Pulmonary Circulation

WILEY

PVRi | Pulmonary Circulation Open Access

RESEARCH ARTICLE OPEN ACCESS

Societal Costs Associated With Pulmonary Arterial Hypertension Subgroups: A Study Utilizing Linked National Registries

Barbro Kjellström[1] | Bodil Ivarsson[2] | Magnus Husberg[3] | Lars-Åke Levin[3] | Lars Bernfort[3]

[1]Department of Clinical Sciences Lund, Clinical Physiology and Skåne University Hospital, Lund University, Lund, Sweden | [2]Department of Clinical Sciences Lund, Cardiothoracic Surgery and Medicine Services University Trust, Region Skåne, Lund University, Lund, Sweden | [3]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Correspondence: Barbro Kjellström (Barbro.kjellstrom@med.lu.se)

Received: 14 October 2024 | **Revised:** 6 February 2025 | **Accepted:** 31 March 2025

Funding: The authors received no specific funding for this work.

Keywords: health care resource utilization | national registry | productivity loss | pulmonary hypertension

ABSTRACT

Pulmonary arterial hypertension (PAH) is a heterogenic diagnosis including idiopathic and hereditary PAH (IPAH/HPAH) and groups associated to connective tissue disease (APAH-CTD) and congenital heart disease (APAH-CHD). Pre- and post-diagnosis societal costs in PAH subgroups are not well known. By linking Swedish national databases, societal costs in a national PAH cohort 5 years before and 5 years after diagnosis were estimated and compared to an age, sex, and geographically matched control group (1:5 match). Incident patients diagnosed 2008–2019 were included (patient/control; IPAH/HPAH = 393/1965, APAH-CTD = 261/1305, APAH-CHD = 89/445). Pre-diagnosis mean societal costs were 2.9, 3.4, and 4.3 times higher for IPAH/HPAH, APAH-CTD and APAH-CHD patients, respectively, than controls. Post-diagnosis, mean costs had increased 3.1, 2.0, and 1.6 times further for IPAH/HPAH, APAH-CTD and APAH-CHD respectively, while it decreased in all control groups. Main cost driver pre-diagnosis were indirect costs (productivity loss) in both patient and control groups, however, 2.7–4.5 times higher in the patient groups. Post-diagnosis, the main cost driver for all groups were health care costs (in- and outpatient-care, drugs) that had increased 7.8, 5.4 and 6.8 times for IPAH/HPAH, APAH-CTD and APAH-CHD, respectively. Corresponding increase for controls were 17%–48%. For the PAH groups, drug treatment accounted for 70%–81% of the direct costs, while hospitalizations were the main driver for the control groups. In conclusion, PAH was associated with large societal costs. Pre-diagnosis, APAH-CHD had the highest societal costs, both in relation to their control group and compared to the other patient groups. Post-diagnosis, highest societal costs were seen in IPAH/HPAH.

1 | Introduction

Patients with pulmonary arterial hypertension (PAH) have a high symptom burden as well as increased levels of morbidity and mortality [1]. PAH is a heterogenic diagnosis with subgroups that include idiopathic and hereditary PAH (IPAH/HPAH) and groups associated to other diseases (APAH) [1]. The most common associated diseases are connective tissue disease (CTD) and congenital heart disease (CHD) [1]. For patients with associated diseases, contact with the health care system before the PAH diagnosis are common and expected [2]. Increasing age at time of PAH diagnosis incurs a higher comorbidity burden that contribute to an increased health care resource utilization (HCRU) [1, 3, 4].

A recent study based on national registries showed that in a period including 5 years before, and 5 years after the PAH diagnosis, the patients had 12 times higher overall HCRU than

an age, sex and geographically matched population without PAH [2]. The same study also showed that the HCRU increased already 3 years before the PAH diagnosis [2], confirming the delay from the first symptom to diagnosis shown in previous studies [5–8]. However, it is not known if and how pre- and post-diagnosis societal costs, including HCRU, differ between the PAH subgroups. In Sweden nationwide health care registries collect data from all citizens from birth to death, allowing for a comprehensive understanding of societal costs related to PAH subgroups.

Therefore, the aim of this study was to estimate the societal costs of PAH subgroups, comprising HCRU and productivity loss for a period of 5 years before and 5 years after diagnosis. The costs will be compared to control groups without PAH, matched for age, sex and geographical area.

2 | Materials and Methods

This retrospective registry-based case-control study included all incident, adult ($\geq$18 years) patients diagnosed with IPAH/HPAH, APAH-CTD or APAH-CHD and registered in the Swedish PAH & CTEPH registry (SPAHR) between January 1, 2008, and June 30, 2019 (excluding patients with $<$6 months follow-up after diagnosis). Patients with other PAH diagnoses (in total 8%) were excluded due to the heterogenic nature of the diagnoses in that group. SPAHR is a national quality registry that includes $>$90% of all patients diagnosed with PAH in Sweden [9]. The PAH diagnosis was set by right heart catheterization according to the European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of pulmonary hypertension effective at the time of diagnosis.

A control group, comprising five controls per included patient, was selected from the national population registry by Statistics Sweden (SCB). The control group were individuals without a PAH diagnosis during the whole 10-year study period and matched for sex, age (birth year) and place of residence (municipality) at the date when the patient was diagnosed with PAH. The patient's date of diagnosis was considered the index date for both groups (index date).

The study was approved by the Swedish Ethical Review Authority (Dnr 2020-02573).

2.1 | Swedish Health Care and Social Security Setting

In Sweden, the health care system is mainly publicly funded, and the state, government, and municipalities share the responsibility for supplying equal health care to all citizens [10]. All working individuals in Sweden are eligible for sick leave benefits from the Swedish Social Insurance Agency to cover any loss of income due to illness, disease or disability [11]. The sick leave benefit can be combined with part-time disability pension. The national pension system is mandatory for all citizens and constitutes the main source of an individual's age pension [12].

2.2 | Data Sources

Individual data from several Swedish national registries (Supporting Information S1: Figure S1), 5 years before and 5 years after the index date, were extracted for all study participants. All data were anonymized by the national registries before delivery to the researchers. All patients in SPAHR were informed locally about their participation in the registry and had the right to decline. Reporting to all other national registries utilized in the study is mandatory and based on health care administrative systems.

SPAHR [9] provided clinical data at time of diagnosis for the patients with PAH (Supporting Information S1: Table S1), i.e. hemodynamic and echocardiography measurements and measurements of clinical status (body mass index, WHO functional class and 6-min walked distance) including date of PAH diagnosis.

Statistics Sweden's longitudinal integration database for health insurance and labor market studies (LISA) [13] provided socioeconomic data on employment status, education attainment, income level and date of death. *The Swedish Social Insurance Agency with the microdata on sickness- and activity compensation registry (MiDAS)* [11] provided data on sick leave and disability pension.

The National Board of Health and Welfare provided data on HCRU from the *National Patient Register* [14] on outpatient visits and hospitalizations, and from the *National Prescribed Drug Register* [15] on prescription drug utilization. Outpatient visits included physician visits at specialist outpatient clinics but not at primary care clinics. Data on health care consumption and drug utilization were limited to predefined, related ICD-10-SE [16] and ATC codes (Supporting Information S1: Table S2). Drug utilization was measured as a defined daily dose (DDD) of dispensed drugs. Comorbidities were based on ICD-10-SE codes in the National Patient Register 5 years before the index date.

With the exception for drug utilization that was only available from July 2005, all variables were available from 2003 (Supporting Information S1: Figure S1). Data on in- and outpatient care, drug utilization, sick leave, and disability pension [17] were available through 2020. Data on socioeconomics was available through 2019, and date of death through 2021.

2.3 | Data Management—Cost Calculations

Study participants were followed for 5 years after index date or until censoring at the date of last contact (time of death or loss to follow-up), whichever occurred first. Annual mean HCRU (hospitalizations, outpatient visits, drug utilization) per patient included uncensored and living patients present at the beginning of each year. Total mean costs were calculated over the total 5 years pre- and 5 years post-index date.

Direct costs related to in- and outpatient-care were calculated using diagnosis-related groups (DRG), a patient classification scheme for health care contacts providing a means of relating

treatment of the groups to the costs incurred [18]. Each visit was attributed a DRG-based cost, without adjusting for extreme outliers. Drug costs were based on pharmacy listing sales prices.

Indirect costs were restricted to productivity loss and estimated using the human capital approach [19]. Thus, the time spent absent from work, manifested as sick leave and disability pension, was valued as the mean gross salary plus payroll taxes per day in Sweden. The analysis of participants receiving disability pension included only individuals with employment, excluding individuals with age pension as the main source of income. The analysis of participants on sick leave further excluded participants with full time disability pension.

Total costs were adjusted for censoring using the Zhao and Tian censoring estimator [20]. The estimator handles censoring in the data set by weighting uncensored costs by the likelihood of being censored, i.e., increased weight in parallel with risk of being censored. In addition, differences in costs between censored and uncensored individuals are adjusted. Costs were adjusted to 2023 prices using the consumer price index (CPI) [21] and converted from SEK to EUR using the average exchange rate in 2023 (1 EUR = 11.47652 SEK) [22].

2.4 | Statistical Methods

Participant characteristics at time of index date are shown as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and frequency (n) and proportions (%) for categorical variables. Costs are presented as mean (95% confidence interval) to reflect the actual societal costs. Differences between the PAH subgroups and their matched control groups were tested using Student's *t*-tests, Mann Whitney *U*-tests, and Chi-2 tests. *P*-values < 0.05 were considered significant (two-sided test). Microsoft Excel 365:2201, SPSS 28 and RStudio 2021.9.2.382 were used for all analyses. Overall survival was analyzed using Kaplan-Meier estimates with follow-up from index date and censoring at the date of last contact or death.

3 | Results

A total of 743 patients were included in the study, 393 patients with IPAH/HPAH, 261 patients with APAH-CTD and 89 patients with APAH-CHD. Corresponding numbers for the matched controls were 1965, 1305 and 445, respectively.

3.1 | Characteristics at Index Date

Patients with APAH-CTD and their matched controls were the oldest, averaging 66 ± 13 years at index date, followed by those with IPAH/HPAH at 63 ± 17 years and APAH-CHD at 44 ± 19 years. The proportion of females was higher than males in all groups (Table 1). Patients with IPAH/HPAH exhibited a lower level of education compared to their matched controls, with fewer patients having attended university. The proportion of individuals whose main income derived from age pension was similar between patients and controls across all groups while fewer patients than controls had employment as their main income (Table 1). The APAH-CHD group had lower disposable income and fewer lived in co-habitation and with children living at home, compared to matched controls.

Essential hypertension, atrial fibrillation, ischemic heart disease, thyroid disorders and kidney disease were more common in the IPAH/HPAH and APAH-CTD groups than their controls, while patients with APAH-CHD more often had essential hypertension, atrial fibrillation, stroke and kidney disease than their controls. Presence of diabetes was four times higher in the IPAH/HPAH group than matched controls (Table 1). Detailed PAH diagnosis characteristics are shown in Supporting Information S1: Table S2.

3.2 | Health Care Resource Utilization and Costs

HCRU costs, including hospitalizations, outpatient visits and drug treatment, was significantly higher already 5 years before index date for all three patient groups compared to their matched controls. HCRU remained higher in patients compared to controls over the full study period (Figure 1; Supporting Information S1: Tables S3–5). Thus, the HCRU results presented hereafter will show the three patient groups. Detailed comparisons between each patient group and its control group can be found in the Supplemental Tables.

Hospitalizations: Five years before diagnosis, hospitalization metrics, including the number of days hospitalized per person/year, proportion of patients hospitalized, and associated costs were similar for IPAH/HPAH and APAH-CTD, but lower for APAH-CHD compared to the other groups (Figures 1 and 2, Supporting Information S1: Table S3a–e). In the year before and after diagnosis, the proportion of patients hospitalized, and the number of days hospitalized reached comparable peaks in the IPAH/HPAH and APAH-CTD groups. Concurrently, the costs associated with in-hospital care increased four to five times for IPAH/HPAH and APAH-CTD and doubled in APAH-CHD, and consequently, costs for APAH-CTD were 29% higher than for IPAH/HPAH and 122% higher than for APAH-CHD. Two years post-diagnosis, costs had decreased by 35% for IPAH/HPAH and increased 9% and 71% for APAH-CTD and APAH-CHD, respectively, compared to the year preceding the diagnosis. Throughout the study, in-hospital care costs remained higher for APAH-CTD compared to the other groups (Figure 1, Supporting Information S1: Table S3a–e).

Outpatient care: Five years before diagnosis, patients with APAH-CTD had 73% more outpatient visits per person/year than patients with IPAH/HPAH and 86% more than patients with APAH-CHD. Costs for APAH-CTD outpatient visits were 77% and 117% higher than for IPAH/HPAH and APAH-CHD respectively. This pattern between groups persisted throughout the entire study period (Figures 1 and 2, Supporting Information S1: Table S4a–S4c).

Drug utilization, measured as the mean number of DDD per person/year was comparable in IPAH/HPAH and APAH-CTD before the index date at about twice the level of APAH-CHD. During the pre-index date period DDD increased 20% across all patient groups. Over this period drug costs for APAH-CHD were 142% higher than IPAH/HPAH and 99% higher than

TABLE 1 | Characteristics at index date patients with PAH by subgroups and their matched control groups. Data presented as mean ± SD, proportion (%), number (*n*) or median [IQR].

	IPAH/HPAH *n* = 393	Control *n* = 1965	*p*-value	APAH-CTD *n* = 261	Control *n* = 1305	*p*-value	APAH-CHD *n* = 89	Control *n* = 445	*p*-value
Age, *years*	63 ± 17	63 ± 17	0.987	66 ± 13	66 ± 13	0.954	44 ± 19	44 ± 19	0.988
Sex, *female*	56%	56%	1.000	79%	79%	1.000	71%	71%	1.000
Highest education level attained									
Primary school	30%	29%	0.005	27%	28%	0.565	30%	21%	0.222
Secondary school	53%	46%		48%	44%		38%	44%	
University *(minimum two years)*	17%	25%		26%	28%		32%	34%	
Main source of income[1]									
Work	16%	27%	< 0.001	11%	24%	< 0.001	24%	63%	< 0.001
Disability pension	9%	3%		13%	3%		29%	3%	
Age pension	62%	63%		67%	69%		20%	19%	
Sickness benefit	6%	1%		6%	1%		5%	2%	
Other[2]	6%	6%		3%	4%		22%	13%	
Disposable annual income, *k€*[3]	21 [17–27]	22 [17–31]	0.115	22 [16–30]	22 [17–32]	0.729	16 [13–25]	24 [18–31]	0.002
Disposable annual family income, *k€*[3]	29 [18–42]	32 [19–50]	0.091	32 [18–48]	31 [18–49]	0.609	22 [14–42]	41 [24–61]	< 0.001
Co-habitation	52%	55%	0.245	58%	53%	0.135	27%	49%	< 0.001
Proportion with children living at home	16%	19%	0.130	13%	14%	0.556	27%	48%	< 0.001
Comorbidities present at any time during the five-years before index date (ICD-10[4])									
Essential (primary) hypertension (I10)	56%	21%	< 0.001	41%	21%	< 0.001	17%	8%	0.008
Diabetes (E10-E14)	30%	7%	< 0.001	10%	7%	0.083	7%	3%	0.103
Atrial fibrillation and flutter (I48)	21%	7%	< 0.001	16%	6%	< 0.001	21%	1%	< 0.001
Stroke (I61, I63, I64)	4%	3%	0.637	4%	2%	0.093	3%	0%	0.009
Ischemic heart diseases (I20–I25)	23%	10%	< 0.001	20%	7%	< 0.001	3%	3%	1.000
Disorders of thyroid gland (E00-E07)	15%	4%	< 0.001	14%	6%	< 0.001	8%	4%	0.070
Acute kidney failure and chronic kidney disease (N17-N19)	8%	2%	< 0.001	6%	1%	< 0.001	3%	0%	0.009

Abbreviations: SD = Standard deviation, IQR = Interquartile range, k€ = thousand Euro.
[1]During the (calendar) year of diagnosis.
[2]Other: Student grants, reimbursement due to care of family member, unemployment benefits, unemployment program/training reimbursement, social security benefits, no known income.
[3]EUR exchange rate, mean 2023 = 11.47652 kr/€uro [22] [3]*ICD-10-SE*, the National Board of Health and Welfare classifications of diseases [16].

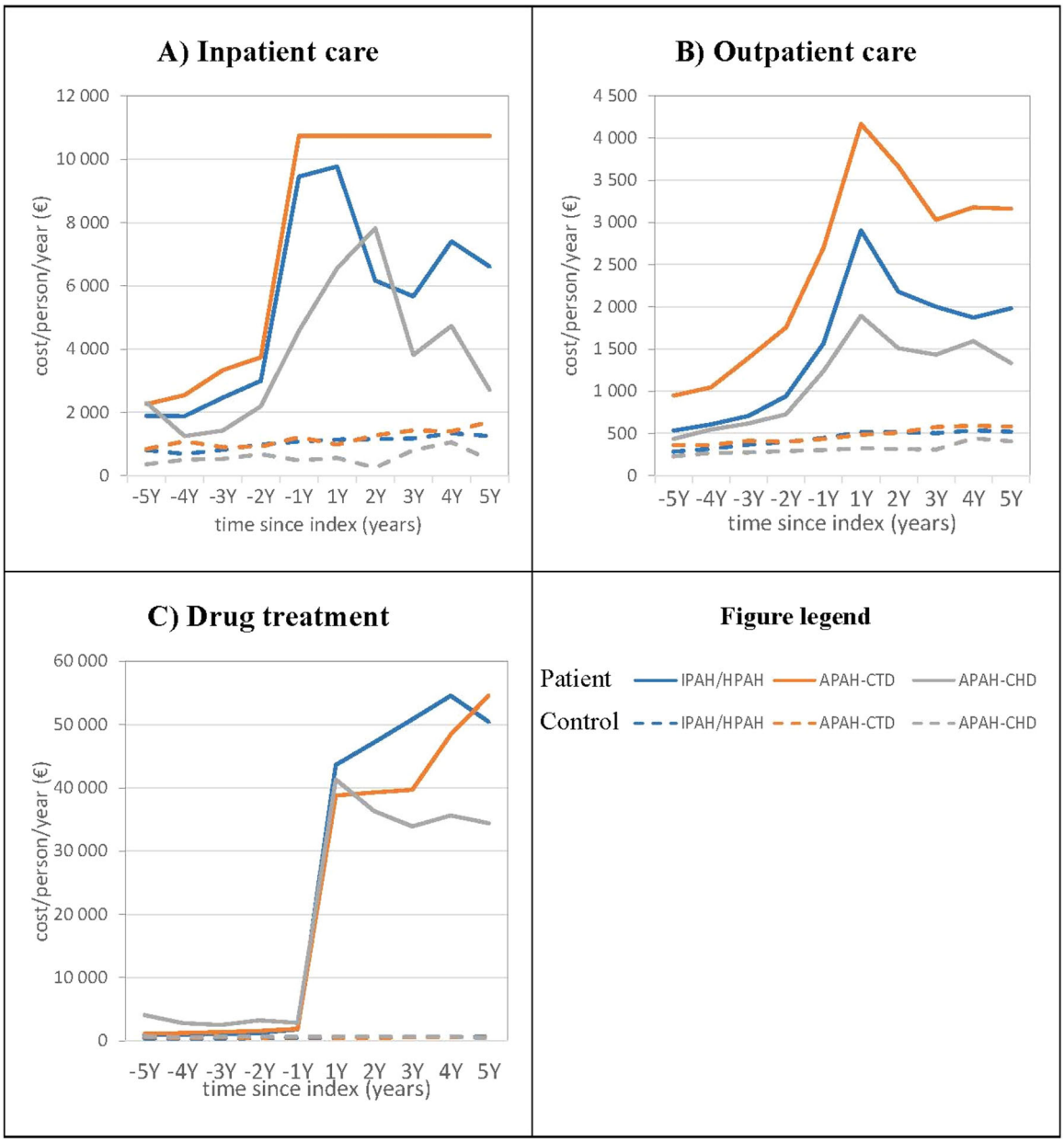

FIGURE 1 | Health care resource utilization costs for PAH subgroups and control groups. Panel A) hospitalizations, Panel B) outpatient visits and C) drug treatment. Figure legend: IPAH/HPAH blue, APAH-CTD orange and APAH-CHD gray. Patient groups are shown as solid lines and control groups as dotted lines. Number of patients and controls included for each year can be found in Supporting Information S1: Tables S3–5.

APAH-CTD (Figures 1 and 2, Supporting Information S1: Table S5a,b). The APAH-CHD group included two patients that started on PAH-targeted treatment 5 years before diagnosis, one patient started 1.8 years before diagnosis and two patients started 64 and 23 days before diagnosis. Post-index date, drug costs per person/year was highest in the IPAH/HPAH group. Over the 5-year post-index date period, DDD were 102% and 136% higher, and costs 36% and 22% higher, for IPAH/HPAH and APAH-CTD, respectively, compared to APAH-CHD.

3.3 | Sick Leave and Disability Pension

Five years before diagnosis, sick leave and disability pension rate were 44% for IPAH/HPAH, 61% for APAH-CTD and 49%, for APAH-CHD. Five years post-diagnosis these rates had increased to 58%, 77%, and 63%. Control groups exhibited stable rates, averaging 22% before and 19% after index date. (Figure 3, Supporting Information S1: Table S6a–6c).

3.4 | Societal Costs

The total societal costs for the IPAH/HPAH, APAH-CTD and APAH-CHD groups were 2.9, 3.4 and 4.3 times higher, respectively, compared to their control groups over the 5-year period before the index date (Table 2). Post-index date, the societal costs increased 3.1 times for IPAH/HPAH, 2.0 times for APAH-CTD, and 1.6 times for APAH-CHD compared to the pre-index date period. Societal costs decreased in all control groups after the index date.

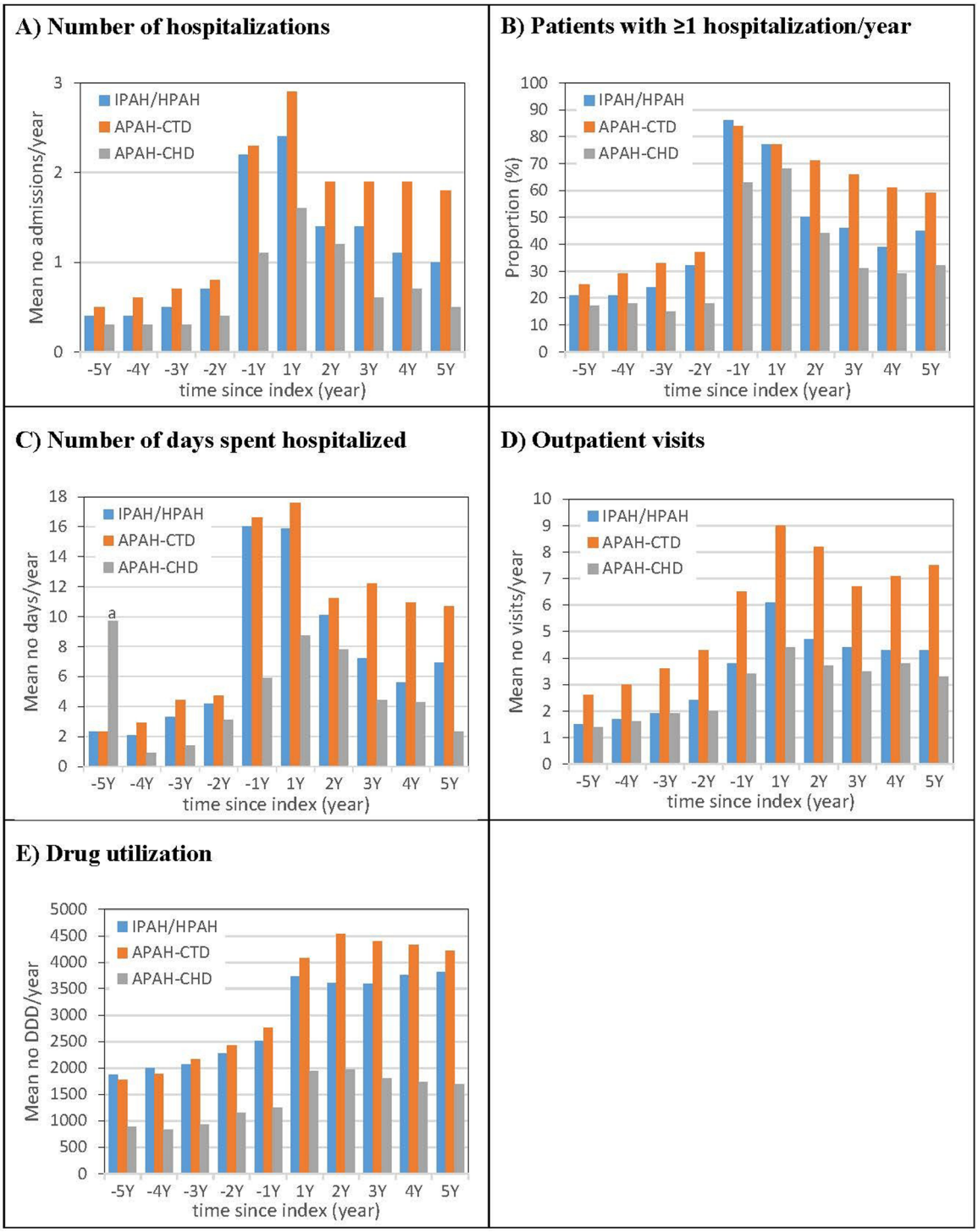

FIGURE 2 | Health care resource utilization presented for the patient groups. Panel A) Number of hospitalizations, Panel B) Patients with ≥ 1 hospitalization/year, Panel C) Number of days spent hospitalized, Panel D) Outpatient visits, Panel E) Drug utilization. *a = one patient spent the whole -5 year in hospital, mean number of days/year excluding this outlier was 0,8 days.* Number of patients included for each year can be found in Supporting Information S1: Tables S3–5.

Indirect costs, primarily productivity loss, was the main cost driver before the index date, accounting for 60%, 62%, and 77% of the total costs for IPAH/HPAH, APAH-CTD and APAH-CHD, respectively (Table 2). Post-index date, the direct costs, including hospitalization, outpatient care and drug treatment, had increased 7.8, 5.4, and 6.8 times for IPAH/HPAH, APAH-CTD, and APAH-CHD, respectively, and became the main cost driver. Prescribed drugs accounted for 70%–81% of the direct costs, whereas hospitalizations were the main cost driver for the control group.

3.5 | Mean Survival

The one, three and 5-year survival was 85%, 64%, and 47% in the IPAH/PAH group, 82%, 59%, and 43% in the APAH-CTD group

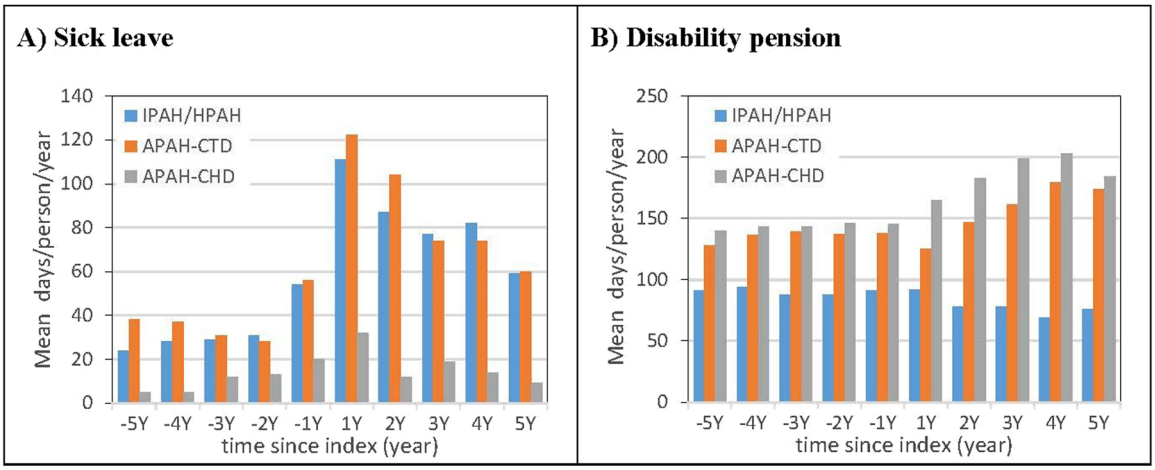

FIGURE 3 | Productivity loss for the patient groups. Data include individuals eligible for sick leave or disability pension, i.e. not yet receiving age pension as main income. Panel A) Sick leave, mean days per person and year (full time equivalents); Panel B) Disability pension, mean days per person and year (full time equivalents). Number of patients and controls included for each year can be found in Supporting Information S1: Table S6.

and 97%, 82%, and 74% in the APAH-CHD group (Figure 4). Corresponding rates for the control groups were 98%, 94%, and 93% (control IPAH/HPAH), 99%, 95%, and 91% (control APAH-CTD) and 99%, 98%, and 96% (control APAH-CHD).

4 | Discussion

Total societal costs over the 5 years before index date was highest in the APAH-CHD group followed by APAH-CTD and IPAH/HPAH in that order. Over the 5 years after index date, total costs were highest in the IPAH/HPAH group and lower, but similar, in the two other patient groups. The main cost driver before index date was indirect costs, i.e. productivity loss, in all patient groups. After index date, the main cost driver was drug treatment, accounting for 70%–80% of the costs. In all control groups, productivity loss was the main cost driver before index date and hospitalizations after index date.

There are diverging results in previous studies whether the main post-diagnosis cost drivers are drug costs [23–25] or nondrug related health care costs [26–28] for patients with PAH. In the present study, hospitalizations and outpatient care was four to six times higher in patients than matched controls in the 5-year period after index date, while the costs for drug treatment was 50–60 times higher. This supports that in the modern treatment era, drug cost is the largest component of the societal costs not only in the total PAH cohort, but also in each of the PAH subgroups. The high national coverage of the Swedish PAH registry [9] and of direct and indirect societal costs from the Swedish national governmental registries [10–22], allow us to present data from a comprehensive national cohort. Thus, possible inclusion disadvantages that insurance claim databases endure can be avoided [4, 23, 26]. In addition, the availability of five randomly selected controls without PAH from the population registry matched by age, sex and geographical area for each patient and with data available from 5 years before as well as 5 years after the PAH diagnosis (index date) these results are strengthened further.

The productivity loss in the APAH-CHD group before diagnosis was more than twice as high as the productivity loss in the IPAH/PAH group and 50% higher than in the APAH-CTD group. Employment rates are in general lower among individuals with CHD compared to healthy individuals [29] and PAH will not lessen this burden. In the present study, patients with APAH-CHD had a higher proportion of their income from disability pension than from work, confirming low employment rates as the source of the productivity loss. Costs for drug treatment was also higher in the APAH-CHD group before diagnosis when compared to the other patient groups. This was largely related to the three patients with APAH-CHD receiving PAH-targeted treatment in the years before the study-defined index date. These patients were likely diagnosed with PAH as children or young adults and on PAH-targeted treatment when registered in SPAHR at the age of 18.

Health care costs, i.e. hospitalizations, outpatient visits and drug treatment, where significantly higher in all three patient groups already 5 years before index date compared to their control groups. This differs partly from our previous study where the total PAH cohort was compared to a matched control group and where the trends in hospitalizations did not separate until 3 years before index date [2]. This highlights both the strong relation between health care costs and underlying diseases and age, and thus, the importance of handling the PAH subgroups individually when analyzing cost. The results are somewhat surprising. That the two groups with associated diseases, APAH-CTD and APAH-CHD, had higher health care related costs than their matched controls already at 5 years before index date was expected. But that a similar pattern was seen for the IPAH/HPAH group has not been shown earlier. As the control groups are matched for age and sex, and geographical area was used as a socioeconomic substitute match, this finding was unexpected. One might speculate that changes in the pulmonary vasculature start earlier in IPAH/HPAH than previously believed. The lower level of education, i.e. lower proportion with a university degree and a significantly higher comorbidity burden than their matched controls already at time of index date is also an indication that IPAH/HPAH have effects on health and life earlier than previously shown. This interesting finding will be investigated further.

TABLE 2 | Societal costs, estimated over the total five-year period pre-index date and five-year period post-index date data using the Zhao and Tian (ZT [20];) estimator to adjust for censoring. Data shown as mean (95% confidence interval), per patient, EUR (exchange rate, mean 2023 = 11.48kr/€uro [22]).

	Five-year period before index date			Five-year period after index date		
	IPAH/HPAH	**Control**	**Difference**	**IPAH/HPAH**	**Control**	**Difference**
Hospitalizations	17 421 (15 311–19 530)	4 349 (3 864–4 833)	13 072 (10 908–15 236)	30 341 (26 158–34 525)	6 808 (6 138–7 478)	23 533 (19 296–27 770)
Outpatient care	4 360 (3 806–4 913)	1 807 (1 528–2 086)	2 553 (1 933–3 173)	8 049 (7 251–8 847)	2 549 (2 258–2 839)	5 500 (4 651–6 350)
Prescribed drugs	5 802 (4 487–7 118)	1 967 (1 774–2 160)	3 835 (2 506–5 165)	171 189 (147 846–194 532)	2 708 (2 321–3 096)	168 481 (145 135–191 827)
Total direct	27 583 (24 638–30 527)	8 122 (7 380–8 864)	19 460 (16 423–22 497)	216 119 (190 700–241 538)	12 009 (10 990–13 027)	204 110 (178 671–229 549)
Productivity loss[1]	41 360 (32 616–50 105)	15 460 (13 050–17 870)	25 900 (16 830–34 971)	1 027 (828–1 226)	209 (164–253)	818 (615–1 022)
Total societal costs	68 943 (59 031–78 855)	23 582 (20 971–26 194)	45 360 (35 110–55 611)	217 146 (191 685–242 607)	12 217 (11 196–13 239)	204 928 (179 447–230 410)

	Five-year period before index date			Five-year period after index date		
	APAH-CTD	**Control**	**Difference**	**APAH-CTD**	**Control**	**Difference**
Hospitalizations	21 603 (18 995–24 212)	4 889 (3 989–5 788)	16 715 (13 955–19 474)	42 190 (36 672–47 708)	7 760 (6 806–8 714)	34 430 (28 830–40 030)
Outpatient care	7 838 (6 541–9 136)	1 965 (1 793–2 137)	5 873 (4 564–7 182)	11 429 (9 434–13 423)	2 717 (2 475–2 959)	8 712 (6 702–10 721)
Prescribed drugs	7 057 (4 972–9 143)	2 621 (2 169–3 074)	4 436 (2 302–6 570)	137 835 (119 025–156 644)	2 825 (2 359–3 290)	135 010 (116 194–153 825)
Total direct	36 499 (32 121–40 877)	9 475 (8 309–10 641)	27 024 (22 493–31 554)	196 279 (175 271–217 287)	13 148 (11 866–14 431)	183 131 (162 084–204 177)
Productivity loss[1]	60 373 (47 947–72 798)	19 011 (15 879–22 143)	41 362 (28 548–54 176)	1 108 (857–1 360)	196 (140–251)	913 (655–1 170)
Total societal costs	96 871 (82 233–111 510)	28 486 (24 997–31 974)	68 386 (53 338–83 434)	197 387 (176 310–218 465)	13 344 (12 058–14 630)	184 043 (162 926–205 160)

	Five-year period before index date			Five-year period after index date		
	APAH-CHD	**Control**	**Difference**	**APAH-CHD**	**Control**	**Difference**
Hospitalizations	11 339 (7 299–15 380)	2 551 (1 793–3 308)	8 789 (4 678–12 900)	24 726 (17 682–31 771)	3 253 (2 192–4 315)	21 473 (14 349–28 597)
Outpatient care	3 564 (2 781–4 347)	1 363 (1 113–1 613)	2 201 (1 379–3 023)	6 858 (5 769–7 947)	1 806 (1 523–2 090)	5 052 (3 927–6 177)
Prescribed drugs	14 015* (−4 364–32 393)	3 093 (−140–6 327)	10 921 (−7 739–29 582)	158 326 (136 634–180 017)	3 067 (584–5 551)	155 258 (133 425–177 091)
Total direct	28 918 (8 777–49 060)	7 007 (3 636–10 377)	21 912 (1 490–42 333)	195 542 (169 604–221 479)	8 196 (5 379–11 013)	187 346 (161 256–213 436)
Productivity loss[1]	94 248 (67 967–120 529)	21 698 (15 872–27 524)	72 550 (45 631–99 469)	1 925 (1 411–2 438)	311 (197–425)	1 613 (1 087–2 139)
Total societal costs	123 167 (91 786–154 547)	28 705 (21 858–35 552)	94 462 (62 343–126 580)	197 466 (171 524–223 408)	8 507 (5 679–11 335)	188 959 (162 863–215 055)

Abbreviations: APAH = associated PAH, CTD = connective tissue disease, CHD = congenital heart disease, HPAH = hereditary PAH, IPAH = idiopathic PAH, PAH = pulmonary arterial hypertension.

[1]Sick leave and disability pension.

*Include two patients started on PAH-targeted treatment 5 years before diagnosis, one patient 1.8 years before diagnosis and two patients 64 and 23 days before diagnosis.

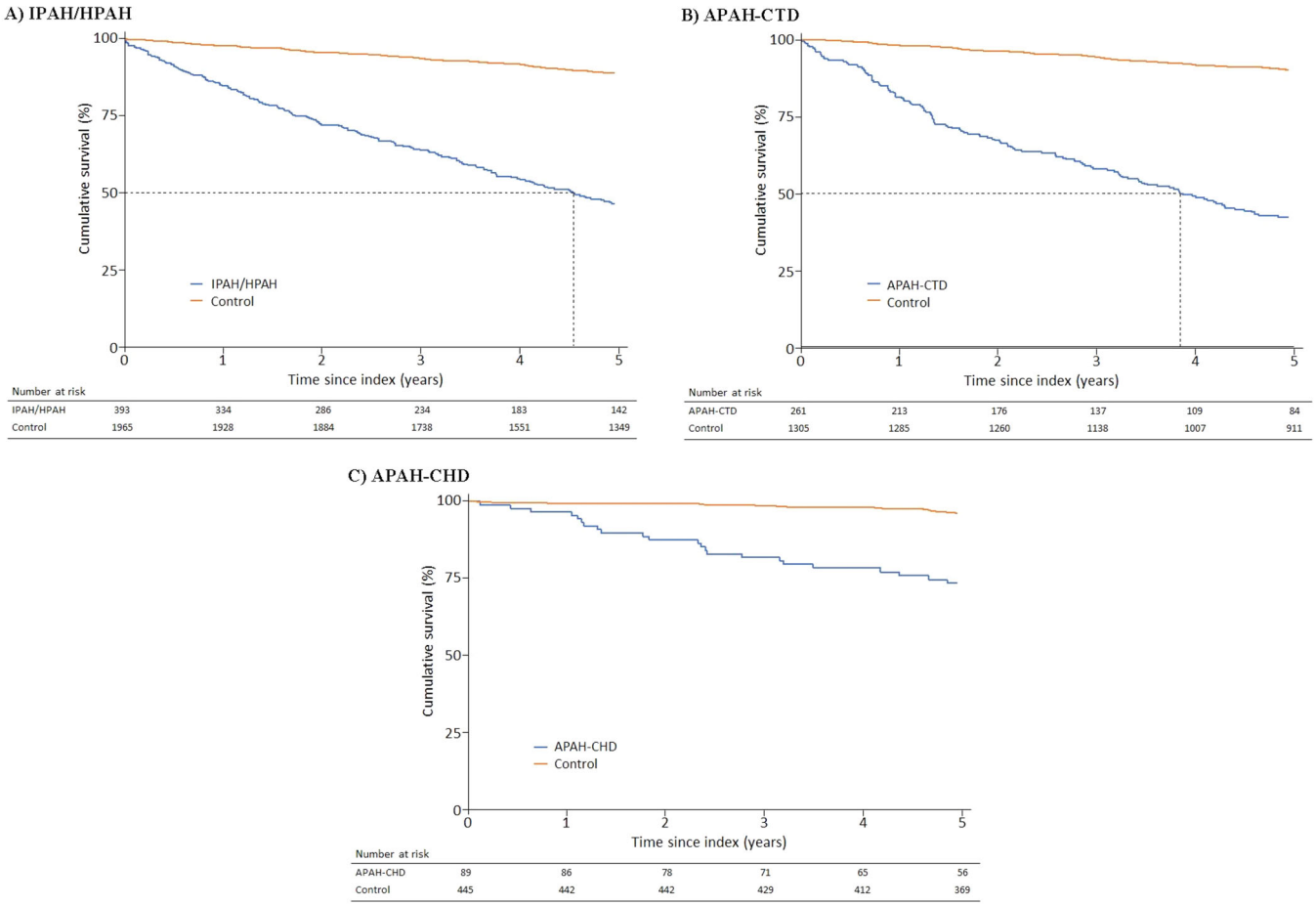

FIGURE 4 | Overall survival for the PAH subgroups (red) and their matched control groups (blue) by Kaplan-Meier estimates for five years follow-up from index date and censored at the date of last contact or death.

Despite improved treatments, long-term prognosis for patients with PAH remains poor. The seriousness of the diagnosis is put in context when the survival is presented in the perspective of an age, sex and geographically matched control group as in the present study. In the first data from the NIH registry, started in 1981 and included patients diagnosed with primary PH, the median survival was 2.8 years [30]. Almost 45 years later, the median survival has not yet risen above 5-years. Already in this first publication by D'Alonzo et al, the importance of reaching a low functional class and the need for an earlier diagnosis was discussed [30]. This is further emphasized in the present study, the rapid increase in health care costs that start two to 3 years before diagnosis in all patient groups, confirm the diagnostic delay as has been described earlier [2, 5–7]. One might have expected that patients with an underlying disease, known to be associated with PAH should have been diagnosed earlier. However, based on the HCRU trends as well as increased sick leave in the year before diagnosis and most patients in WHO FC III/IV at time of diagnosis in the present study, this do not seem to be the case. Improved diagnostic tools for primary care, emergency care and specialist in rheumatology and cardiac care are clearly warranted.

Strengths of the present study are the mainly tax-funded national systems of health care, social insurance and pension in Sweden that provide high national coverage of all the included registries, and the inclusion of an age, sex, and geographically matched control group, five controls per patient. All PAH-specialist centers in Sweden participate in SPAHR allowing for a national coverage of > 90% of all patients diagnosed with PAH in Sweden. The presentation of indirect effects of PAH such as sick leave, disability pension and related productivity loss is another strength of the study.

Limitations of the study include the censoring of data where patients diagnosed late in the study period had a shorter follow-up time. Additionally, drug utilization data was unavailable before mid-2005, which resulted in missing data for the first couple of years for patients included between 2008 and mid-2010. Moreover, the health care resource utilization did not encompass primary care. To illustrate the utilization progress in the living cohort, the HCRU analyses were limited to living and non-censored individuals inducing a bias towards individuals diagnosed with PAH early in the data collection period. Limitations typically associated with observational registry studies, such as selection bias, lack of standardization of registered variables and missing follow-up data might be present.

In conclusion, all PAH subgroups incurred significant societal costs, exceeding those of matched controls already 5 years before diagnosis. Pre-diagnosis costs were primarily driven by productivity loss, whereas post-diagnosis costs were dominated by inpatient and outpatient care as well as drug treatment. Before diagnosis, APAH-CHD exhibited the highest societal

costs, while after diagnosis the highest societal costs were seen in IPAH/HPAH. This highlights both the economic burden imposed on society as well as the importance of handling the PAH subgroups individually in HCRU analyses.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Magnus Husberg, Barbro Kjellström, Lars Bernfort and Lars-Åke Levin. The first draft of the manuscript was written by Barbro Kjellström and all authors commented on all versions of the manuscript. All authors have read and approved the final manuscript.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Acknowledgments

We acknowledge the work of the SPAHR registrars at the PAH/CTEPH-specialist clinics, the members of the SPAHR steering committee and Uppsala Clinical Research Center for administrating SPAHR. This study was funded by a grant from the Swedish heart and lung foundation and an unrestricted grant from Actelion Pharmaceuticals, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland.

Ethics Statement

The study was approved by the Regional Ethics Committee in Lund, Sweden (LU 2016/766), and performed in accordance with the Declaration of Helsinki. The study used retrospective, anonymized data from Swedish National Registries and in accordance to Swedish law, no informed consent from patients was needed.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. M. Humbert, G. Kovacs, M. M. Hoeper, et al., "2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension," *European Heart Journal* 43 (2022): 3618–3731.

2. H. Runheim, B. Kjellström, A. Beaudet, et al., "Societal Costs Associated With Pulmonary Arterial Hypertension: A Study Utilizing Linked National Registries," *Pulmonary Circulation* 13 (2023): e12190.

3. E. Bergot, L. De Leotoing, H. Bendjenana, et al., "Hospital Burden of Pulmonary Arterial Hypertension in France," *PLoS One* 14 (2019): e0221211.

4. F. Exposto, R. Hermans, Å. Nordgren, et al., "Burden of Pulmonary Arterial Hypertension in England: Retrospective HES Database Analysis," *Therapeutic Advances in Respiratory Disease* 15 (2021): 1753466621995040.

5. M. Ginoux, S. Turquier, N. Chebib, et al., "Impact of Comorbidities and Delay in Diagnosis in Elderly Patients With Pulmonary Hypertension," *ERJ Open Research* 4, no. 4 (2018): 00100-2018.

6. V. Khou, J. J. Anderson, G. Strange, et al., "Diagnostic Delay in Pulmonary Arterial Hypertension: Insights From the Australian and New Zealand Pulmonary Hypertension Registry," *Respirology* 25 (2020): 863–871.

7. L. M. Brown, H. Chen, S. Halpern, et al., "Delay in Recognition of Pulmonary Arterial Hypertension," *Chest* 140 (2011): 19–26.

8. B. Ivarsson, A. Johansson, and B. Kjellström, "The Odyssey From Symptom to Diagnosis of Pulmonary Hypertension From the Patients and Spouses Perspective," *Journal of Primary Care & Community Health* 12 (2021): 21501327211029241.

9. SPAHR (Swedish Pulmonary Arterial Registry). Årsrapport 2022, Updated 2023-03-23, accessed June 18, 2024, https://www.ucr.uu.se/spahr/arsrapporter/arsrapporter/arsrapport-spahr-2022.

10. A. Anell, A. H. Glenngård, and S. Merkur, "Sweden Health System Review," *Health Systems in Transition* 14 (2012): 1–159.

11. The Swedish Social Insurance Agency (FK). Social Insurance in Figures 2021. Stockholm; 2021.

12. The Swedish Pensions Agency. Pension system in Sweden [Updated 2023-11-01, accessed July 04, 2024], https://www.pensionsmyndigheten.se/other-languages/english-engelska/english-engelska/pension-system-in-sweden.

13. Statistics Sweden (SCB). Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), Accessed July 04, 2024, https://www.scb.se/en/services/ordering-data-and-statistics/register/longitudinal-integrated-database-for-health-insurance-and-labour-market-studies-lisa/.

14. The National Board of Health and Welfare (SoS). National Patient Register, Updated 2024-09-04, accessed August 10, 2024, https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/.

15. The National Board of Health and Welfare (SoS). National Prescribed Drug Register [Updated 2024-02-08, accessed August 10, 2024], https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-prescribed-drug-register/.

16. The National Board of Health and Welfare (SoS). Klassifikationen ICD-10 [Updated 2024-09-09, accessed August 10, 2024], https://www.socialstyrelsen.se/statistik-och-data/klassifikationer-och-koder/icd-10/.

17. The National Board of Health and Welfare (SoS). Sjukpenning och Rehabiliteringspenning, Version 1.02, accessed July 4, 2024, https://www.forsakringskassan.se/download/18.5b8b0bec183b9d817dc11f/1666183936381/dokumentation-av-midas-sjukpenning-och-rehabiliteringspenning.pdf.

18. The National Board of Health and Welfare (SoS). Viktlistor för NordDRG, Updated 2024-03-18, accessed July 4, 2024, https://www.socialstyrelsen.se/statistik-och-data/klassifikationer-och-koder/drg/viktlistor/.

19. Office of Health Economics. Productivity Costs: Principles and Practice in Economic Evaluation. London; 2000.

20. H. Zhao and L. Tian, "On Estimating Medical Cost and Incremental Cost-Effectiveness Ratios With Censored Data," *Biometrics* 57 (2001): 1002–1008.

21. Statistics Sweden (SCB). Consumer Price Index (CPI), accessed July 4, 2024, http://www.scb.se/pr0101-en.

22. The Riksbank. Annual average exchange rates (aggregated), accessed July 4, 2024, https://www.riksbank.se/en-gb/statistics/interest-rates-and-exchange-rates/search-annual-and-monthly-average-exchange-rates/.

23. C. D. Burger, A. B. Ozbay, H. M. Lazarus, et al., "Treatment Patterns and Associated Health Care Costs Before and After Treatment Initiation Among Pulmonary Arterial Hypertension Patients in the United States," *Journal of Managed Care & Specialty Pharmacy* 24 (2018): 834–842.

24. L. N. Pizzicato, V. R. Nadipelli, S. Governor, et al., "Real-World Treatment Patterns, Healthcare Resource Utilization, and Cost Among Adults With Pulmonary Arterial Hypertension in the United States," *Pulmonary Circulation* 12 (2022): e12090.

25. M. Sikirica, S. R. Iorga, T. Bancroft, and J. Potash, "The Economic Burden of Pulmonary Arterial Hypertension (Pah) in the Us on Payers and Patients," *BMC Health Services Research* 14 (2014): 676.

26. A. Ogbomo, Y. Tsang, R. Mallampati, and S. Panjabi, "The Direct and Indirect Health Care Costs Associated With Pulmonary Arterial Hypertension Among Commercially Insured Patients in the United States," *Journal of Managed Care & Specialty Pharmacy* 28 (2022): 608–616.

27. R. Copher, A. Cerulli, A. Watkins, and M. Laura Monsalvo, "Treatment Patterns and Healthcare System Burden of Managed Care Patients With Suspected Pulmonary Arterial Hypertension in the United States," *Journal of Medical Economics* 15 (2012): 947–955.

28. N. Y. Kirson, H. G. Birnbaum, J. I. Ivanova, T. Waldman, V. Joish, and T. Williamson, "Excess Costs Associated With Patients With Pulmonary Arterial Hypertension in a Us Privately Insured Population," *Applied Health Economics and Health Policy* 9 (2011): 293–303.

29. H. S. Girouard and A. H. Kovacs, "Congenital Heart Disease: Education and Employment Considerations and Outcomes," *International Journal of Cardiology Congenital Heart Disease* 1 (2020): 100005.

30. G. E. D'Alonzo, R. J. Barst, S. M. Ayres, et al., "Survival in Patients With Primary Pulmonary Hypertension. Results From a National Prospective Registry," *Annals of Internal Medicine* 115, no. 5 (September, 1991): 343–349, https://doi.org/10.7326/0003-4819-115-5-343.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.