (82.1%), other medical service utilization (82.1%), and pharmacy utilization (85.7%). PDE-5 inhibitors and ERAs were used by 50.0% and 42.9% of patients, respectively. Within 6 months before the estimated death date, 82.1% of patients had ≥1 hospitalization with a median (IQR) total length of stay of 19.0 (6.0–37.0) days. Nearly all patients had ≥1 outpatient visit (96.4%), other medical service utilization (100.0%), and pharmacy utilization (100.0%), while half of patients had ≥1 ED visit. Most patients used PDE-5 inhibitors (78.6%), while ERAs were used by 53.6% of patients. No patients had evidence of lung transplant surgery within 6 months before the estimated death date.

The mean total healthcare costs (medical and pharmacy) for the PAH EOL cohort were $48,846 (±$61,031) and $167,524 (±$150,223) during 30-day and 6-month before the estimated death date, respectively. Specifically, the mean total costs of medical services were $37,915 (±$60,061), driven primarily by hospitalization costs of $34,579 (±$134,223) during 30-day before the estimated death date. Similarly, the mean hospitalization costs of $98,487 (±$127,043) accounted for the majority of mean total medical costs ($115,058 ± $134,223) during 6-month before estimated death date. 60.7% ($N = 17$) and 82.1% ($N = 23$) patients had ≥1 hospitalization within 30 days and 6 months before the estimated death date, respectively. Among patients with ≥1 hospitalization, the mean cost per hospitalization per patient was $46,105 (±$42,534) within 30 days before the estimated death date and $53,032 (±$82,149) within 6 months before the estimated death date. Total pharmacy costs were the second leading contributor to total healthcare costs, with a mean of $10,931 (±$15,903) during 30-day before estimated death and $52,466 (±$74,194) during 6-month before estimated death date, Figure 7.

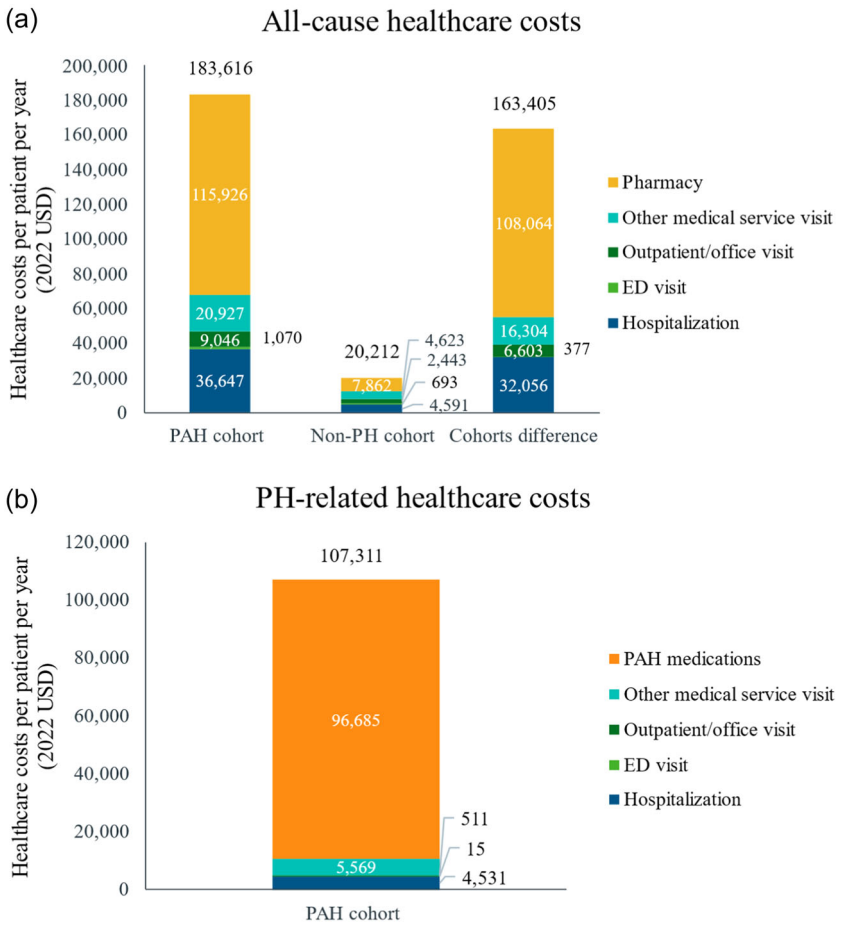

FIGURE 6 All-cause (a) and PH-related (b) healthcare costs of the matched PAH and non-PH cohorts. Other medical service included laboratory and pathology test, radiology, surgery, medical procedures/supplies/products during office visits, and other ancillary services. PH-related medical services (hospitalization, ED visit, outpatient/office visit, other medical service visit) were defined by a primary diagnosis with I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 on the claim or a primary diagnosis with Q21.1 or Q20.0 accompanied with a diagnosis of I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 in any position of the same claim. PAH Medications included phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin receptor agonists, and prostacyclin analogues. ED, emergency department.

DISCUSSION

This retrospective database study provides a contemporary estimate of the economic burden of patients with PAH compared to patients without PH. Also, to our knowledge, this is the first study to explore the real-world EOL-related HCRU and costs among commercially-insured patients with PAH. The total all-cause healthcare costs were about eight times higher in the PAH cohort compared to the non-PH comparator cohort after matching on key patient characteristics. The excess costs accrued by patients with PAH were primarily driven by the use of PAH medications, followed by hospitalizations. Further, a claims-based algorithm was leveraged to identify mortality among patients with PAH, and the average monthly healthcare costs increased significantly in the 6 months and 30 days before estimated death compared to overall healthcare costs. In this cohort, pharmacy costs were exceeded by hospitalization costs, demonstrating the increased burden of medical services patients face near end of life.

Before PS-matching, the PAH cohort was older and consisted of a higher proportion of females, HMO enrollees, and patients with a higher comorbidity burden as compared to the non-PH cohort. Similar demographics and clinical characteristics of PAH patients were reported in the literature.[18–20] After PS-matching, most demographic and clinical characteristics were well balanced between the PAH and matched non-PH cohorts but the prevalence of dyspnea and coronary heart disease remained higher in the PAH cohort as compared to the matched non-PH cohort. These comorbidities reflect the hallmark symptom and specific phenotype of PAH,[4] which can contribute to the overall burden of PAH.

Consistent with published literature,[3,21,22] the presence of PAH was associated with significant HCRU and healthcare cost burden. The PAH cohort had significantly higher all-cause utilization of medical services across all care settings and prescription drugs as compared to the non-PH cohort, with the largest difference observed in all-cause hospitalizations. The higher HCRU translated to higher direct healthcare costs. Patients with PAH had all-cause total costs of $183,616 PPPY ($16,135 PPPM in 2022 USD), which was approximately eight times higher than the costs of patients without PH matched on key demographic and clinical characteristics. This estimation is in line with published literature, indicating that the monthly

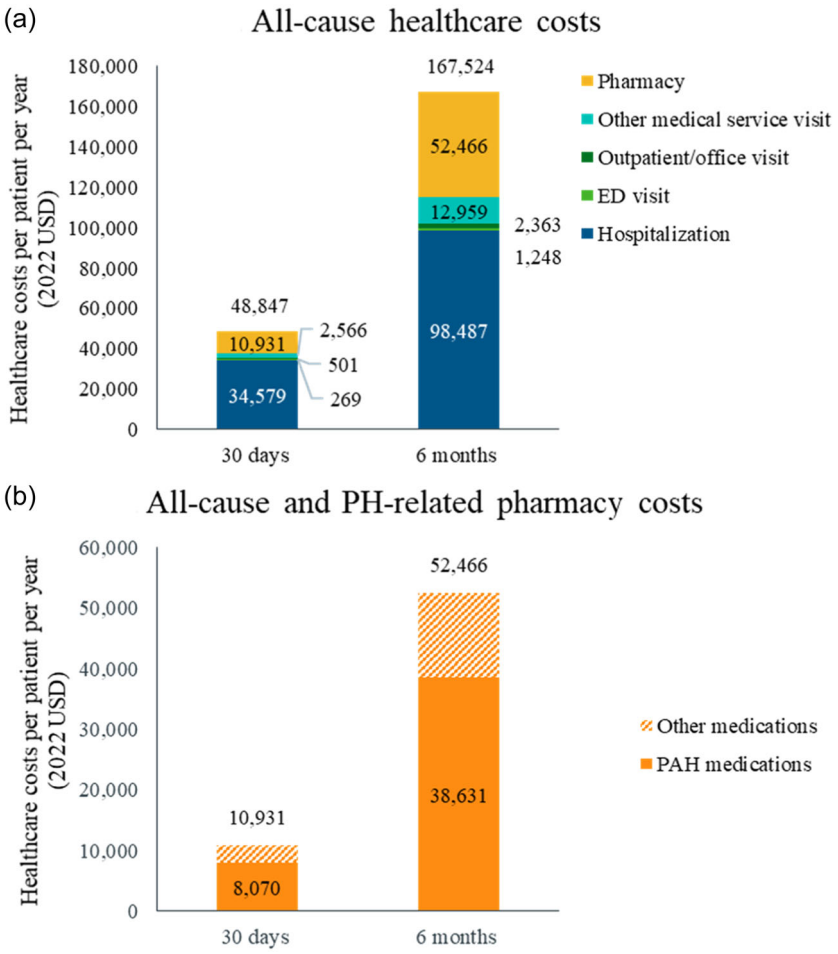

FIGURE 7 Total all-cause healthcare costs, overall and by category (a) and PH-related pharmacy costs (b) during 30 days and 6 months before estimated death date in the PAH EOL cohort ($N = 28$). Other medical service included laboratory and pathology test, radiology, surgery, medical procedures/supplies/products during office visits, and other ancillary services. PH-related medical services (hospitalization, ED visit, outpatient/office visit, other medical service visit) were defined by a primary diagnosis with I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 on the claim or a primary diagnosis with Q21.1 or Q20.0 accompanied with a diagnosis of I27.0, I27.2, I27.21, I27.9, I27.89, or I27.83 in any position of the same claim. PAH Medications included phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin receptor agonists, and prostacyclin analogues. ED, emergency department.

healthcare costs of patients with PAH ranged from $3109 to $14,910 (2022 USD).[10,23,24] Pharmacy utilization, especially the use of FDA-approved medications for PAH, was the major cost driver among patients with PAH, contributing to 63.2% of all-cause healthcare costs and 90.1% of PH-related costs. Although an earlier database study analyzing 2006–2008 data reported PAH-related hospitalization to be the major cost driver for patients with PAH,[25] our findings are in line with a more recent claims-based study using 2013–2016 data.[26] The shift in cost drivers in the past two decades may be explained by newly approved targeted medications (e.g., riociguat, selexipag) for PAH and the prevalent use of combination therapies.[27] The cost driver shift may also be reflective of our cohort selection, which required patients to either have at least two PAH medications from different classes on or after PAH diagnosis (57% of the PAH cohort) if no RHC procedure was observed during the study period. Furthermore, there has been evidence showing a cost benefit of PAH medications and combination therapy with increased pharmacy costs partially offset by reduced hospitalizations.[26,28,29]

To understand the EOL-related economic burden among a patient population with a high 5-year mortality,[30,31] this study adapted a claims-based mortality algorithm to PAH patients to quantify EOL HCRU and healthcare costs. Due to the lack of mortality data in administrative claims, a claims-based algorithm was employed to identify PAH patients who appeared to have evidence of death during the follow-up period. The claims-based algorithm was built on an algorithm that has been validated among patients with cardiovascular diseases[11] and was adapted to patients with PAH by adding additional diagnoses, procedures, and medications that are suggestive of death in patients with PAH based on clinical expert opinion (e.g., cardiogenic shock, IV morphine and derivatives usage, atropine injections). In addition, clinical expert opinion was incorporated to augment the algorithm in scenarios where evidence of death was unclear. Leveraging this algorithm, we estimated a mortality rate of 5.6% over a median of 21 months, which was lower than expected given the estimated mortality rate for PAH patients of 40% over 5 years.[5] It is thus likely the claims-based algorithm

underestimated the mortality rate by not capturing all real-world fatal scenarios of patients with PAH.

As expected, PAH patients with evidence of death had substantial HCRU and costs within 30 days and 6 months before the estimated death date. Our results showed that the mean total healthcare costs in the final month of life were almost twice the average monthly costs within 6 months before estimated death and more than three times the average monthly cost of patients with PAH who survived for more than 6 months. The high EOL costs were primarily driven by hospitalizations, which can be attributed to the long length of stay and multiple admissions. Pharmacy costs, especially the cost of PAH medications, was the second leading driver of EOL costs. The high comorbidity burden (e.g., 26.0% cardiovascular disease, and 30.2% heart failure) among PAH patients could have also contributed toward the high EOL costs.

This study has limitations inherent to a retrospective study using claims databases, including potential misclassification of diagnoses, data entry errors, and lack of clinical data (e.g., symptoms, disease severity). For example, patients with PAH were identified based on ICD-10-CM diagnosis codes of PH and evidence of PAH medications. However, it is possible patients with other types of PH who had off-label use of PAH medications were included. This study utilized administrative claims data; costs of clinically relevant events that do not require healthcare services and services that are not documented in claims data (e.g., over the counter medications; medications not covered by insurance or those obtained through cash payments) were not included in the study estimation. Therefore, the direct healthcare costs could be underestimated. Also, the study period included the COVID-19 pandemic period. HCRU and associated costs during this period may be different from those before the pandemic. COVID-19 related medical claims were observed in 0.3% of patients in the PAH and non-PH cohorts and 9.8% of patients in the PAH EOL cohort.

Due to the lack of mortality information in administrative claims data, a claims-based algorithm was used to identify patients with fatal events in patients with PAH. This published algorithm has been used in predicting mortality in other cardiovascular diseases,[11] and modifications were made to adapt the algorithm to patients with PAH; however, the modified algorithm was not validated in this study and is based on a list of common diagnoses and procedures that are suggestive of death and therefore may lead to misclassification of mortality in the study. Expert opinion was leveraged to increase the validity of the algorithm as some clinical events may not necessarily result in mortality among PAH patients. To that end, while the algorithm helped screen for patients who likely died, it may not be sufficient in identifying mortality in the absence of such expert opinion. Further development and validation are needed to allow for a broader application of the algorithm to facilitate identification of deaths among PAH patients using claims data.

The findings from this study suggest that PAH imposes substantial economic burden on the US healthcare system. The excess costs accrued by patients with PAH were primarily driven by the use of PAH medications and hospitalizations. Largely attributable to hospitalizations, the healthcare costs were further elevated in the 6 months and 30 days before death, highlighting the immense burden of EOL care among PAH patients. Whether better management of the underlying disease, through improvements in time to diagnosis, adherence to treatment guidelines, or use of next-generation medications in patients might help abrogate these costs warrants further consideration and exploration.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Aimee M. Near, Dajun Tian, Nazneen Fatima Shaikh, Ngan Pham, Xiaohui Zhao, Tracey Weiss, Dena R. Ramey, Dominik Lautsch, and Steven D. Nathan. *Data analysis*: Aimee M. Near, Dajun Tian, Nazneen Fatima Shaikh, Ngan Pham, and Xiaohui Zhao. *Interpretation of results*: Aimee M. Near, Dajun Tian, Nazneen Fatima Shaikh, Ngan Pham, Xiaohui Zhao, Tracey Weiss, Dena R. Ramey, Dominik Lautsch, and Steven D. Nathan. All authors contributed to manuscript preparation and approved the final version of this manuscript.

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CONFLICT OF INTEREST STATEMENT

T. W., D. R., and D. L. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. A. N., D. T., N. F. S., and X. Z. are employees of IQVIA, Inc., which received consulting fees for conducting this study. N. P. was an employee of IQVIA at the time of study conduct. S. N. has received consulting fees and serves on the advisory board for Merck & Co., Inc., United Therapeutics Corporation, Bellerophon Therapeutics, Third Pole Therapeutics and F. Hoffmann-La Roche AG.

ETHICS STATEMENT

This was a retrospective database study using deidentified data compliant with the USA Health Insurance

Portability and Accountability Act of 1996. Therefore, ethics approval from the Institutional Review Board (IRB) was not required for this study.

ORCID

Nazneen Fatima Shaikh http://orcid.org/0000-0002-4184-1610

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APPENDIX

TABLE A1 Clinical conditions and procedures for the claims-based mortality algorithm.

Mortality algorithm events that are likely fatal		
Diagnoses suggestive of grave medical condition	**Specified complications during procedures**	**Procedure codes associated with end-of-life care**
• Cardiac arrest • Respiratory arrest • Sudden death • Myocardial infarct (must be inpatient claim) • Brain death • Stroke (must be inpatient claim) • Coma • Intracranial hemorrhage (must be inpatient claim) • Septic shock • Cardiogenic shock • Do not resuscitate (DNR)	• Cerebrovascular complications • Cardiac complications	• Cardiopulmonary resuscitate (CPR) • Defibrillation • Cerebral death • Hospice care • Epinephrine/Atropine • Revascularization (must be inpatient claim) • Mechanical ventilation • IV morphine and derivatives
Mortality algorithm events that are potentially nonfatal/routine		
Diagnoses suggestive of grave medical condition	**Specified complications during procedures**	**Procedure codes associated with end-of-life care**
• Palliative care • Unstable angina (must be inpatient claim) • Heart failure (must be inpatient claim) • Arrythmia (must be inpatient claim)	• None	• Critical care • Ambulance—Critical • Critical care transport • Emergency transport • Advance care plan • Home mechanical respiratory care • Lidocaine injection

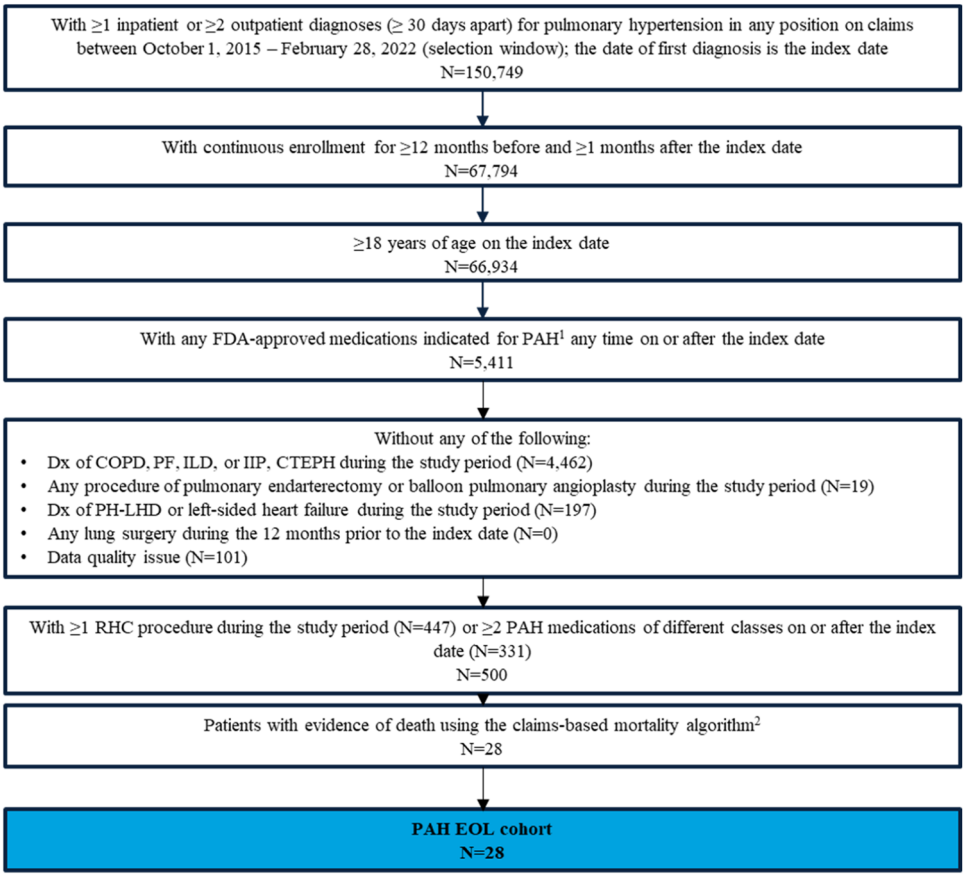

FIGURE A1 Patient selection of the PAH EOL cohort. [1]Medications approved for PAH included phosphodiesterase-5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists, prostacyclin receptor agonists, and prostacyclin analogues. [2]Clinical codes indicating potentially fatal events were identified from published literature and expert opinions. Patients with any fatal event codes (Table A1) were identified, and the time from the last fatal event code observed (a) to the last medical claim in the data (b) and the last medical claim to the end of insurance eligibility (c), or end of study (d) were determined. A flag indicating possible death was assigned to the patients with ≥30 days of follow-up after A (i.e., a to c) and the time between (a and b) ≤30 days. Patients who had <30 days of follow-up after (a) and the end of insurance eligibility before the study end (i.e., c and d ≥1 day), a flag indicating possible death was assigned upon review of the potentially fatal events and final healthcare claims by a clinical expert. The date of the last claim was considered as the estimated death date among patients with a flag indicating possible death. CTEPH, chronic thromboembolic pulmonary hypertension; Dx, diagnosis; EOL, end-of-life; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; PAH, pulmonary artery hypertension; PF, pulmonary fibrosis; PH-LHD, PH due to left heart disease; RHC, right heart catheterization.