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RESEARCH ARTICLE

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Economic burden of illness among patients with pulmonary arterial hypertension (PAH) associated with connective tissue disorders (CTD)

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Abstract

Pulmonary arterial hypertension (PAH) is commonly associated with connective tissue disorders (CTDs). This study provides a contemporary assessment of the economic burden of CTD + PAH and PAH in the United States. Eligible adult patients identified from Optum's deidentified Clinformatics® Data Mart Database (10/01/2015-09/30/2021) were classified into mutually exclusive cohorts based on recorded diagnoses: (1) CTD + PAH, (2) PAH, (3) CTD, (4) control without CTD/PAH. The index date was a randomly selected diagnosis date for PAH (CTD + PAH, PAH cohorts) or CTD (CTD cohort), or a random date (control cohort). Entropy balancing was used to balance characteristics across cohorts. Healthcare costs and healthcare resource utilization (HRU) per patient per month (PPPM) were assessed for ≤12 months postindex and compared among balanced cohorts. A total of 552,900 patients were included (CTD + PAH: $n = 1876$; PAH: $n = 8177$; CTD: $n = 209{,}156$; control: $n = 333{,}691$). Average total all-cause costs were higher for CTD + PAH than PAH cohort ($16,854 vs. $15,686 PPPM; $p = 0.02$); both cohorts incurred higher costs than CTD and control cohorts ($4476 and $2170 PPPM; all $p < 0.001$). Average HRU PPPM was similar between CTD + PAH and PAH cohorts (inpatient stay: 0.15 vs. 0.15, outpatient visits: 4.23 vs. 4.11; all $p > 0.05$), while CTD and control cohorts incurred less HRU (inpatient stay: 0.07 and 0.03, outpatient visits: 2.67 and 1.69; all $p < 0.001$). CTD + PAH and PAH are associated with a substantial economic burden. The incremental burden attributable to PAH versus the general population and patients with CTD without PAH highlights significant unmet needs among PAH patients.

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KEYWORDS
healthcare costs, healthcare resource utilization, pulmonary hypertension, retrospective cohort study, systemic sclerosis

BACKGROUND

Pulmonary arterial hypertension (PAH) is a rare, incurable, and fatal subtype of pulmonary hypertension (PH), which can be idiopathic, heritable, drug or toxin-induced, or may arise as a complication of other conditions, most notably connective tissue disorders (CTDs).[1–3] CTD-related PAH (CTD + PAH) is the second most prevalent type after idiopathic PAH (iPAH), representing 11%–28% of PAH cases.[4] Among the CTDs, systemic sclerosis (SSc) is the most likely to lead to PAH and accounts for almost 75% of CTD + PAH cases in the United States (US).[1] The prognosis among patients with CTD + PAH is poor,[5] with significantly worse survival rates relative to iPAH.[5–9] Moreover, SSc-PAH has a poorer survival rate when compared to PAH associated with other CTDs.[5] In one study, the median overall survival following PAH diagnosis was 7.8 years in iPAH versus only 3.0 years in SSc-PAH.[9]

Evidence suggests that patients with CTD + PAH have a unique clinical profile when compared to PAH overall, which has important implications for disease management. One study using the REVEAL registry observed the presence of higher-risk disease markers among patients with CTD + PAH including elevated mean B-type natriuretic peptide levels, higher renal insufficiency rates, shorter mean 6-min walk distance, and more hospitalizations when compared to patients with iPAH; additionally, patients with SSc-PAH were more likely to be categorized as World Health Organization Functional class (FC) IV.[5] Due to the potentially greater disease severity associated with CTD + PAH, a more complex therapeutic approach relying on combination therapy may be warranted.[1] According to the latest 2022 guidelines of the European Society of Cardiology (ESC) and European Respiratory Society (ERS), the treatment of patients with CTD + PAH should follow the same treatment algorithm as iPAH, which includes combination therapies targeting the nitric oxide, endothelin, and prostacyclin pathways.[10] In the absence of cardiopulmonary comorbidities, the 2022 ESC/ERS guidelines recommend the use of initial oral double combination therapy with a phosphodiesterase type 5 inhibitor (PDE5i) or endothelin receptor antagonist (ERA) for treatment-naïve patients who are low-intermediate risk and initial triple therapy including an injectable prostacyclin analogue for those who are high-risk; among patients with cardiopulmonary comorbidities, the guidelines recommend initial monotherapy with a PDE5i or ERA, while the addition of another PAH medication among intermediate-to-high risk patients may be considered on an individual basis.[10] The early use of PAH-specific combination therapies may be especially critical for patients with CTD + PAH, as they are more likely to be at high risk of progressive disease and early mortality.[1] In addition, the co-management of CTDs including the use of immunosuppressant drugs may further complicate the treatment of patients with CTD + PAH.[1]

To date, several studies have reported that PAH is associated with a substantial burden in terms of healthcare resource utilization (HRU) and costs in the United States (US),[11–21] which may be exacerbated among patients with greater PAH severity.[22] However, there is currently limited information specific to the burden of illness among patients with CTD + PAH in the real-world setting. Further, given the evolving landscape of treatment options and recommendations, contemporary data on the burden of CTD + PAH and PAH are needed to better understand the burden of PAH overall from a clinical and healthcare payer perspective. To address this knowledge gap, the present study aimed to describe and compare the clinical characteristics, healthcare costs, and HRU among patients with CTD + PAH compared to other patients with PAH or CTD, and patients without CTD nor PAH.

METHODS

Data source

Data available through the Optum's deidentified Clinformatics® Data Mart Database (CDM) from 10/01/2015 to 09/30/2021 were used to conduct this study. The CDM is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans in the United States. These administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and deidentified before inclusion. The data comprises both commercial and Medicare Advantage health plans and is geographically diverse, spanning all 50 states (as well as District of Columbia and Puerto Rico). In addition to

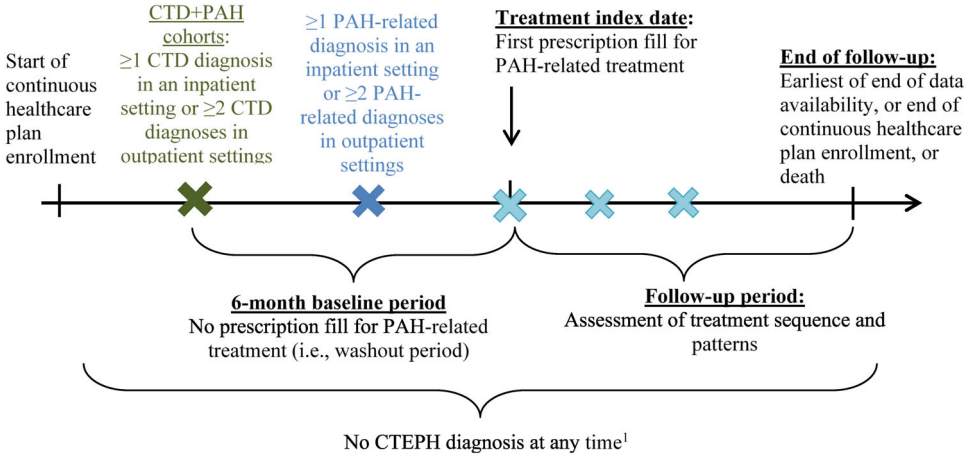

FIGURE 1 Study design. CTEPH diagnosis code was used starting 2017, so patients identified between 2015 and 2017 would not be excluded due to CTEPH. CTD, connective tissue disorder; HRU, healthcare resource utilization; PAH, pulmonary arterial hypertension.

medical claims and pharmacy claims, the data includes information on member eligibility and demographic characteristics and death. The CDM is statistically deidentified under the Expert Determination method consistent with Health Insurance Portability and Accountability Act.

Study design

A retrospective cohort study design was used to address the study objectives (Figure 1). Eligible patients were classified into mutually exclusive cohorts: (1) CTD + PAH cohort, (2) PAH cohort (without CTD), (3) CTD cohort (without PAH), and (4) control cohort (i.e., without CTD nor PAH). For patients in the CTD + PAH and PAH cohorts, the index date was defined as a randomly selected PAH-related diagnosis date, while the index date was a randomly selected CTD diagnosis date for the CTD cohort, and a random date for the control cohort. The random selection of the index date helped to capture a snapshot of patients with various disease durations and severities, with the aim of approximating the clinical reality within a real-world setting. The follow-up period spanned from the index date until the earliest among (1) 12 months postindex, (2) death, (3) end of continuous enrollment in healthcare plan, or (4) end of data availability, whichever came first. No minimal duration of follow-up was required to limit survival bias.

Study population

Adult patients were selected for the CTD + PAH cohort based on the following criteria: (1) ≥1 documented PAH-related diagnosis (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM]: I27.0x, I27.20, I27.21, I27.89) in an inpatient setting or ≥2 PAH-related diagnoses on distinct dates in an outpatient setting; (2) had ≥1 prescription fill for a PAH-related treatment at any time; (3) had ≥1 documented diagnosis for CTD (ICD-10-CM: M32.xx, M33.xx, M34.xx, M35.0x, M35.1x, M35.5x, M35.9x, M36.8x) in an inpatient setting or ≥2 diagnoses for CTD on distinct dates in an outpatient setting; (4) had no documented diagnosis for chronic thromboembolic pulmonary hypertension (CTEPH; ICD-10-CM: I27.24) at any time (Figure 2). Adult patients in the PAH cohort were subject to the same criteria, except that they were required to have no documented diagnosis for CTD at any time. Adult patients were selected for the CTD cohort if they met the CTD diagnosis criterion but had no diagnosis for PH, no procedure claim for right heart catheterization, and no prescription fill for a PAH-related treatment at any time. Finally, adult patients were selected for the control cohort if they had no diagnosis for CTD, no diagnosis for PH, no procedure claim for right heart catheterization, and no prescription fill for a PAH-related treatment at any time.

Measures, outcomes, and statistical analyses

Entropy balancing was used to reweight patients in the comparator groups (i.e., PAH cohort, CTD cohort, and control cohort) such that they had similar characteristic as the CTD + PAH cohort, based on patient demographics (i.e., age, gender, geographic region, insurance type) and calendar year at the index date.[23] The balance of patient characteristics between weighted cohorts was assessed using standardized differences (<0.1 was considered well balanced).[24] Patient characteristics were

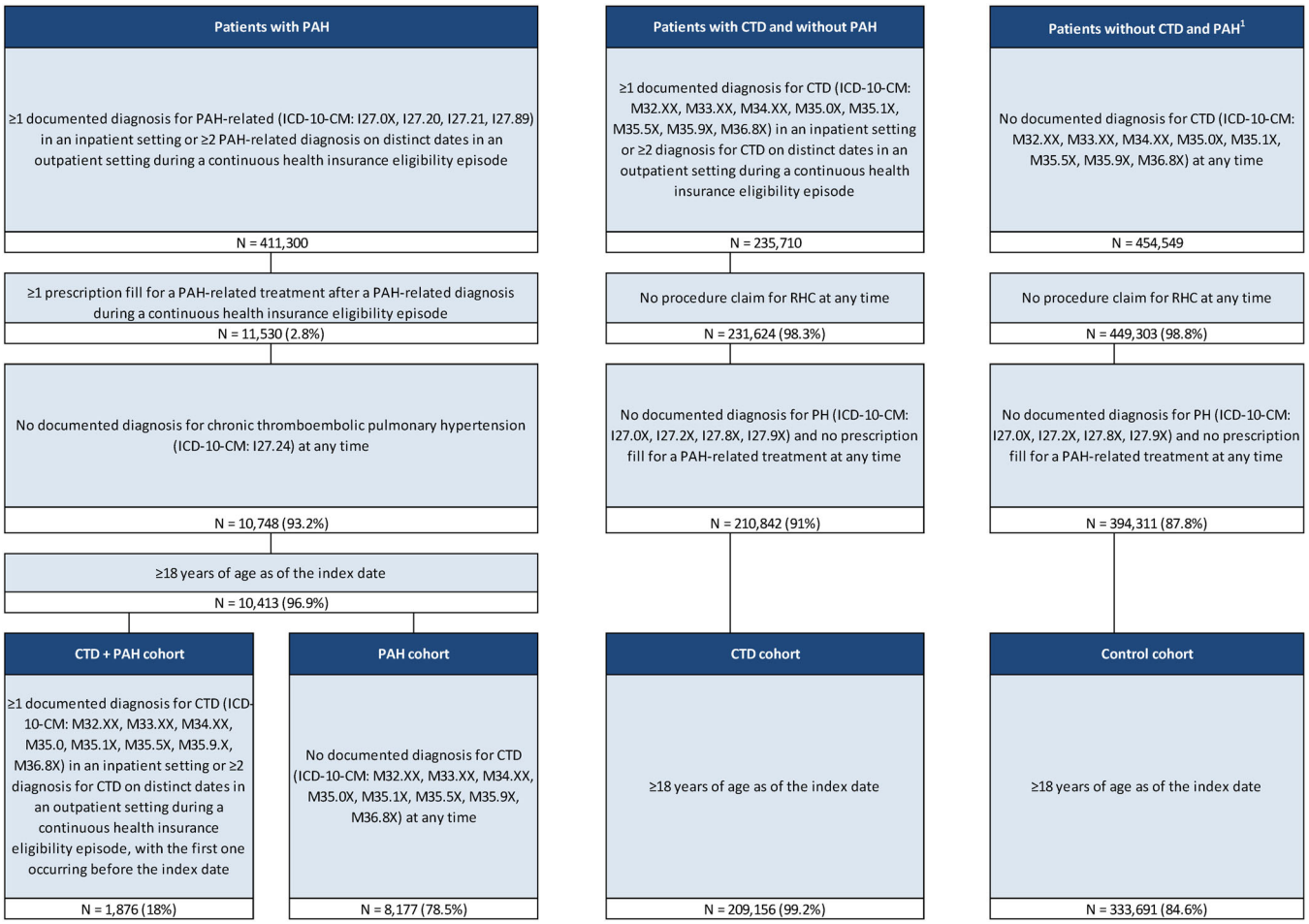

FIGURE 2 Sample selection. [1]A random sample of patients was taken from the entire database. CTD, connective tissue disorder; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization.

measured at the index date. Clinical characteristics (e.g., Quan-Charlson Comorbidity Index [CCI][25]; see list of codes in Table S1), healthcare costs, and HRU were measured during the follow-up period. Total all-cause healthcare costs were calculated as the sum of medical costs (i.e., inpatient, emergency department, outpatient, and other costs [e.g., home health services]) and pharmacy costs. To account for varying length of the follow-up period, healthcare costs and HRU were reported in per patient per month (PPPM) units. Healthcare costs were inflated to 2021 US dollars based on the Medical Care component of the Consumer Price Index.[26] Patient characteristics and outcomes were descriptively reported among weighted cohorts using means, standard deviations (*SD*), and medians for continuous variables, and frequencies and proportions for categorical variables. Healthcare costs PPPM were compared across weighted cohorts using mean cost differences, while HRU PPPM was compared across weighted cohorts using incidence rate ratios (IRRs) derived from Poisson regression models. Nonparametric bootstrap procedures with 499 replications were used to evaluate statistical significance and 95% confidence interval of mean cost differences and IRRs.

RESULTS

After applying the eligibility criteria, the study sample comprised a total of 1876 patients in the CTD + PAH cohort, 8177 patients in the PAH cohort, 209,156 patients in the CTD cohort, and 333,691 patients in the control cohort (Figure 2).

Patient characteristics

Patient characteristics before and after weighting are presented in Table 1. Before weighting, patients in the CTD + PAH cohort tended to be younger (63.5 years old)

TABLE 1 Patient characteristics before and after weighting.

Patient characteristics at the index date	CTD + PAH cohort *N* = 1876	PAH cohort *N* = 8177		CTD cohort *N* = 209,156		Control cohort *N* = 333,691	
		Before weighting[a]	SDF, %[b]	Before weighting[a]	SDF, %[b]	Before weighting[a]	SDF, %[b]
Age, years, mean ± *SD* [median]	63.5 ± 12.9 [65.0]	67.4 ± 13.6 [69.0]	29.1[c]	59.2 ± 15.7 [61.0]	29.6[c]	51.9 ± 19.0 [53.0]	71.1[c]
Female, *n* (%)	1626 (86.7%)	5198 (63.6%)	55.5[c]	180,793 (86.4%)	0.7	184,769 (55.4%)	73.5[c]
Region, *n* (%)							
South	898 (47.9%)	3949 (48.3%)	0.9	102,936 (49.2%)	2.7	154,941 (46.4%)	2.9
North central	398 (21.2%)	1838 (22.5%)	3.1	43,129 (20.6%)	1.5	63,975 (19.2%)	5.1
West	389 (20.7%)	1559 (19.1%)	4.2	39,823 (19.0%)	4.3	75,051 (22.5%)	4.3
Northeast	188 (10.0%)	822 (10.1%)	0.1	22,984 (11.0%)	3.2	38,778 (11.6%)	5.2
Unknown	NR[d]	NR[d]		284 (0.1%)	0.6	946 (0.3%)	2.6
Insurance type, *n* (%)							
Medicare advantage	1357 (72.3%)	6396 (78.2%)	13.7[c]	113,309 (54.2%)	38.4[c]	122,698 (36.8%)	76.5[c]
Commercial insurance	519 (27.7%)	1781 (21.8%)	13.7[c]	95,847 (45.8%)	38.4[c]	210,993 (63.2%)	76.5[c]
Point of service	355 (18.9%)	1267 (15.5%)	6.0	70,158 (33.5%)	10.6[c]	153,984 (46.1%)	10.1[c]
Health maintenance organization	75 (4.0%)	212 (2.6%)	7.5	12,450 (6.0%)	4.3	28,909 (8.7%)	2.2
Exclusive provider organization	54 (2.9%)	176 (2.2%)	1.7	10,961 (5.2%)	3.3	24,189 (7.2%)	3.4
Indemnity	20 (1.1%)	93 (1.1%)	6.6	740 (0.4%)	20.6[c]	130 (0.0%)	27.6[c]
Preferred provider organization	14 (0.7%)	26 (0.3%)	8.7	1079 (0.5%)	11.5[c]	2343 (0.7%)	11.6[c]
Other	NR[d]	NR[d]		459 (0.2%)	5.0	1438 (0.4%)	7.4
Calendar year, *n* (%)							
2015	62 (3.3%)	336 (4.1%)	4.3	6576 (3.1%)	0.9	1385 (0.4%)	21.5[c]
2016	170 (9.1%)	903 (11.0%)	6.6	28,169 (13.5%)	14.0[c]	30,493 (9.1%)	0.3
2017	195 (10.4%)	1047 (12.8%)	7.5	30,662 (14.7%)	12.9[c]	46,857 (14.0%)	11.2[c]
2018	372 (19.8%)	1516 (18.5%)	3.3	30,914 (14.8%)	13.4[c]	51,120 (15.3%)	11.9[c]
2019	362 (19.3%)	1531 (18.7%)	1.5	34,420 (16.5%)	7.4	58,000 (17.4%)	5.0
2020	351 (18.7%)	1524 (18.6%)	0.2	37,461 (17.9%)	2.1	67,605 (20.3%)	3.9
2021	364 (19.4%)	1320 (16.1%)	8.5	40,954 (19.6%)	0.5	78,231 (23.4%)	9.9
		After weighting[a]	SDF, %[b]	After weighting[a]	SDF, %[b]	After weighting[a]	SDF, %[b]
Age, years, mean ± *SD* [median]	63.5 ± 12.9 [65.0]	63.5 ± 12.9 [65.0]	0.0	63.5 ± 12.9 [65.0]	0.1	63.5 ± 13.0 [65.0]	0.1
Female, *n* (%)	1626 (86.7%)	7080 (86.6%)	0.3	181,266 (86.7%)	0.0	289,192 (86.7%)	0.0

(Continues)

TABLE 1 (Continued)

		After weighting[a]	SDF, %[b]	After weighting[a]	SDF, %[b]	After weighting[a]	SDF, %[b]
Region, *n* (%)							
South	898 (47.9%)	3913 (47.9%)	0.0	100,109 (47.9%)	0.0	159,712 (47.9%)	0.0
North central	398 (21.2%)	1735 (21.2%)	0.0	44,376 (21.2%)	0.0	70,801 (21.2%)	0.0
West	389 (20.7%)	1696 (20.7%)	0.0	43,373 (20.7%)	0.0	69,200 (20.7%)	0.0
Northeast	188 (10.0%)	820 (10.0%)	0.0	20,970 (10.0%)	0.0	33,453 (10.0%)	0.0
Unknown	NR[d]	13 (0.2%)	0.1	329 (0.2%)	0.1	525 (0.2%)	0.1
Insurance type, *n* (%)							
Medicare advantage	1357 (72.3%)	5915 (72.3%)	0.0	151,271 (72.3%)	0.0	241,278 (72.3%)	0.1
Commercial insurance	519 (27.7%)	2262 (27.7%)	0.0	57,885 (27.7%)	0.0	92,413 (27.7%)	0.1
Point of service	355 (18.9%)	1547 (18.9%)	0.0	39,583 (18.9%)	0.0	63,197 (18.9%)	0.0
Health maintenance organization	75 (4.0%)	327 (4.0%)	0.0	8363 (4.0%)	0.0	13,350 (4.0%)	0.0
Exclusive provider organization	54 (2.9%)	235 (2.9%)	0.0	6022 (2.9%)	0.0	9614 (2.9%)	0.0
Indemnity	20 (1.1%)	87 (1.1%)	0.0	2230 (1.1%)	0.0	3557 (1.1%)	0.0
Preferred provider organization	14 (0.7%)	61 (0.8%)	0.1	1575 (0.8%)	0.2	2515 (0.8%)	0.2
Other	NR[d]	NR[d]	0.0	112 (0.1%)	0.0	179 (0.1%)	0.0
Calendar year, *n* (%)							
2015	62 (3.3%)	270 (3.3%)	0.0	6913 (3.3%)	0.0	11,033 (3.3%)	0.0
2016	170 (9.1%)	741 (9.1%)	0.0	18,956 (9.1%)	0.0	30,245 (9.1%)	0.0
2017	195 (10.4%)	850 (10.4%)	0.0	21,751 (10.4%)	0.0	34,703 (10.4%)	0.0
2018	372 (19.8%)	1622 (19.8%)	0.0	41,477 (19.8%)	0.0	66,176 (19.8%)	0.0
2019	362 (19.3%)	1578 (19.3%)	0.0	40,363 (19.3%)	0.0	64,394 (19.3%)	0.0
2020	351 (18.7%)	1530 (18.7%)	0.0	39,136 (18.7%)	0.0	62,435 (18.7%)	0.0
2021	364 (19.4%)	1586 (19.4%)	0.0	40,560 (19.4%)	0.0	64,703 (19.4%)	0.0

Abbreviations: CTD, connective tissue disorder; PAH, pulmonary arterial hypertension; *SD*, standard deviation; SDF, standardized difference.

[a]Entropy balancing was used to balanced cohorts based on age, gender, region, insurance type, and calendar year at the index date (Reference: Hainmueller J. Entropy Balancing for Causal Effects: A Multivariate Reweighting Method to Produce Balanced Samples in Observational Studies. Political Analysis. 2012;20(1):25–46).

[b]Standardized differences were reported as percentage using the CTD + PAH cohort as the reference.

[c]Denotes standardized difference ≥10%.

[d]Outcomes with count <10 are not reported per CDM's policy.

than those in the PAH cohort (67.4 years old), and older than those in the CTD (59.2 years old) or control cohort (51.9 years old). The proportion of female patients was higher in the CTD + PAH (86.7%) and CTD cohort (86.4%) compared to the PAH (63.6%) and control cohort (55.4%). After weighting, cohorts were similar in terms of their characteristics at the index date (standardized difference <10%).

Clinical characteristics

Clinical characteristics among the weighted cohorts are shown in Table 2. The follow-up period ranged from 0 to 12 months, with a mean (median) of 8–9 (10–12) months across cohorts. During this period, patients in the CTD + PAH cohort tended to use more classes of PAH-related treatments than those in the PAH cohort (1.6 vs. 1.4 classes per patient, respectively), and a larger proportion received ≥2 agents (44.5% vs. 35.3%, respectively). Patients in the CTD + PAH and PAH cohorts tended to have a higher comorbidity burden, as evidenced by a mean CCI of 4.3 in the CTD + PAH and PAH cohorts compared to 2.7 and 1.5 in the CTD and control cohorts, respectively. Moreover, the proportion of patients who died during the follow-up period tended to be larger in the CTD + PAH cohort (14.7%) and PAH cohort (12.7%) than in the CTD cohort (3.7%) and control cohort (3.2%).

Healthcare costs

As shown in Figure 3 and Table S2, total all-cause healthcare costs among the weighted cohorts were significantly higher in the CTD + PAH cohort ($16,854 PPPM; PAH-related costs: $11,682 PPPM) compared to the PAH cohort ($15,686 PPPM, $p = 0.02$; PAH-related costs: $10,287 PPPM, $p < 0.001$) and compared to the CTD ($4476 PPPM, $p < 0.001$) and control cohorts ($2170 PPPM, $p < 0.001$). The total all-cause cost difference between the CTD + PAH and PAH cohorts ($1168 PPPM, $p = 0.02$) was driven by a cost difference in pharmacy costs ($1337 PPPM, $p < 0.001$; Figure 3), notably PAH-related pharmacy costs ($1279 PPPM, $p < 0.001$). Overall, nearly three-quarters of the total all-cause healthcare costs among the CTD + PAH and PAH cohorts were due to pharmacy costs (46.9% and 41.9%, respectively) and inpatient costs (28.7% and 31.9%, respectively). The total all-cause cost differences between the CTD + PAH cohort versus the CTD cohort ($12,378 PPPM, $p < 0.001$) and versus the control cohort ($14,684 PPPM, $p < 0.001$; Figure 3) was driven by cost differences in both medical

TABLE 2 Clinical characteristics among weighted cohorts.[a]

Characteristics during the follow-up period (up to 12 months)	CTD + PAH cohort *N* = 1876	PAH cohort *N* = 8177	SDF, %[b]	CTD cohort *N* = 209,156	SDF, %[b]	Control cohort *N* = 333,691	SDF, %[b]
Follow-up period, months, mean ± *SD* [median]	8.5 ± 4.0 [11.0]	8.5 ± 4.1 [11.0]	1.3	8.8 ± 4.1 [12.0]	7.9	8.1 ± 4.4 [10.4]	10.4[c]
CCI, mean ± *SD* [median]	4.3 ± 2.9 [4.0]	4.3 ± 3.2 [4.0]	1.1	2.7 ± 2.6 [2.0]	58.1[c]	1.5 ± 2.3 [1.0]	102.8[c]
Most frequent comorbidities, *n* (%)							
Systemic hypertension	1268 (67.6%)	5789 (70.8%)	6.9	120,425 (57.6%)	20.8[c]	159,324 (47.7%)	41.0[c]
Anemia	985 (52.5%)	3555 (43.5%)	18.1[c]	53,666 (25.7%)	57.2[c]	46,474 (13.9%)	89.8[c]
Renal disease	734 (39.1%)	3521 (43.1%)	8.0	41,186 (19.7%)	43.7[c]	39,176 (11.7%)	66.3[c]
Chronic obstructive pulmonary disease	697 (37.2%)	4035 (49.3%)	24.8[c]	34,346 (16.4%)	48.2[c]	39,632 (11.9%)	61.5[c]
Pulmonary fibrosis	586 (31.2%)	840 (10.3%)	53.5[c]	5707 (2.7%)	82.1[c]	2483 (0.7%)	91.5[c]
Diabetes mellitus	442 (23.6%)	3535 (43.2%)	42.6[c]	50,428 (24.1%)	1.3	79,923 (24.0%)	0.9
Most frequent PAH-related symptoms, *n* (%)							
Dyspnea	1311 (69.9%)	5568 (68.1%)	3.9	46,211 (22.1%)	109.3[c]	43,771 (13.1%)	140.9[c]
Fatigue	595 (31.7%)	2563 (31.3%)	0.8	60,921 (29.1%)	5.6	54,156 (16.2%)	36.9[c]

(Continues)

TABLE 2 (Continued)

Characteristics during the follow-up period (up to 12 months)	CTD + PAH cohort *N* = 1876	PAH cohort *N* = 8177	SDF, %[b]	CTD cohort *N* = 209,156	SDF, %[b]	Control cohort *N* = 333,691	SDF, %[b]
Chest pain	508 (27.1%)	2299 (28.1%)	2.3	40,671 (19.4%)	18.1[c]	38,795 (11.6%)	39.9[c]
Most frequent PAH-related procedures, *n* (%)							
Echocardiography chest/thorax	1211 (64.6%)	5126 (62.7%)	3.9	35,488 (17.0%)	110.7[c]	33,936 (10.2%)	135.9[c]
Electrocardiogram	1133 (60.4%)	5274 (64.5%)	8.5	80,720 (38.6%)	44.7[c]	91,878 (27.5%)	70.2[c]
CT chest/thorax	645 (34.4%)	2016 (24.7%)	21.4[c]	20,776 (9.9%)	61.6[c]	17,656 (5.3%)	78.4[c]
Right heart catheterization	365 (19.5%)	1687 (20.6%)	2.9	– –	–	– –	–
CT angiography	231 (12.3%)	954 (11.7%)	2.0	8891 (4.3%)	29.6[c]	7685 (2.3%)	39.2[c]
PAH-related treatment							
Number of different classes of agents, mean ± *SD* [median]	1.6 ± 0.8 [1.0]	1.4 ± 0.7 [1.0]	17.6[c]	–	–	–	–
0, *n* (%)	54 (2.9%)	263 (3.2%)	2.0	–	–	–	–
1, *n* (%)	988 (52.7%)	5026 (61.5%)	17.9[c]	–	–	–	–
2, *n* (%)	563 (30.0%)	2018 (24.7%)	12.0[c]	–	–	–	–
≥3, *n* (%)	271 (14.4%)	870 (10.6%)	11.5[c]	–	–	–	–
CTD-related treatment, *n* (%)							
Oral corticosteroids	870 (46.4%)	2668 (32.6%)	28.4[c]	70,005 (33.5%)	26.6[c]	52,839 (15.8%)	69.9[c]
Antimalarial agent	493 (26.3%)	106 (1.3%)	77.7[c]	57,301 (27.4%)	2.5	2467 (0.7%)	80.6[c]
Calcium channel blocker	458 (24.4%)	1484 (18.1%)	15.4[c]	35,264 (16.9%)	18.8[c]	44,864 (13.4%)	28.3[c]
Immunomodulators	255 (13.6%)	389 (4.8%)	31.0[c]	25,486 (12.2%)	4.2	4898 (1.5%)	47.2[c]
Other pharmacological treatments, *n* (%)							
Antihypertensive	1552 (82.7%)	7031 (86.0%)	9.0	113,632 (54.3%)	64.2[c]	159,133 (47.7%)	79.1[c]
Antidepressant	742 (39.6%)	3154 (38.6%)	2.0	79,228 (37.9%)	3.4	99,834 (29.9%)	20.3[c]
Anticoagulant	442 (23.6%)	2906 (35.5%)	26.5[c]	16,861 (8.1%)	43.5[c]	17,669 (5.3%)	53.8[c]
Recorded death, *n* (%)	276 (14.7%)	1036 (12.7%)	6.0	7712 (3.7%)	38.9[c]	10,672 (3.2%)	41.2[c]

Abbreviations: CI, confidence interval; CCI, Quan-Charlson comorbidity index; CT, computed tomography; CTD, connective tissue disorder; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; PPA, prostacyclin SD, standard deviation; SDF, standardized difference.

[a]Entropy balancing was used to balance cohorts based on age, gender, region, insurance type, and calendar year at the index date (Reference: Hainmueller J. Entropy Balancing for Causal Effects: A Multivariate Reweighting Method to Produce Balanced Samples in Observational Studies. Political Analysis. 2012;20(1):25–46).

[b]Standardized differences were reported using the CTD + PAH cohort as the reference.

[c]Denotes standardized difference ≥10%.

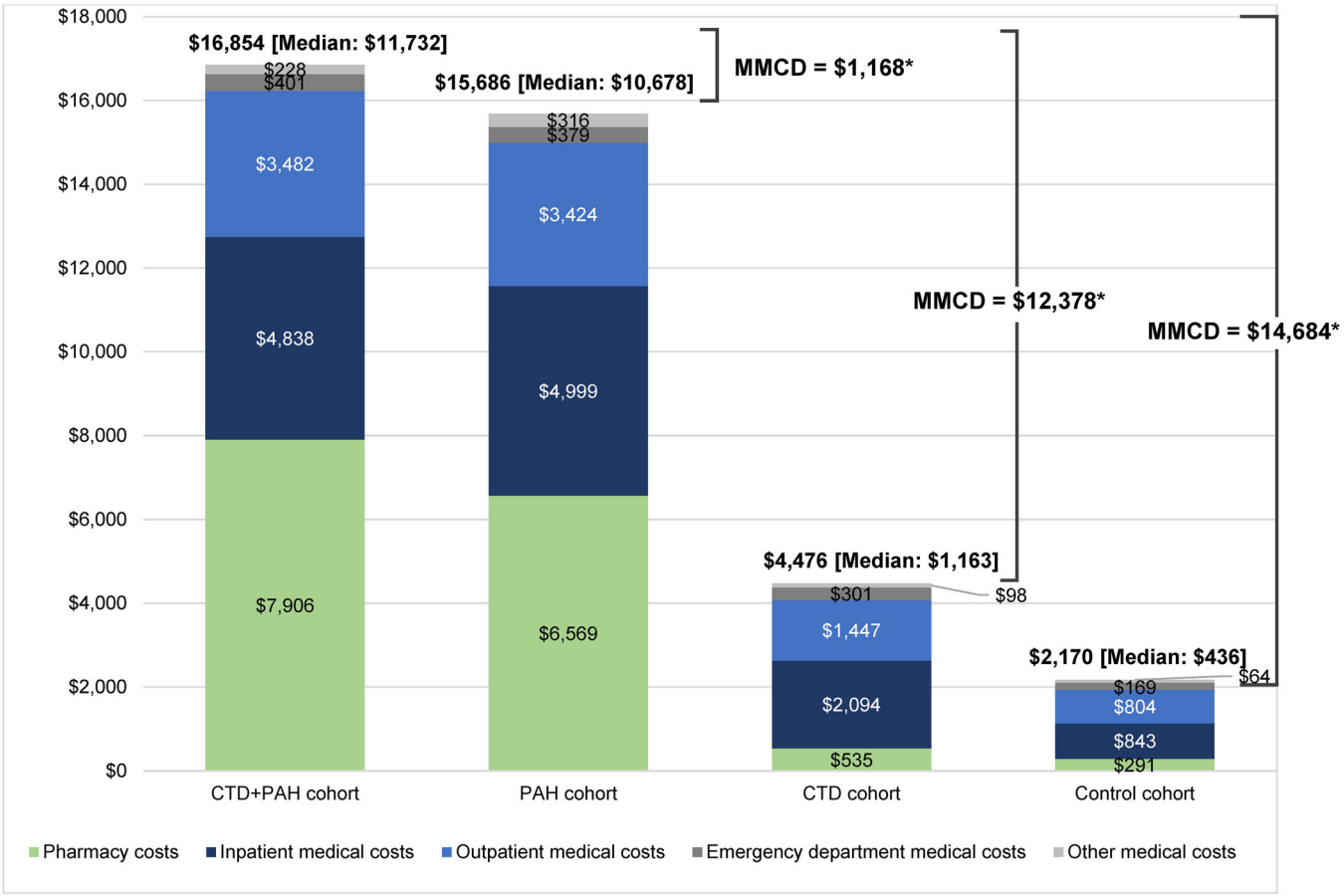

FIGURE 3 Average all-cause healthcare costs PPPM among weighted cohorts. *Denotes $p \leq 0.05$. [1]Differences were calculated as the differences between weighted costs in a given cohort compared to the CTD + PAH cohort. All p values were obtained using nonparametric bootstrap (499 resamples). CI, confidence interval; CTD, connective tissue disorder; MMCD, mean monthly cost difference; PAH, pulmonary arterial hypertension; PPPM, per patient per month.

($5008 PPPM and $7096 PPPM, respectively, $p < 0.001$) and pharmacy costs ($7370 PPPM and $7615 PPPM, respectively, $p < 0.001$).

Healthcare resource utilization

Comparisons of HRU among weighted cohorts are presented in Figure 4 and Table S3. Patients in the CTD + PAH cohort incurred substantial all-cause HRU PPPM, with an average of 0.15 inpatient stays (2.19 inpatient days, including 1.53 days in the intensive care unit [ICU] among patients with ≥1 inpatient stay), 0.13 emergency department visits, 4.23 outpatient visits, and 1.08 other visits. While rates of all-cause HRU visits PPPM were generally similar between the CTD + PAH cohort and the PAH cohort (i.e., inpatient stay and days, ICU stay and days, emergency department visits, and outpatient visits were not significantly different; all $p > 0.05$), the rate of specialist visits PPPM differed between the two cohorts. Specifically, the CTD + PAH cohort had a 1.15 times higher incidence rate of pulmonologist visits (0.73 vs. 0.63 visits PPPM) and a 12.13 times higher rate of rheumatologist visits (0.21 vs. 0.02 visits PPPM) when compared to the PAH cohort, but a lower rate of cardiologist visits (0.66 vs. 0.82 visits PPPM; all $p < 0.05$).

Moreover, patients in the CTD + PAH cohort incurred more HRU PPPM than those in the CTD and control cohorts. Specifically, the incidence rate for inpatient stay was 2.12 times higher for patients in the CTD + PAH cohort than for those in the CTD cohort and 5.19 times higher than for those in the control cohort; among patients with ≥1 inpatient stay, the incidence rate for inpatient days was 2.49 times higher for the CTD + PAH cohort than in the CTD cohort and 5.32 times higher than for those in the control cohort (all $p < 0.001$). Compared to the CTD and control cohorts, the CTD + PAH cohort also had a higher incidence of ICU stays (2.70 and 8.01 times higher, respectively) and a greater number of ICU days among those with ≥1 ICU stay (3.40 and 10.06 times higher, respectively; all $p < 0.001$). The

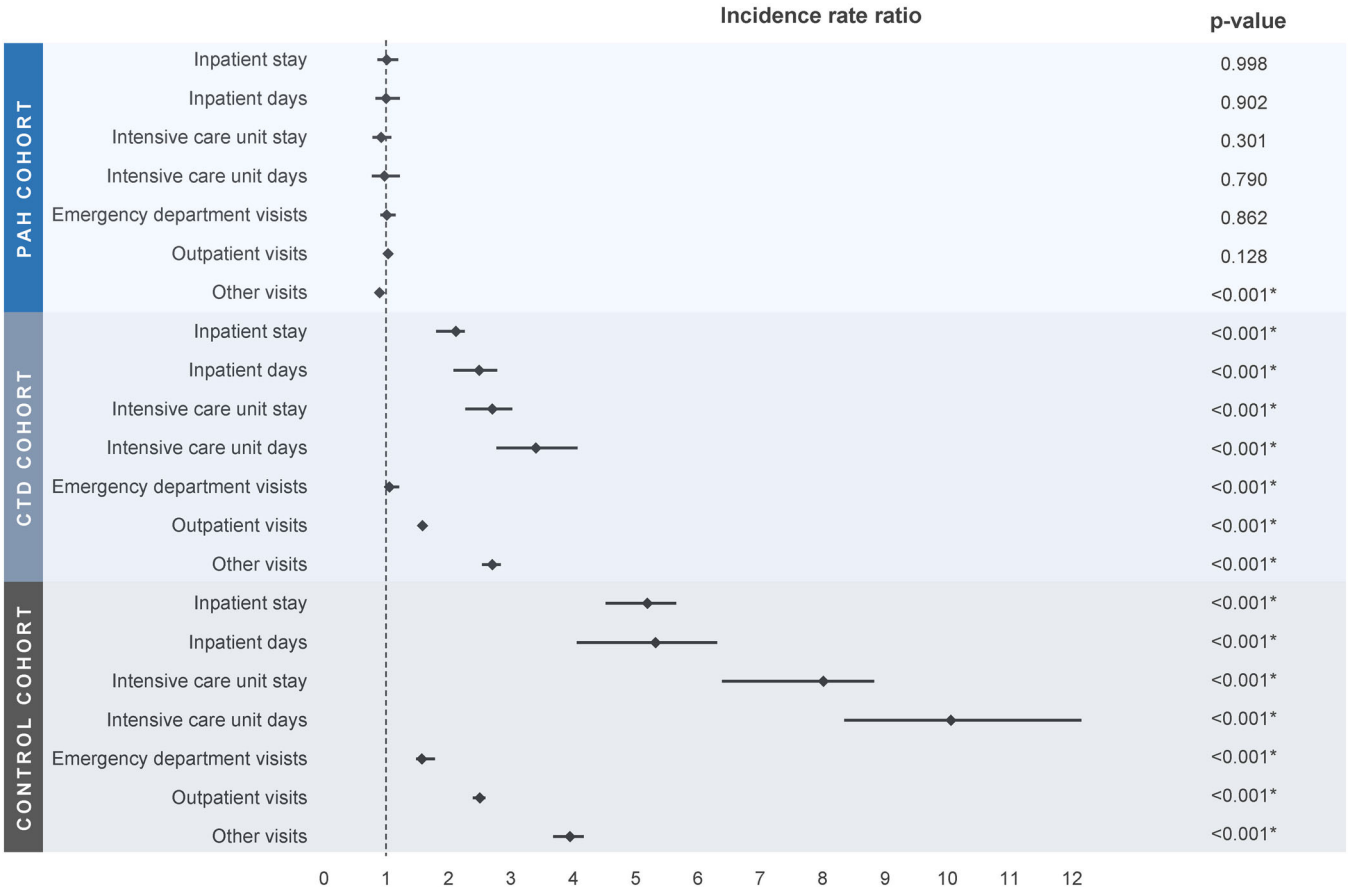

FIGURE 4 Incidence rate ratios for all-cause healthcare resource utilization among the CTD + PAH cohort compared to weighted PAH, CTD, and control cohorts. *Denotes $p \leq 0.05$. [1]Incidence rate ratios compared to the CTD + PAH cohort were obtained using a weighted Poisson regression model. All p values were obtained using nonparametric bootstrap (499 resamples). An incidence rate ratio >1 indicates that the incidence of a given HRU component is greater in the CTD + PAH cohort versus the comparator cohort. CI, confidence interval; CTD, connective tissue disorder; PAH, pulmonary arterial hypertension; PPPM, per patient per month.

incidence rate for outpatient visits was 1.58 times higher for patients in the CTD + PAH cohort than those in the CTD cohort and 2.50 times higher than those in the control cohort (all $p < 0.001$). Finally, the CTD + PAH cohort had higher rates of specialist visits compared to the CTD and control cohorts. In particular, the CTD + PAH cohort had a 3.73- and 7.04-times higher rate of cardiologist visits, and a 7.54- and 19.38-times higher rate of pulmonologist visits relative to the CTD and control cohorts, respectively (all $p < 0.001$). The CTD + PAH cohort had a similar rate of rheumatologist visits relative to the CTD cohort ($p = 0.316$), but a 16.27 times higher rate relative to the control cohort ($p < 0.001$).

DISCUSSION

This study assessed the burden of disease among patients with CTD-related PAH compared to other patients with PAH or CTD, as well as those without either condition in a real-world US setting. The results of this study indicate that patients with CTD + PAH incur substantial healthcare costs and HRU. While the total all-cause healthcare costs among patients with CTD + PAH were higher than among those with PAH, this difference was primarily driven by PAH-related pharmacy costs, whereas HRU rates were generally similar between the two cohorts. Higher pharmacy costs in the CTD + PAH cohort, which were driven by PAH-related pharmacy costs, might reflect the use of initial combination therapy among high-risk treatment-naïve patients or treatment escalation among patients with an inadequate response to therapy per the 2015 ESC/ERS guidelines that were in effect during the period covered by the data.[27] Although these guidelines apply to all PAH patients regardless of etiology, patients with CTD + PAH might be treated more aggressively in routine clinical practice due to the severe and progressive nature of this subtype of PAH.[1] Taken together, our study underscores the substantial burden of disease associated with CTD + PAH and PAH overall, as patients with PAH

(with or without CTD) incurred significantly higher HRU and costs than patients with CTD in the absence of PAH or patients without either PAH or CTD.

To date, evidence regarding the burden of disease associated with CTD-related PAH has been limited. A few prior studies have observed poorer clinical outcomes including shorter overall survival among patients with CTD + PAH compared to those with PAH.[5–8] In our study, patients with CTD + PAH and PAH (without CTD) had similar outcomes in terms of healthcare costs and HRU, which could reflect improvements in the standard of care for PAH in recent years.[28–30] For instance, increased use of combination therapy among patients with CTD + PAH compared to those with PAH (without CTD) may have resulted in improved outcomes among the former.[31,32] That being said, CTD + PAH has also been associated with substantial healthcare costs in a few prior studies. In an earlier US study using data from 2003 to 2014, average annual all-cause total healthcare costs in 2014 USD over the 5-year follow-up period postdiagnosis ranged from $44,454 to $63,320 among patients with SSc and PAH and from $18,513 to $23,269 among patients with SSc without PAH.[33] Similarly, an Australian study using data from 2008 to 2015 found that healthcare costs were almost twice as high among patients with SSc and PAH compared to those without PAH.[34] Our findings using more recent US data confirm the higher healthcare costs associated with CTD + PAH compared to CTD (without PAH), but also suggest a marked increase in the costs of CTD + PAH and CTD in the US with average annual all-cause total healthcare costs of $202,248 and $53,711, which is much more than expected from inflation.

Our findings are also consistent with prior studies reporting a substantial burden associated with PAH. A claims-based study among patients with PAH using data from 2010 to 2016 found that average all-cause total healthcare costs PPPM ranged between $6271 and $16,240 depending on the treatment received,[11] which is in the range of the present study findings. Also consistent with our study, a recent claims-based analysis by Ogbomo et al.[14] using data from 2016 to 2018 reported significantly higher average all-cause total healthcare costs PPPM among patients with prevalent PAH, driven by higher inpatient and pharmacy costs, compared to their matched controls without PAH ($9915 vs. $359 PPPM); higher all-cause total healthcare costs were also observed among patients with incident PAH versus matched controls. It should be noted that the estimated HRU rates and healthcare costs in that study are lower than those of the present study, which may reflect differences in sample characteristics. In particular, patients in our study were largely Medicare Advantage enrollees and were nearly 10 years older on average than in the study by Ogbomo et al.,[14] which included only commercially-insured employed patients; furthermore, there was a much larger proportion of females in the current study (86.7% in weighted analyses) than in the Ogbomo et al. study (47.5%).

The present study findings have important implications given the trends in PAH care observed in previous studies using the US Nationwide Inpatient Sample Database (NIS).[17,19] In one study using US NIS data from 2001 to 2012,[17] the rate of PAH-related hospitalizations was found to have decreased over time, which may reflect improvements in the standard of care for PAH. On the other hand, hospitalization costs from a healthcare payer perspective were found to rise over time, which may be related to an increase in comorbidities among patients admitted with PAH.[17] A similar decrease in hospitalization rates accompanied by rising costs was observed among patients with iPAH in another study using US NIS from 2007 to 2017.[19] In light of these previously reported trends, along with the substantial cost impact observed in the present study, there is a continued need for PAH management strategies that could address this growing burden of disease.[35]

Contemporary prescribing practices, such as the increased use of early combination therapy, may help to prevent further increases in the HRU burden among patients with CTD + PAH despite higher pharmacy costs. This treatment strategy is also supported by prior analyses of clinical trial data and evidence from retrospective claims-based studies.[12,36–39] In the single-arm, open label OPTIMA study, initial double combination therapy with a PDE5i and ERA led to significant improvements in multiple clinical outcomes among treatment-naïve patients with PAH.[38] In a subgroup analysis of treatment-naïve patients with CTD + PAH enrolled in the randomized, double-blind AMBITION trial, initial combination therapy with an ERA and PDE5i significantly reduced the risk of a first clinical failure event (first occurrence of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) when compared to monotherapy.[39] Finally, a recent meta-analysis of randomized controlled trials and registries from 2000 to 2019 found that modern PAH therapies were associated with a comparable reduction in morbidity and mortality risk among CTD + PAH patients compared to PAH population overall.[30] Although the risk of death in CTD + PAH was found to be worse than for PAH overall, survival has improved considerably among CTD + PAH patients in the past 10 years, which may partly reflect improved treatment approaches, particularly with respect to the use of combination therapies.[30]

While these aforementioned findings support the timely use of combination therapy in PAH per clinical

guidelines,[10,40] this treatment strategy may be underutilized in routine clinical practice partly due to concerns regarding the costs of treatment.[13] However, such concerns are likely to be overstated given that increased pharmacy costs may be at least partly offset by HRU benefits among patients.[13] Indeed, claims-based studies have reported an increase in pharmacy costs accompanied by stabilization or concomitant reduction in medical costs following the initiation of PAH-specific treatments, including combination therapies.[12,36,37] Thus, the clinical burden of disease in PAH could be alleviated if patients had timely access to all available PAH treatment classes, including combination therapies targeting the nitric oxide, endothelin, and prostacyclin pathways.[10,13,35]

Finally, findings from the current study suggest that patients with CTD + PAH are receiving more frequent care from specialists relative to patients with PAH (without CTD). The significantly increased rate of pulmonologist visits among patients with CTD + PAH is consistent with prior evidence of more severe and progressive disease among this patient population relative to those with iPAH.[5–8] However, we note that this could also reflect a higher incidence of parenchymal lung diseases, such as pulmonary fibrosis, among patients with CTD + PAH,[41–45] with about one-third of the CTD + PAH cohort having a recorded diagnosis for pulmonary fibrosis. The more frequent visits to rheumatologists speaks to the added complexity of co-managing CTDs among this patient population.[1] In general, a pulmonologist or cardiologist are more likely to make an initial diagnosis of PAH, although rheumatologists also play a critical role in the detection and ongoing management of PAH among patients with high-risk conditions such as CTDs.[46] In regard to future research, it would be helpful to better understand prescribing practices among these different types of specialists, as certain healthcare payers may require a pulmonologist or cardiologist to prescribe treatments as opposed to the rheumatologists who typically follow patients with CTD. While it is typical and appropriate for patients with CTD + PAH to have a cardiologist or pulmonologist involved in their care in addition to their rheumatologist, this more complex care may contribute to the higher healthcare costs associated with CTD-related PAH.

Limitations

The present study is subject to limitations. First, patients were classified into study cohorts based on information available in health insurance claims data such as diagnosis codes and treatment received. As a result, patients may have been misclassified into a given cohort (e.g., if they had a rule-out diagnosis or had information recorded incorrectly). For instance, since the ICD-10-CM for CTEPH was not effective until 10/1/2017, it is possible that some patients with CTEPH followed only between 10/01/2015 and 10/1/2017 may have been considered as having PAH if they were diagnosed with PH and had received a PAH-related treatment. Similarly, some patients with Group 3 PH could have been included, particularly given the high proportion of patients with pulmonary fibrosis reported in the CTD + PAH cohort. Second, death information is reported based on social security information and discharge status. However, not all deaths are necessarily captured in the data and mortality may therefore be underestimated. Third, although the analyses were adjusted for observable characteristics, there may have been residual confounding due to unobserved confounders (e.g., disease severity, which is not available in health insurance claims data). Specifically, the CTD + PAH cohort might have had more patients with higher WHO FCs (i.e., Class III or IV), who are in turn known to experience worse outcomes.[22] However, the impact of WHO FC could not be assessed in our study due to a lack of availability of this information in claims data. Further, given the data are only available after the start of continuous enrollment in their healthcare plan (i.e., left censoring), the time since initial diagnosis cannot be assessed, and could also be an unobserved confounder. Finally, while our study population is broadly representative of commercially insured US patients, the study results might not be generalizable to patients without health insurance or those with insurance plans other than commercial ones.

CONCLUSION

Findings from this study suggest that PAH, either CTD-related or from other etiologies, is associated with a high burden of disease in terms of healthcare costs and HRU. Notably, patients with CTD + PAH incurred higher healthcare costs relative to those with PAH. However, this was primarily due to higher PAH-related pharmacy costs, while HRU rates were generally similar between the two cohorts. Although patients with CTD-related PAH have tended to present with poorer outcomes historically, contemporary prescribing practices may help to mitigate the clinical and economic burden of CTD-related PAH relative to PAH. Further research would be needed to better understand the impact of the changing PAH treatment and management landscape on these outcomes. More broadly, the incremental burden among patients with PAH relative to both the general population and patients with CTD but no PAH is of interest, as it may reflect significant unmet needs in this population.

AUTHOR CONTRIBUTIONS

All authors: have made substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data, drafting the manuscript and revising it critically for important intellectual content, and have provided final approval of this version to be published and agree to be accountable for all aspects of the work.

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CONFLICTS OF INTEREST STATEMENT

YT, SP, VF, and HG are employees of Janssen Scientific Affairs, LLC and may own stock/stock options. MGL, AMM, SL, MC, and PL are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Janssen Scientific Affairs, LLC, which funded the development and conduct of this study and manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Optum ClinformaticsTM Data Mart (CDM). Restrictions may apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of Optum CDM.

ETHICS STATEMENT

Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996; therefore, no review by an institutional review board was required per Title 45 of CFR, Part 46.101(b)(4) (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#46.101).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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