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RESEARCH ARTICLE

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Societal costs associated to chronic thromboembolic pulmonary hypertension: A study utilizing linked national registries

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but serious complication after a pulmonary embolism. Healthcare resource utilization (HCRU; hospitalization, outpatient visits, and drug utilization) as well as productivity loss (sick leave and disability pension) before and after the CTEPH diagnosis is sparsely studied. By linking several Swedish national databases, this study estimated the societal costs in a national CTEPH cohort ($n = 369$, diagnosed with CTEPH in 2008−2019) 5 years before and 5 years after diagnosis (index date) and compared to an age, sex, and geographically matched control group ($n = 1845$, 1:5 match). HCRU and productivity loss were estimated per patient per year. Patients were stratified as operated with pulmonary endarterectomy (PEA group) or not operated (non-PEA group). Direct and indirect societal costs were 2.1 times higher before, and 8.1 times higher after the index date for patients with CTEPH compared to the matched control groups. The higher costs were evident already several years preceding the index date. The main cost driver before the index date in both the PEA and the non-PEA groups was productivity loss. The productivity loss remained high for both groups in the 5-year period following the index date, but the main cost drivers were prescribed drugs and hospitalizations for patients that underwent PEA and prescribed drugs in the non-PEA group. In conclusion, CTEPH was associated with large societal costs related to healthcare consumption and productivity loss, both before and after diagnosis.

KEYWORDS
burden of disease, burden of illness, mortality, national registry, pulmonary embolism

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but serious complication after a pulmonary embolism (PE).[1,2] A cumulative incidence ranging from 0.1% to 9.1% after a PE has been reported.[1] Still, 40%−66% of patients diagnosed with CTEPH lack a known medical history of acute PE.[3,4] The incidence and prevalence of CTEPH is estimated to 2−6 and 26−38 cases/million adult inhabitants, respectively.[5,6]

Approximately two thirds of patients with CTEPH are eligible for pulmonary endarterectomy (PEA), a procedure that can improve functional status and exercise capacity significantly.[1,6] However, up to a third of patients will have persistent or recurrent pulmonary hypertension after PEA and might require disease-targeted drug therapy and/or balloon pulmonary angioplasty (BPA).[1,4,5] Patients with CTEPH who are not eligible for surgery, but with symptoms, are recommended to receive disease-targeted drug therapy and/or BPA.[5] Independent of surgical or medical treatment, patients with CTEPH require lifelong anticoagulant therapy.[1,5]

High healthcare resource utilization (HCRU) after CTEPH diagnosis has been reported[7] as well as reduced work ability, leading to productivity loss.[8,9] Diagnostic delays of more than 1 year, due to the unspecific characteristics of early symptoms, are common.[6,10] These diagnostic delays will likely affect societal costs related to the diagnosis of CTEPH.[11,12] However, detailed information on HCRU and productivity loss in the years before the CTEPH diagnosis is missing and corresponding data for the time after diagnosis is only sparsely studied.[7,11,12]

Swedish national population registries record information about healthcare utilization and societal costs. The aim of this study was to describe the HCRU and productivity loss associated with CTEPH, dichotomized for PEA, 5 years before and 5 years after diagnosis compared to matched control groups without CTEPH.

MATERIALS AND METHODS

Study design and population

This was a retrospective registry-based case-control study including all adult (≥18 years) patients diagnosed with CTEPH ($n = 387$) registered in The Swedish PAH & CTEPH registry (SPAHR) between January 1, 2008 and June 30, 2019.[13] All patients in SPAHR were informed locally about their participation in the registry and had the right to decline. The CTEPH population was stratified by PEA surgery, that is, those that had undergone the surgical treatment (PEA) and those that had not undergone PEA (non-PEA). Patients with a BPA ($n = 3$) were comprised within the non-PEA group.

A control group ($n = 1935$, five controls per patient) was selected from the national population registry by Statistics Sweden (SCB). The control group consisted of individuals without a CTEPH diagnosis and were matched based on birth year (age), sex, and place of residence (municipality) at the date of the patients' CTEPH diagnosis (index date). The control group was stratified to match the PEA and non-PEA groups.

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

Swedish healthcare and social security setting

In Sweden, the healthcare system is mainly publicly funded, and the state, regions, and municipalities share the responsibility for supplying equal healthcare to all citizens.[14] All working individuals in Sweden are eligible for sick leave benefits from the Swedish Social Insurance Agency to cover loss of income due to illness, disease, or disability.[15] 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.[16]

Data sources

The study database consists of individual data merged from several Swedish national registries. All data were anonymized by the national registries. Data from 5 years before and 5 years after the index date were extracted for all study participants from the following registries:

SPAHR[13] provided the date of CTEPH diagnosis and clinical data for the CTEPH group.

Statistics Sweden's longitudinal integration database for health insurance and labor market studies (LISA)[17] provided socioeconomic data on employment status, education attainment, income level, and date of death. The Swedish Social Insurance Agency with the micro-data on sickness- and activity compensation registry (MiDAS)[15] provided data on sick leave and disability pension.

The National Board of Health and Welfare provided data on HCRU from the National Patient Register[18] on outpatient visits and hospitalizations, and from the National Prescribed Drug Register[19] on prescription drug utilization. Outpatient visits included physician visits at specialist outpatient clinics but not at primary care clinics. Data on healthcare consumption and drug

utilization were limited to predefined, related ICD-10-SE and ATC codes (Supporting Information: Table S1). Drug utilization was measured as defined daily dose (DDD) of dispensed drugs. Comorbidities were based on ICD-10-SE codes[20] in the National Patient Register during the 5-year period before the index date.

With the exception of drug utilization, which was only available from 2005, all variables were available from 2003 (Supporting Information: Figure S1). Data on socioeconomics, in- and outpatient care and drug utilization were available through 2019, data on sick leave and disability pension[21] were available through 2020, and date of death was available through September 2022.

Data management

After the index date, study participants were followed for 5 years 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 healthcare contacts providing a means of relating care for the groups to the costs incurred.[22] Each visit was attributed a DRG based cost, without adjusting for extreme outliers. Drug costs were based on pharmacy listing sales prices. Costs for PEA and BPA performed outside Sweden (Denmark or Norway) included cost for the procedure and the hospitalization.

Indirect costs were restricted to productivity loss and estimated using the human capital approach.[23] 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 of working age, 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 societal costs summed all direct and indirect costs and were adjusted for censoring using the Zhao and Tian censoring estimator.[24] The estimator handles censoring in the data set by weighting uncensored costs by the likelihood of being censored, that is, increased weight in parallel with risk of being censored. In addition, differences in costs between censored and uncensored individuals were adjusted. Costs were adjusted to 2020 prices using the consumer price index[25] and converted from SEK to EUR using the average exchange rate in 2021 (1 EUR = 10.4867 SEK).[26]

Statistical methods

Participant characteristics at time of index date are shown as mean ± standard deviation or median and interquartile range for continuous variables, and frequency (n) and proportions (%) for categorical variables. Differences between the CTEPH and the control groups were tested using Student's t-tests, Mann−Whitney U tests, and χ^2 tests. p Values <0.05 were considered significant. 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.

RESULTS

Of 387 available patients with CTEPH, 18 patients were excluded due to <6 months of follow-up data, leaving 369 patients with CTEPH and 1845 matched controls available for analyses. The mean age of the whole study population was 67 ± 13 years and 49% were male (Table 1). Of patients with CTEPH, 90% had a history of a PE (ICD-10 I26.0 & I26.9) within the 5 years before diagnosis. Median (Q1−Q3) time from PE to CTEPH diagnosis was 13 (7−29) months.

Baseline characteristics

The mean age in the PEA group ($n = 109$) and their matched controls ($n = 545$) were 62 ± 14 years and 64% were male, corresponding numbers for the non-PEA group ($n = 260$) and their controls ($n = 1300$) were 69 ± 12 years and 43% male (Table 2). In the PEA and the non-PEA groups, fewer individuals received their main income from work compared to their controls. During the 5 years before index date, 97% in the PEA group, 87% in the non-PEA group, and 1% of all controls had a record of a PE (Table 2). Median (Q1−Q3) time from PE to CTEPH diagnosis was 11 (5−17) months in the PEA group and 15 (7−37) months in the non-PEA group. Time from CTEPH diagnosis to PEA was 8 (4−11) months. Compared to their matched controls, systemic hypertension was more common in the PEA group, and systemic hypertension and ischemic heart disease in the

TABLE 1 Characteristics of the CTEPH group at time of diagnosis (index date) shown for the PEA, non-PEA, and the whole group.

	CTEPH PEA ($n = 109$)	CTEPH non-PEA ($n = 260$)	CTEPH all ($n = 369$)
Sex, male	64%	43%	49%
Age, years	62 ± 14	69 ± 12	67 ± 13
History of pulmonary embolism in the 5 years preceding diagnosis	97%	87%	90%
Hemodynamic measurements			
Mean pulmonary artery pressure (mmHg)	45 ± 11	41 ± 11	42 ± 11
Right atrial pressure (mmHg)	7 ± 5	8 ± 6	8 ± 5
Pulmonary artery wedge pressure (mmHg)	9 ± 4	9 ± 4	9 ± 4
Cardiac index (L/min/m)^2	2.3 ± 0.5	2.3 ± 0.6	2.3 ± 0.6
Pulmonary vascular resistance (Wood units)	8.6 ± 3.6	8.0 ± 4.4	8.1 ± 4.2
Echocardiography			
Right atrial area (cm)^2	26 ± 7	23 ± 8	24 ± 8
Pericardial effusion (%)	8.5%	8.4%	8.4%
Clinical status			
Body mass index (kg/m)^2	27 ± 5	27 ± 5	27 ± 5
WHO functional class, I/II/III/IV	19/76/3/2%	23/70/5/2%	22/72/4/2%
Six-minute walk distance (m)	372 ± 126	322 ± 134	337 ± 133

Note: Data presented as proportion (%) or mean ± SD.

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; WHO, world health organization.

non-PEA group. Diabetes was present in 10% of individuals in the non-PEA group and both control groups, and in 3% of the PEA group (Table 2).

HCRU

Over the entire study period, the mean number of hospitalizations per person and year was 5.4 times higher in the PEA group and 3.6 times higher in the non-PEA group compared to their control groups (Figure 1a, Supporting Information: Table S2a). The total mean number of days spent hospitalized was similar between the PEA and non-PEA groups (9.0 vs. 9.0 days; Supporting Information: Table 2c). However, in the PEA group the majority of hospitalizations (58%) occurred during the year before or after the index date, while in the non-PEA group only 40% of the hospitalizations occurred during the year before or after the index date (Supporting Information: Table S2a). Similar patterns were seen for the proportion of individuals with at least one hospitalization per year and mean number of days spent hospitalized per person and year (Figure 1b,c, Supporting Information: Tables S2b and S2c)

The mean number of outpatient visits per person and year during the full study duration was 2.9 times higher in the PEA and non-PEA groups compared to their matched control groups however, in the PEA group only the years around the index date reached a statistically significant difference (Figure 2a, Supporting Information: Table S3a). The mean number of outpatient visits per year over the entire study period was lower in the PEA than the non-PEA group (2.8 vs. 3.5 visits).

Drug utilization, measured as mean number of DDD per person and year, were 1.7 times higher in the PEA and non-PEA groups compared to their respective control groups when summarized over the 10-year study period (Figure 2b, Supporting Information: Table S4a). Total DDD was 33% higher and costs for drug treatment were 49% higher in the non-PEA group compared to the PEA group over the 10-year period (Supporting Information: Table S4b).

Sick leave and disability pension

For study participants eligible for sick leave and disability pension, the number of days with sick leave or disability pension per person and year were twice as high in the

TABLE 2 Characteristics at index date for PEA, non-PEA, and their matched control groups.

	PEA ($n = 109$)	Control ($n = 545$)	p Value	non-PEA ($n = 260$)	Control ($n = 1300$)	p Value
Age, years	62 ± 14	62 ± 14	0.987	69 ± 12	69 ± 12	0.989
Sex, male	64%	64%	1.000	43%	43%	1.000
Highest education level attained			0.538			0.133
Primary school	22%	28%		31%	32%	
Secondary school	56%	51%		49%	43%	
University (minimum 2 years)	22%	21%		19%	25%	
Missing values, (n)	5	22		24	90	
Main source of income[a]			<0.001			0.020
Work	26%	39%		12%	18%	
Disability pension	5%	2%		6%	2%	
Age pension	53%	53%		78%	76%	
Sickness benefit	13%	1%		2%	1%	
Other[b]	4%	4%		3%	3%	
Missing values, (n)	5	17		20	75	
Disposable annual income, k€[c]	20 (12)	20 (15)	0.391	17 (9)	18 (12)	0.208
Disposable annual family income, k€[c]	34 (35)	32 (32)	0.520	28 (24)	30 (29)	0.092
Cohabitation	60%	57%	0.648	54%	57%	0.381
Proportion with children living at home	22%	20%	0.670	9%	12%	0.247
Comorbidities present at any time during the 5-years before index date (ICD-10[d])						
Pulmonary emboli (I26.0, I26.9)	97%	1%	<0.001	87%	1%	<0.001
Essential (primary) hypertension (I10)	39%	19%	<0.001	50%	26%	<0.001
Diabetes (E10–E14)	3%	10%	0.016	10%	10%	1.000
Atrial fibrillation and flutter (I48)	8%	5%	0.140	13%	10%	0.158
Stroke (I61, I63, I64)	6%	2%	0.059	3%	3%	0.061
Ischemic heart diseases (I20–I25)	10%	10%	0.859	20%	10%	<0.001
Disorders of thyroid gland (E00–E07)	5%	3%	0.392	8%	6%	0.071
Acute kidney failure and chronic kidney disease (N17–N19)	2%	1%	0.196	7%	2%	<0.001

Note: Data presented as mean ± SD, proportion (%), number (n), or median (IQR).

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; IQR, interquartile range; PEA, pulmonary endarterectomy; SD, standard deviation; k€, thousand Euro.

[a]During the (calendar) year of diagnosis.

[b]Other: Student grants, reimbursement due to care of family member, unemployment benefits, unemployment program/training reimbursement, social security benefits, no known income.

[c]EUR exchange rate, mean 2021 = 10.4867kr/€uro.[26]

[d]ICD-10-SE, the National Board of Health and Welfare classifications of diseases.[20]

PEA group compared to their control group 2 years before the index date (71 vs. 33, $p = 0.024$, Figure 3, Supporting Information: Table S5a). Five years after the index date, days on sick leave or disability pension was 3.5 times higher in the PEA group compared to the control group (134 vs. 38, $p = 0.002$).

In the non-PEA group, already 5 years before index date, days with sick leave or disability pension per person

FIGURE 1 Healthcare resource utilization by hospitalizations. Graphs to the left show PEA versus controls and graphs to the right show non-PEA versus controls. (a) Mean number of hospitalizations per person and year (analysis includes only surviving patients with complete following data per year). (b) Proportion with at least one hospitalization per year. (c) Mean number of days spent hospitalized per person and year. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. PEA, pulmonary endarterectomy.

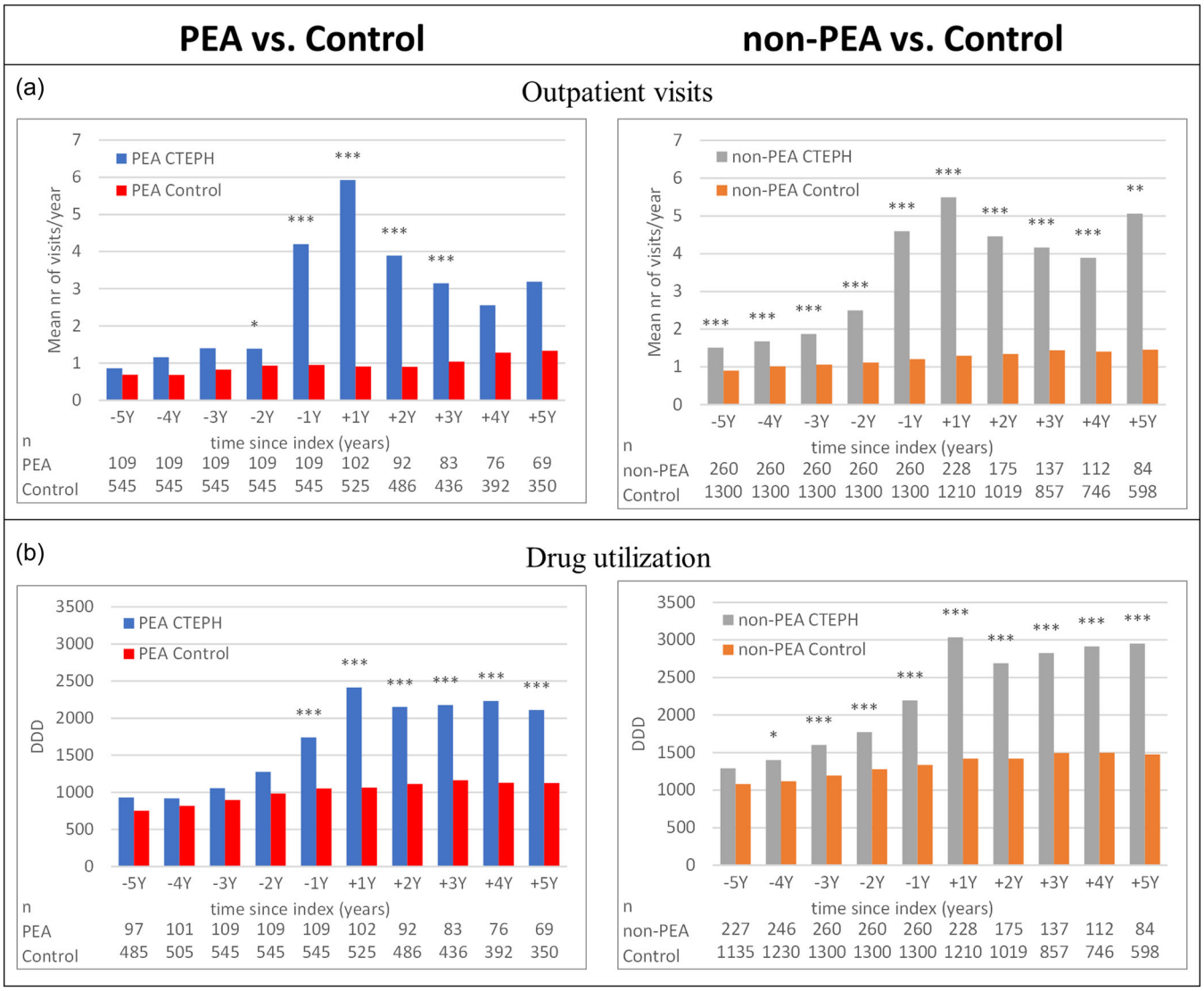


FIGURE 2 Healthcare resource utilization by outpatient visits and dispensed drugs (defined daily dose; DDD). Graphs to the left show PEA versus controls and graphs to the right show non-PEA versus controls. (a) Mean number of outpatient visits per person and year (analysis includes only surviving patients with complete following data per year). (b) Drug utilization, DDD of drugs per person, and year. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. PEA, pulmonary endarterectomy.

and year were twice as high as in the control group (108 vs. 57, $p = 0.002$; Figure 3, Supporting Information: Table S5a). Except for an increase in days with sick leave or disability pension the year before and the year after the index date in the non-PEA group, the difference between the non-PEA group and their controls were stable throughout the full, 10-year, study period.

Societal costs

The total societal costs for the PEA group and non-PEA group were twice as high, respectively, compared to their control groups over the 5-year period before the index date (Table 3). In the 5-year period after the index date, the societal costs had increased 4.0 times for the PEA group and 2.5 times for the non-PEA group compared to the 5 years before the index date. Total societal costs decreased in both control groups after the index date.

Before the index date, the main cost drivers in the PEA group were productivity loss and hospitalizations, constituting 61% and 26% of the total 5-year costs, respectively (Table 3). After the index date, costs for outpatient care had doubled with the main cost drivers being hospitalizations (37%), prescribed drugs (36%), and productivity loss (23%). Compared to their controls, productivity loss was 1.7 times higher in the PEA group before index and increased to 4.2 times higher after the index date.

In the non-PEA group the productivity loss (53%) was the main cost driver, followed by hospitalizations (29%)

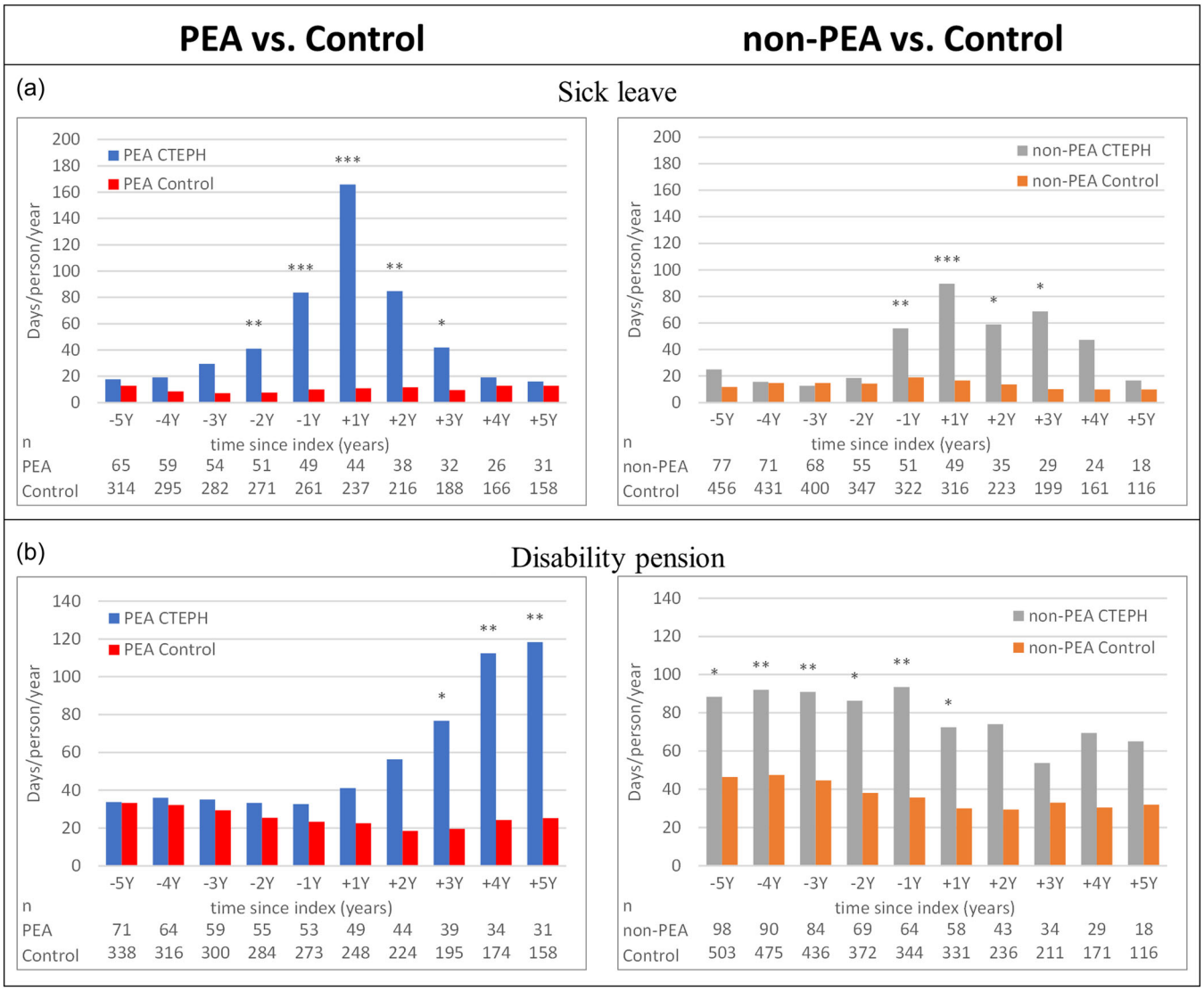


FIGURE 3 Productivity loss for individuals eligible for sick leave or disability pension, that is, not yet receiving age pension as main income. Graphs to the left show PEA versus controls and graphs to the right show non-PEA versus controls. (a) Sick leave, mean days per person, and year (full time equivalents), individuals on disability pension excluded. (b) Disability pension, mean days per person, and year (full time equivalents). ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. PEA, pulmonary endarterectomy.

during the 5 years before the index date. After the index date, costs for prescribed drugs constituted 62% of total costs while productivity loss and hospitalizations accounted for 13% and 19%, respectively. Productivity loss was 1.9 times higher in the non-PEA group compared to their controls before index and 2.7 times higher after the index date.

Mean survival

The 1, 3, and 5-year survival was 95%, 91%, and 88% in the PEA group and 98%, 95%, and 90% in the PEA matched control group (Figure 4). Corresponding numbers for the non-PEA group was 92%, 77%, and 62% and for their matched controls 98%, 93%, and 87%, respectively.

DISCUSSION

Direct and indirect societal costs were higher for patients with CTEPH compared to the age, sex, and geographic area matched control group. The higher costs were evident already several years preceding the index date. The main cost driver before the index date was productivity loss in both the PEA and the non-PEA groups. In the 5-year period following the index date,

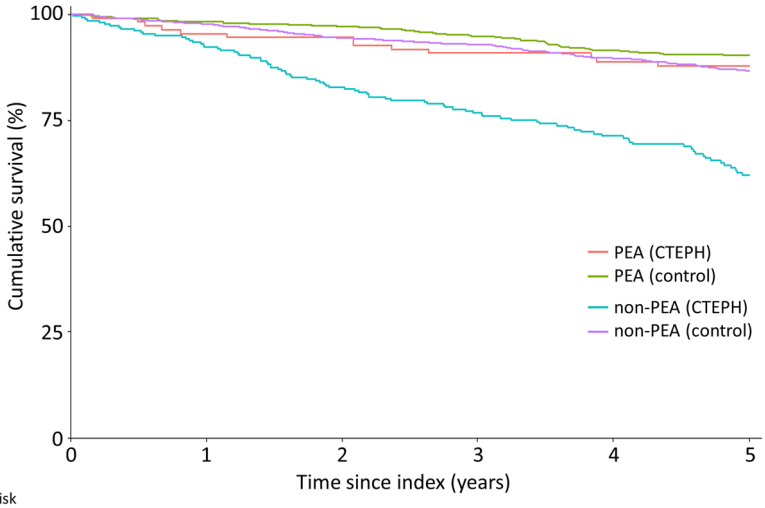
TABLE 3 Societal costs, estimated over the total 5-year period pre-index date and 5-year period post-index date data using the Zhao and Tian[24] estimator to adjust for censoring.

	Five-year period before index date			Five-year period after index date		
	PEA	**Control**	**Difference**	**PEA**	**Control**	**Difference**
Hospitalizations	11,626 (9289–13,964)	3065 (2384–3746)	8561 (6127–10,996)	67,175 (60,657–73,693)	5010 (3995–6024)	62,165 (55,568–68,761)
Outpatient care	3264 (2587–3940)	1438 (1242–1633)	1826 (1122–2530)	7339 (6541–8137)	1964 (1223–2705)	5375 (4286–6464)
Prescribed drugs	2776 (1957–3596)	1829 (1480–2177)	948 (57–1838)	64,516 (47,133–81,898)	2020 (1639–2402)	62,495 (45,109–79,882)
Total direct	17,666 (14,577–20,756)	6331 (5330–7332)	11,335 (8087–14,582)	139,029 (119,768–158,291)	8994 (7347–10,641)	130,035 (110,704–149,367)
Productivity loss[a]	27,877 (15,195–40,559)	16,404 (11,834–20,974)	11,473 (2007–24,953)	42,008 (25,664–58,352)	9991 (6232–13,750)	32,017 (15,247–48,788)
Total societal costs	45,543 (31,769–59,317)	22,735 (17,916–27,553)	22,808 (8 215–37,400)	181,038 (153,175–208,901)	18,985 (14,872–23,099)	162,052 (133,887–190,218)
	Five-year period before index date			**Five-year period after index date**		
	non-PEA	**Control**	**Difference**	**non-PEA**	**Control**	**Difference**
Hospitalizations	14,956 (12,894–17,019)	4909 (4315–5503)	10,047 (7901–12,193)	24,311 (19,680–28,942)	7107 (6282–7931)	17,204 (12,500–21,908)
Outpatient care	4396 (3891–4902)	1900 (1706–2094)	2496 (1955–3037)	7347 (6453–8241)	2202 (2000–2403)	5145 (4229–6061)
Prescribed drugs	4778 (3845–5711)	2469 (2131–2808)	2309 (1316–3301)	79,293 (67,974–90,612)	3548 (2938–4158)	75,745 (64,410–87,080)
Total direct	24,131 (21,322–26,939)	9279 (8406–10,152)	14,852 (11,911–17,793)	110,950 (97,149–124,752)	12,857 (11,641–14,072)	98,094 (84,239–111,948)
Productivity loss[a]	26,887 (18,069–35,705)	14,451 (11,625–17,276)	12,436 (3176–21,696)	16,607 (9472–23,743)	6266 (4176–8356)	10,342 (2907–17,777)
Total societal costs	51,018 (40,668–61,367)	23,729 (20,702–26,756)	27,288 (16,505–38,071)	127,558 (110,617–144,499)	19,122 (16,642–21,603)	108,435 (91,314–125,557)

Note: Data shown as mean (95% confidence interval), per patient, EUR (exchange rate, mean 2021 = 10.4867kr/€uro).[26]

Abbreviation: PEA, pulmonary endarterectomy.

[a]Sick leave and disability pension.



Number at risk						
PEA (CTEPH)	109	104	103	95	88	80
PEA (control)	545	535	529	499	453	413
non-PEA (CTEPH)	260	240	215	181	143	110
non-PEA (control)	1300	1270	1226	1108	925	780

FIGURE 4 Overall survival for the PEA and non-PEA groups and their matched control groups by Kaplan–Meier estimates for 5 years with follow-up from index date censored at the date of last contact or death. PEA, pulmonary endarterectomy.

productivity loss remained high for both groups, however, the main cost drivers were prescribed drugs and hospitalizations for patients in the PEA group and prescribed drugs in the non-PEA group.

The finding that direct societal costs were high for all patients after the CTEPH diagnosis (index date) compared to matched individuals without known CTEPH have been presented earlier.[7,27] However, direct and indirect costs during a 5-year period before the CTEPH diagnosis and indirect costs 5 years after diagnosis have not been shown earlier. Neither have, to the best of our knowledge, costs before and after the CTEPH diagnosis stratified for PEA surgery and compared to matched controls been presented earlier.

One previous study has estimated HCRU related costs for 12 months before and after a CTEPH diagnosis and compared to matched controls.[27] The differences in costs between patients and controls were substantially smaller than in the present study.[27] Since the earlier study, availability and use of costly treatments such as PEA, BPA, and CTEPH specific medical drugs have increased. This may explain the proportionally higher costs for hospitalizations and treatments for patients compared to controls in the present study. That their study population was identified from an insurance claim database, that is, both patients and controls had medical needs, might also have affected the costs.[27] A more recently published study including patients with CTEPH that were either inoperable or with persistent pulmonary hypertension after PEA, presented pulmonary hypertension specific treatments as the main cost driver after diagnosis,[7] which is similar to the non-PEA group in the present study.

HCRU in the non-PEA group was increased already 5 years before the index date compared to their control group, while in the PEA group, the HCRU started to diverge from their control group only 2 years before the index date. That a vast majority of the patients had a history of PE before CTEPH diagnosis likely contributed to these increased costs. This is further supported by the considerably longer time from the PE event to the CTEPH diagnosis in the non-PEA group compared to the PEA group. However, the higher pre-index HCRU in the non-PEA group compared to the PEA group was likewise reflected in their respective control groups. This suggests that age and subsequent comorbidities also contributed to this difference.[12]

In the year preceding the index date, the number of hospitalizations and outpatient visits increased rapidly, and to similar levels, for both the non-PEA and PEA groups. This increase was likely related to CTEPH symptoms, in line with previous reports showing a diagnostic delay of about 1 year for patients with CTEPH from symptom onset.[1,10] The increased HCRU before the CTEPH diagnosis, as well as a median elapsed time of more than a year between the PE and CTEPH diagnosis, further strengthens the notion that screening programs early after a PE are warranted.[11,27]

Screening programs are not implemented on a national level in Sweden, and thus, are unlikely to have contributed to the considerable higher proportion of patients with a history of a PE before CTEPH diagnosis in the present study than previously reported.[3,6] The study design, using data from national health registries with ICD-codes recorded at all hospital and specialist care visits likely revealed a higher number of patients with a

history of PE than studies using self-reporting, search in local hospital files or insurance claim databases. However, it is also likely that patients with unspecific symptoms like dyspnea and fatigue were underdiagnosed.[1,6,10,12] Post PE surveillance programs and a structured investigation of unexplained dyspnea might help to identify patients with CTEPH earlier.[11,28,29]

In the present study, the indirect cost for individuals eligible for sick leave or disability pension was higher in the patient groups than in the control groups, both before, as well as after the index date. Trends in number of days on sick leave and disability pension in the PEA group corresponds well to their trends in HCRU. Sick leave starts to be higher than controls 2 years before the index date and remains high until 3 years after index, when the number of days with disability pension increase. This shift from being on sick leave to receiving disability pension in the PEA group is likely related to the Swedish Social Insurance system that limits time on sick leave. Patients not expected to be able to return to work before age pension, are eligible to apply for disability pension. In the non-PEA group the pattern is reversed, where higher numbers of days on disability pension than controls was seen before the index date and more days on sick leave after index. This can likely be attributed to age related retirement from work at time of, or shortly after, the CTEPH diagnosis in the non-PEA group.

The 5-year survival rate for the PEA group was similar to their matched controls indicating that the PEA surgery, with or without subsequent disease specific treatment, more or less normalizes the survival rate for at least 5 years after the CTEPH diagnosis. Interestingly, the control group matched for the non-PEA patients had a similar survival rate as the PEA group, despite the mean age being 7 years higher. In contrast, survival in the non-PEA group remain poor. However, results in the present study suggest that there is room for improvement. While the history of a PE was high in both CTEPH groups, the non-PEA group had longer time from PE to CTEPH diagnosis than the PEA group and, compared to other reports, PEA was underutilized in the present study population.[2] Taken together, these notions suggest room for earlier detection of CTEPH, which might also identify more patients eligible for PEA and likely save lives, decrease suffering and lower societal costs.

In the present study new and important knowledge of how the burden of CTEPH affects the healthcare system, the society, and the patients with CTEPH have been revealed. However, for a better understanding on how this burden can be reduced, further and more detailed studies of direct and indirect costs are warranted.

Strengths of the present study are the system of tax funded national healthcare, social insurance, and pension systems in Sweden, where data is retained in registries available for research. This system provides a high national coverage and also makes it possible to create an age, sex, and geographically matched control group with five controls per patient. The high national coverage in SPAHR of patients diagnosed with CTEPH was made possible by all PAH/CTEPH-specialist centers in Sweden participating in SPAHR. Another strength was the inclusion of only incident patients with a confirmed diagnosis of CTEPH as well as providing indirect costs such as sick leave, disability pension, and the related productivity loss.

Limitations of the present study include censoring of data from patients with short follow up time due to being diagnosed late in the study period and that primary care was not included in the HCRU. Limiting the HCRU analyses to living and non-censored individuals, might have induced a bias toward individuals diagnosed with CTEPH early in the data collection period.

In conclusion, CTEPH was associated with large societal costs related to healthcare consumption and productivity loss, both before and after diagnosis. Strategies for earlier diagnosis of CTEPH are called for to alleviate the burden for CTEPH patients and possibly enable PEA for a larger part of the patient group.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Barbro Kjellström, Hannes Runheim, Magnus Husberg, 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.

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participated in study design, interpretation of data and drafting the manuscript, but did not participate in data analyses. Additional funding was received in terms of a scholarship from SveFPH/SPAHR. Lund University, Lund, Sweden is the guarantor.

CONFLICTS OF INTEREST STATEMENT

Amélie Beaudet and Nadia Pillai are employees of Actelion Pharmaceuticals, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

ETHICS STATEMENT

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

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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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