DOI: 10.1002/pul2.12038

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Epidemiology of chronic thromboembolic pulmonary hypertension (CTEPH) in the Czech Republic

Pavel Jansa[1] | **David Ambrož**[1] | **Matyáš Kuhn**[2] | **Vladimír Dytrych**[1] | **Michael Aschermann**[1] | **Vladimír Černý**[3] | **Virginie Gressin**[4] | **Samuel Heller**[1] | **Jan Kunstýř**[5] | **Michal Širanec**[1] | **Ci Song**[6] | **Aleš Linhart**[1] | **Jaroslav Lindner**[7] | **Audrey Muller**[4]

[1]2nd Department of Medicine, Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[2]Data Analysis Department, Institute of Biostatistics and Analysis, Brno, Czech Republic

[3]Department of Radiology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[4]Actelion Pharmaceuticals Ltd., Allschwil, Switzerland

[5]Department of Anesthesiology and Intensive Care, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[6]Janssen Pharmaceutical Companies of Johnson & Johnson, Solna, Sweden

[7]2nd Department of Surgery, Department of Cardiovascular Surgery, Charles University and General University Hospital, Prague, Czech Republic

Correspondence
Pavel Jansa, 2nd Department of Medicine, Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital, Prague 128 08, Czech Republic.
Email: pavel.jansa@vfn.cz

Funding information
Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, a Janssen pharmaceutical company of Johnson and Johnson

Abstract

This study investigated the epidemiology and survival outcomes of chronic thromboembolic pulmonary hypertension (CTEPH) in the Czech Republic, wherein pulmonary endarterectomy (PEA) surgery was the only targeted treatment option until 2015. This study included all consecutive adults newly diagnosed with CTEPH in the Czech Republic between 2003 and 2016. Incidence/prevalence rates were calculated using general population data extracted from the Institute of Health Information and Statistics of the Czech Republic. Kaplan–Meier estimates of survival from diagnosis until 2018 were calculated. Of a total of 453 patients observed, 236 (52.1%) underwent PEA (median time from diagnosis to PEA: 2.9 months) and 71 (34.1%) had residual pulmonary hypertension (PH) post-PEA. CTEPH incidence rate (95% confidence interval [CI]) between 2006 and 2016 was 4.47 (4.05; 4.91) patients per million (ppm) per year, and the prevalence (95% CI) was 37.43 (33.46; 41.73) ppm in 2016. The rate of CTEPH-related hospitalizations (95% CI) per 100 person-years was 24.4 (22.1; 26.9) for operated patients and 34.2 (30.9; 37.7) for not-operated patients. Median overall survival (95% CI) for all patients from CTEPH diagnosis was 11.2 (9.4; not reached) years. Five-year survival probability (95% CI) was 95.3% (89.9; 97.9) for operated patients without residual

PH, 86.3% (75.3; 92.7) for operated patients with residual PH and 61.2% (54.0; 67.6) for not-operated patients. This study reported epidemiological estimates of CTEPH in the Czech Republic consistent with estimates from other national systematic registries; and indicates an unmet medical need in not-operated patients and operated patients with residual PH.

KEYWORDS
hospitalization, incidence, prevalence, pulmonary endarterectomy survival, survival

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and severe progressive pulmonary vascular disease, often resulting from a complication of acute pulmonary embolism (PE).[1] The exact global incidence and prevalence of CTEPH are unknown and the latest country-specific estimates vary. A recent critical appraisal of published epidemiology estimates of CTEPH reported that the range of published estimates was large for both incidence (0.9–39 patients per million [ppm] per year) and prevalence (14.5–144 ppm) of CTEPH in adults.[2] This large range of estimates is partly due to the differences between the study designs and healthcare systems.[2] Additional studies with high national coverage are required to further describe the epidemiology of CTEPH.

If left untreated, CTEPH is associated with poor survival.[1] Pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH. For the majority of patients eligible for this surgery, it provides considerable relief from symptoms, hemodynamic improvement, and lowers mortality risk.[3,4] However, up to 40% of patients with CTEPH cannot benefit from PEA, mostly because of the distal location of the thrombotic material (termed technically inoperable patients), or because of an unfavorable benefit-risk ratio as well as patient refusal (termed medically inoperable patients hereafter).[5–7] New treatment options have emerged in the past decade for patients with inoperable CTEPH or residual pulmonary hypertension (PH) following PEA.[8–10] This includes balloon pulmonary angioplasty (BPA), which was established in Japan and subsequently introduced to other countries, including Germany in 2013 and France in 2014.[5,11–15] The efficacy and safety of BPA has improved since its introduction as a result of advances in technique and centers becoming more experienced in the procedure.[16–18] Two medications received regulatory approval for CTEPH in the last decade.[19–21] Only one of those (riociguat) is currently widely available, but pulmonary arterial hypertension medications have often been prescribed off-label, particularly before the introduction of riociguat.[22] Riociguat is an oral, soluble guanylate cyclase stimulator which is approved in many countries for the treatment of CTEPH in adults (with approval in Europe since 2014)[9,10,20,21] and subcutaneous treprostinil, a prostacyclin analogue, was approved in Europe in 2020 for the treatment of patients with inoperable or persistent/recurrent CTEPH after PEA.[19,23] Multimodal treatment, an integrated approach that combines surgical, interventional and medical therapy, is a recent development in the management of CTEPH.[8,9] This approach is recommended by The European Society of Cardiology/European Respiratory Society (ESC/ERS) 2015 guidelines,[3,4] and has been further reinforced by subsequent expert panels.[8,9] The treatment landscape for this rare disease is continually evolving, and real-world data are important for understanding its epidemiology and management.

Several aspects of CTEPH management in the Czech Republic make this a unique setting to study CTEPH and a valuable, exhaustive source of data to describe the natural history and epidemiology of the disease. In the Czech Republic, diagnosis and management of CTEPH are centralized in a single expert center in Prague; all patients with suspected CTEPH from across the country are referred to this center and receive a consistent approach to operability assessment and treatment decision by a unique multidisciplinary team. This national coverage allows the collection of comprehensive data on all CTEPH patients in the country. The only treatment option available to patients with CTEPH in the Czech Republic was PEA (introduced 2004)[24] until BPA was introduced in 2013 (with routine use from 2017 onward),[25] and riociguat became commercially available in the Czech Republic in 2015. Off-label use is not permitted in the Czech Republic, and unlicensed treatments are therefore only available through participation in clinical trials.

This study is based on a historical, observational cohort of all consecutive patients diagnosed with CTEPH in the Czech Republic between 2003 and 2016, a time period in which PEA was the only treatment option for the vast majority of patients. As such, it provides an opportunity to

describe the natural history of the disease and outcomes for both operated and not-operated patients. Specifically, it describes the clinical characteristics at diagnosis, treatment patterns as per routine care practice, hospitalization, and survival according to patients' operability status.

METHODS

Study design

This was a noninterventional, historical, cohort study observing adult (aged ≥ 18 years) patients newly diagnosed with CTEPH at the Prague General University Hospital between January 1, 2003, and December 31, 2016. The observation period for each patient lasted from the time of CTEPH diagnosis to the earliest of death or December 31, 2018, data cut-off.

The study was approved by the Prague General University Hospital's research ethics committee. As this study was based on retrospective and deidentified data, no informed consent was required from individual patients.

Patient population

The criteria for the diagnosis of CTEPH were according to the latest PH guidelines:[3,4] mean pulmonary arterial pressure ≥25 mmHg, mismatched perfusion defects on lung ventilation perfusion scintigraphy, and diagnostic signs for CTEPH on multidetector CT angiography and conventional pulmonary angiography.

Patients' operability status (PEA) was determined at diagnosis by an interdisciplinary team consisting of a PEA surgeon, PH specialist, cardiac anesthesiologist, and radiologist. Patients in this study were categorized into subgroups as operated (those who underwent PEA surgery during the observation period) or not-operated. Operated patients were further categorized according to their residual PH status (as determined by echocardiographic estimation of pulmonary artery systolic pressure ≥40 mmHg at 6 months post-PEA with subsequent confirmation of residual PH by right heart catheterization parameters, and defined as mean pulmonary artery pressure ≥25 mmHg and pulmonary vascular resistance [PVR] > 3 Wood units) into the subgroups: residual PH, no residual PH, and not assessed (due to death within the first 6 months post-PEA). Not-operated patients were further classified into: technically inoperable (due to distal disease) and medically inoperable (due to comorbidities or patient refusal). The vast majority of patients were not medically treated during the observation period (as off-label use is not permitted), hence patients were not grouped according to whether they received PH treatment.

DATA COLLECTION

Patient demographics (age, sex) and clinical characteristics at diagnosis (time from first PE to diagnosis, medical history of venous thromboembolism and PE, functional status, brain natriuretic peptide levels, and hemodynamics) were collected from patients' medical charts at Prague General University Hospital, along with patients' treatments during the observation period (administration of PH-specific medication, PEA and BPA). Vital status and hospitalizations data during the observation period were extracted from national databases led by the Institute of Health Information and Statistics of the Czech Republic (IHIS CR).[26] The date and cause of death were extracted from the Czech Republic national death register.[26] CTEPH-related hospitalizations were defined as hospitalizations that were nonelective and were identified based on the International Statistical Classification of Diseases codes listed in Table S1. Each reason (ICD code) was reviewed and adjudicated by the first author of this manuscript to ensure CTEPH-related hospitalizations were correctly identified. CTEPH diagnosis and treatment-related hospitalizations (i.e., due to PEA, BPA, or clinical trial participation), were not considered CTEPH-related.

For calculation of incidence, prevalence, and standardized mortality ratio (SMR), aggregated data on the Czech general adult population were extracted from the Czech Statistical Office database[27,28]; demographic data for the study population were obtained from the IHIS CR.[26] For context, the general adult population of the Czech Republic recorded in 2016 was 8.7 million people.[27]

Statistical analyses

Descriptive statistics were used for patient demographics, clinical characteristics, and clinical outcomes. Categorical variables were summarized using counts and percentage, and continuous variables using median (range or interquartile range [IQR]) values. The number of patients with available data (n) was used as the denominator in the calculation of summary statistics.

The incidence rate was calculated by dividing the number of incident patients by the total number of adults in the Czech Republic in each year and then obtaining an average incidence rate between 2006 and 2016. Point prevalence was calculated using the number of incident patients between 2006 and 2016. The confidence intervals

(CIs) were estimated on the assumption that the number of newly diagnosed patients in each year followed a Poisson distribution.

Hospitalization rates were calculated by dividing the number of hospitalizations by the total time at risk. The CI's were estimated from the Poisson distribution.

Kaplan–Meier overall survival probability estimates from time of diagnosis were used to perform survival analyses for each group and subgroup. Median overall survival and 95% CIs were calculated, as well as 5-year survival probabilities. SMR was standardized to the general population by sex and age.

RESULTS

Patient distribution

A total of 453 patients were diagnosed in Prague General University Hospital between January 1, 2003, and December 31, 2016. During the observation period (median of 6.1 [range: 0; 16] years), 52.1% ($n = 236$) of patients underwent PEA surgery (operated patients) (Figure 1), with a median time from diagnosis to PEA of 2.9 (range: 0.0; 101.2 and IQR: 2.0; 4.7) months. Of those, 208 patients were assessed for residual PH 6 months post-PEA, the majority of which (65.9%, $n = 137$) had no residual PH. Residual PH status was not assessed for 28 patients due to two patients not being under center care after PEA and 26 patients who died within 6 months of PEA.

Of the 217 patients who did not undergo PEA surgery (not-operated patients), the main reason (129 patients [59.4%]) was the distal nature of the disease (technically inoperable patients) (Figure 1). Among the 88 medically inoperable patients, 38 (43.2%) were considered unfit for surgery following multidisciplinary assessment, 22 (25.0%) had other contributors to symptoms in addition to clot burden, 16 (18.2%) chose to decline the surgery, and the reason for the decision was not clear for 12 (13.6%) patients.

In terms of other treatments, 22 patients underwent the BPA procedure (mostly at the end of the observation period) and 123 patients were treated with PH-specific therapies, with 71 patients receiving treatment through participation in clinical trials (CHEST-1; NCT00855465, BENEFIT; NCT00313222, CTREPH; NCT01416636), and 52 receiving commercial riociguat (early experience available between 2015 and cut-off 2018). Of the 86 patients who received riociguat at any time during the 2003–2018 observation period, 27 were in the operated group (26 had residual PH and 1 had no residual PH) and 59 were in the not-operated group (49 technically inoperable; 10 medically inoperable).

Clinical characteristics at diagnosis

Of the 453 patients included in total, 45.5% were female and the median age at diagnosis was 65.2 (range: 19; 85) years. Overall, 78.1% of patients had a history of PE and the median time to diagnosis of CTEPH from first PE was 2.2 years. In total, 43.2% of women underwent PEA compared with 59.5% of men. Of those who did not have surgery, 58.0% of men and 60.7% of women were technically inoperable (Table 1).

The majority of patients had severe disease at diagnosis; approximately 90% were in New York Heart Association functional class (NYHA FC) III/IV (Tables 1 and 2). Among the 444 patients with available data, the three most common

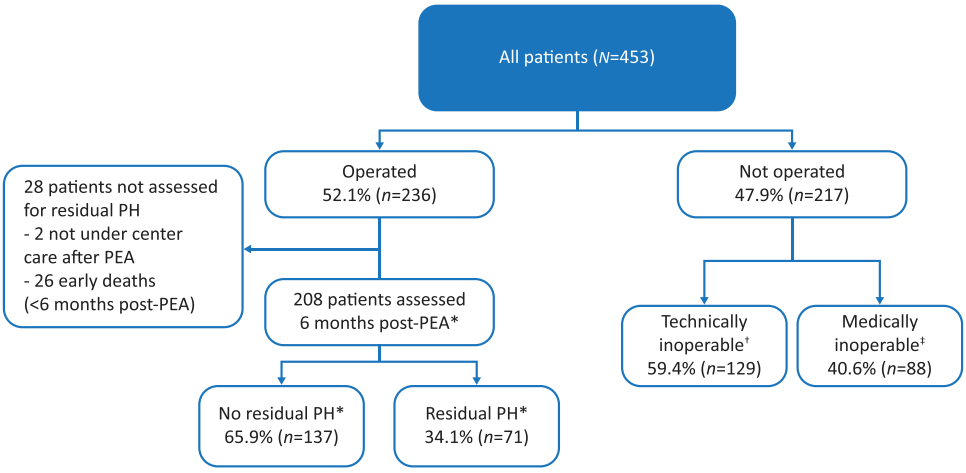


FIGURE 1 Patient disposition. *Residual PH was determined by echocardiographic estimation of pulmonary artery systolic pressure (≥40 mmHg) followed by subsequent confirmation by RHC. †Due to distal disease. ‡Due to comorbidities or refusal. *N*, total number of patients; *n*, number of patients; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; RHC, right heart catheterization

TABLE 1 Patient demographics and disease characteristics at diagnosis

Parameter	All, $N = 453$	Operated, $N = 236$	Not-operated		
			Overall not-operated, $N = 217$	Technically inoperable, $N = 129$	Medically inoperable, $N = 88$
Age, years, median (range)	65.2 (19; 85)	62.2 (21; 81)	69.9 (19; 85)	70.6 (19; 83)	67.9 (26; 85)
Sex, *n* (%), female	206 (45.5)	89 (37.7)	117 (53.9)	71 (55.0)	46 (52.3)
DVT history, *n* (%)	186 (41.9)	99 (42.5)	87 (41.2)	45 (35.4)	42 (50.0)
PE history, *n* (%)	354 (78.1)	190 (80.5)	164 (75.6)	94 (72.9)	70 (79.5)
Time from first PE to diagnosis, years, median (range)	2.2 (0; 43)	2.4 (0; 43)	2.0 (0; 42)	2.1 (0; 31)	1.9 (0; 42)
NYHA FC, *n*	437	234	203	115	88
FC I/II, *n* (%)	36 (8.3)	22 (9.4)	14 (6.9)	4 (3.5)	10 (11.3)
FC III/IV, *n* (%)	401 (91.8)	212 (90.6)	189 (93.1)	111 (96.5)	78 (88.6)
Median (range) 6MWD, *m* [*n*]	335.5 (40; 645) [372]	344.0 (106; 645) [206]	321.0 (40; 627) [166]	322.5 (40; 627) [94]	319.5 (50; 605) [72]
RHC, median (range)					
mPAP, mmHg [*n*]	48.0 (11; 91) [439]	51.0 (11; 87) [228]	43.0 (17; 91) [211]	44.0 (21; 91) [123]	43.0 (17; 73) [88]
PVR, dyn × s/cm^5 [*n*]	684.0 (83; 2197) [436]	756.8 (83; 2197) [228]	594.0 (112; 1723) [208]	607.2 (112; 1723) [121]	584.8 (133; 1525) [87]
CI, L/min/m^2, [*n*]	2.2 (1; 5) [429]	2.1 (1; 4) [223]	2.3 (1; 5) [206]	2.2 (1; 5) [120]	2.3 (1; 4) [86]
Median (range) BNP, pg/ml [*n*]	204.0 (10; 4828) [196]	254.5 (14; 4828) [94]	159.0 (10; 1531) [102]	197.0 (10; 1531) [55]	151.0 (11; 1526) [47]
Anticoagulation, *n*	446	233	213	127	86
NOAC, *n* (%)	13 (2.9)	4 (1.7)	9 (4.2)	5 (3.9)	4 (4.7)
Other anticoagulants, *n* (%)	433 (97.1)	229 (98.3)	204 (95.8)	122 (96.1)	82 (95.3)

Note: The number of patients with data available for a variable is those for the overall population and subgroups described in Figure 1.

Abbreviations: 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; CI, cardiac index; DVT, deep vein thrombosis; ESC, European Society of Cardiology; ERS, European Respiratory Society; mPAP, mean pulmonary artery pressure; *N*, number of patients; NOAC, non-vitamin K antagonist oral anticoagulants; NYHA FC, New York Heart Association functional class; PE, pulmonary embolism; PVR, pulmonary vascular resistance; RHC, right heart catheterization.

TABLE 2 Demographics and disease characteristics at diagnosis of operated patients ($N = 236$) according to residual PH status post-PEA

Parameter	PH not assessed, $N = 28$	No residual PH, $N = 137$	Residual PH, $N = 71$
Age, years	63.2 (49; 77)	58.6 (21; 81)	66.2 (24; 77)
Sex, *n* (%), female	9 (32.1)	44 (32.1)	36 (50.7)
DVT history, *n* (%)	8 (30.8)	58 (42.6)	33 (46.5)
PE history, *n* (%)	19 (67.9)	112 (81.8)	59 (83.1)
Time from first PE to diagnosis, years	4.5 (0; 40)	1.5 (0; 36)	3.5 (0; 43)
NYHA FC, *n*	27	137	70
FC I/II, *n* (%)	2 (7.4)	15 (10.9)	5 (7.1)
FC III/IV, *n* (%)	25 (92.6)	122 (89.1)	65 (92.9)
6MWD, *m* [*n*]	307.0 (106; 536) [24]	359.5 (150; 645) [116]	313.5 (133; 600) [66]
RHC at diagnosis			
mPAP, mmHg [*n*]	50.0 (34; 81) [26]	50.0 (11; 79) [133]	52.0 (32; 87) [69]
PVR, dyn × s/cm^5 [*n*]	682.4 (244; 2197) [26]	727.6 (83; 1914) [132]	810.8 (286; 1688) [70]
CI, L/min/m^2 [*n*]	2.1 (1; 4) [26]	2.1 (1; 4) [128]	2.1 (1; 4) [69]
BNP, pg/ml [*n*]	444.5 (40; 2000) [12]	195.0 (14; 1699) [55]	285.0 (39; 4828) [27]

Note: Unless specified otherwise, data are presented as median (range) and the number of patients with data available for a variable is those for the overall population and subgroups described in Figure 1.

Abbreviations: 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; CI, cardiac index; DVT, deep vein thrombosis; ESC, European Society of Cardiology; ERS, European Respiratory Society; mPAP, mean pulmonary artery pressure; *N*, number of patients; NYHA FC, New York Heart Association functional class; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization.

comorbidities were ischemic heart disease (14.6% of operated and 23.2% of not-operated patients), chronic obstructive pulmonary disease (11.2% of operated and 12.3% of not-operated), and diabetes (5.2% of operated and 13.7% of not-operated patients). All patients (with data available) were taking or had taken, anticoagulants at the time of diagnosis. The vast majority (83.6%) were treated with vitamin K antagonists, with only a small proportion taking new oral anticoagulants (non-vitamin K antagonist oral anticoagulant [NOAC]) (2.9%) or other anticoagulants (13.5%).

Epidemiology estimates

The incidence rate of CTEPH in the Czech Republic (95% CI) between 2006 and 2016 was 4.47 (4.05; 4.91) ppm per year, and the prevalence was 37.43 (33.46; 41.73) ppm in 2016.

Hospitalizations

From CTEPH diagnosis, there were 2705 all-cause hospitalization events, during a median observation time of 6.1 (range: 0, 16) years (Table 3); of these, 803 (29.7%) were CTEPH-related. The rate of CTEPH-related hospitalizations (95% CI) per 100 person-years was 24.4 (22.1; 26.9) for operated patients and 34.2 (30.9; 37.7) for not-operated patients.

Underlying disease was the most common reason for CTEPH-related hospitalizations, with CTEPH and heart failure being the reason for 490 (61.0%) and 186 (23.2%) of CTEPH-related hospitalizations. During the observation period (median of 6.1 years), patients experienced a median (range) of 1.0 (0; 13) CTEPH-related hospitalizations, with 48.3% of patients reported to have had 1–3 hospitalizations, 10.8% with 4–6 hospitalizations and 4.6% of patients experiencing more than six hospitalizations.

SURVIVAL

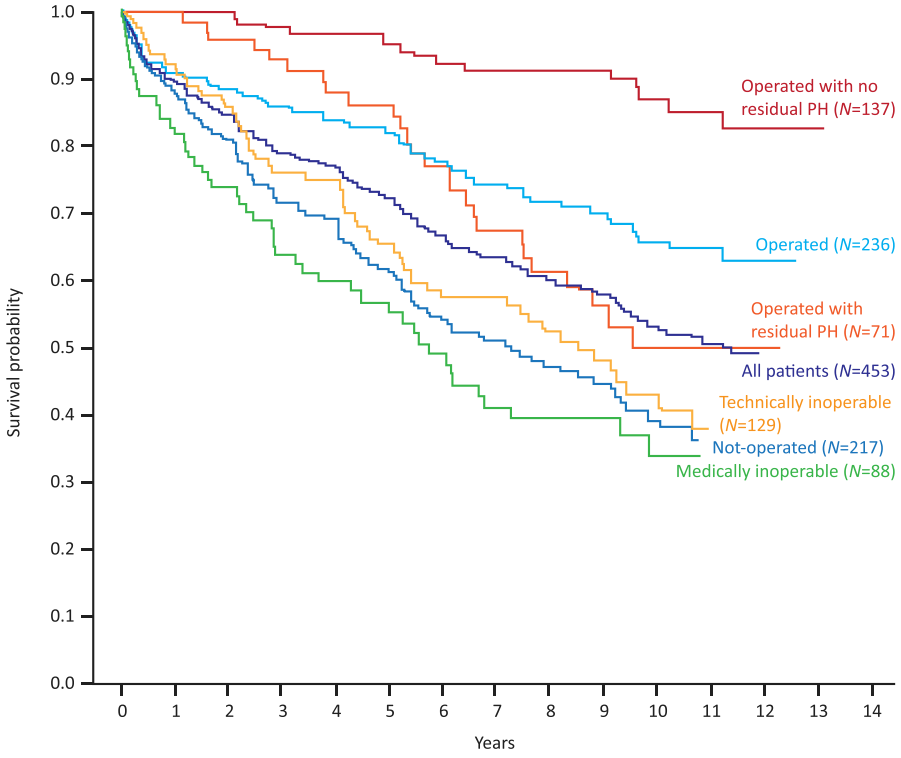
Overall survival for patients across the observation period is shown in Figure 2. The median overall survival (95% CI) for all patients from CTEPH diagnosis was 11.2 (9.4; not reached) years. The survival median was reached close to the end of follow-up, so the upper confidence limit for the overall survival of all patients from CTEPH diagnosis was unable to be estimated, hence the not

TABLE 3 Hospitalizations during the observation period (2003–2018)

Parameter	All patients, $N = 453$	Operated, $N = 236$	Not-operated		
			Not-operated, $N = 217$	Technically inoperable, $N = 129$	Medically inoperable, $N = 88$
Hospitalization events, *n*	2705	1531	1174	759	415
CTEPH-related[a], *n* (%)	803 (29.7)	408 (26.6)	395 (33.6)	245 (32.3)	150 (36.1)
Treatment-related, *n* (%)	419 (15.5)	274 (17.9)	145 (12.4)	123 (16.2)	22 (5.3)
Not-related, *n* (%)	1483 (54.8)	849 (55.5)	634 (54.0)	391 (51.5)	243 (58.6)
All-cause hospitalizations					
Hospitalization rate (95% CI), per 100 person-years	95.7 (92.1; 99.3)	91.6 (87.1; 96.3)	101.5 (95.8; 107.5)	102.5 (95.3; 110.1)	99.9 (90.5; 109.9)
Most common (≥5% in any subgroup) reasons for hospitalizations, *n* (%)					
CTEPH	620 (22.9)	319 (20.8)	301 (25.6)	220 (29.0)	81 (19.5)
PEA or BPA	277 (10.2)	243 (15.9)	34 (2.9)	25 (3.3)	9 (2.2)
Heart failure	186 (6.9)	62 (4.0)	124 (10.6)	66 (8.7)	58 (14.0)
Infection	146 (5.4)	76 (5.0)	70 (6.0)	47 (6.2)	23 (5.5)
Arrhythmia	134 (5.0)	83 (5.4)	51 (4.3)	27 (3.6)	24 (5.8)
Injury (not related to PEA surgery)	110 (4.1)	49 (3.2)	61 (5.2)	28 (3.7)	33 (8.0)
CTEPH-related hospitalizations					
Rate of hospitalization visits—rate (95% CI), per 100 person-years	28.4 (26.5; 30.4)	24.4 (22.1; 26.9)	34.2 (30.9; 37.7)	33.1 (29.1; 37.5)	36.1 (30.5; 42.4)
Most common (≥5% in any subgroup) reasons for hospitalizations, *n* (%)					
CTEPH[a]	490 (61.09)	288 (70.4)	202 (51.1)	133 (54.3)	69 (46.0)
Heart failure	186 (23.2)	62 (15.2)	124 (31.4)	66 (26.9)	58 (38.7)
Respiratory failure	45 (5.6)	18 (4.4)	27 (6.8)	18 (7.3)	9 (6.0)

Abbreviations: BPA, balloon pulmonary angioplasty; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; *N*, number of patients; PE, pulmonary embolism; PEA, pulmonary endarterectomy.

[a]CTEPH-related hospitalizations were defined as hospitalizations that were nonelective and were identified based on the ICD codes listed in Table S1. CTEPH diagnosis and treatment-related hospitalizations (i.e., due to PEA, BPA, or clinical trial participation), were excluded. Any other hospitalizations that were not CTEPH- or treatment-related were classified as "not-related."



All patients	453	406	385	335	300	265	227	197	157	132	96	60	
Operated	236	215	209	197	175	160	137	123	98	84	65	45	21
No residual PH	137	137	137	131	121	110	95	88	71	65	51	34	22
Residual PH	71	71	68	63	52	49	41	34	27	19	14	11	9
Not-operated	217	191	176	138	125	105	90	74	59	48	31		
Technically inoperable	129	119	111	90	84	69	58	49	39	32	19		
Medically inoperable	88	72	65	48	41	36	32	25	20	16	12		

FIGURE 2 Overall survival by subgroups. Overall survival was calculated for the observation period lasting from January 1, 2003, to December 31, 2018, data cut-off. *N*, number of patients; PH, pulmonary hypertension

reached value. Five-year survival probability (95% CI) was 82.2% (76.5; 86.5) for operated patients; 95.3% (89.9; 97.9) for patients with no residual PH; 86.3% (75.3; 92.7) for patients with residual PH; 61.2% (54.0; 67.6) for not-operated patients; 65.3% (56.0; 73.2) for technically inoperable patients; and 55.2% (43.6; 65.4) for medically inoperable patients. For patients in whom residual PH could not be assessed as a result of death within 6 months post-PEA, the five-year survival probability was 5.4% (95% CI: 0.5; 20.0). The 1-, 3-, and 10-year survival probabilities (95% CI) for all patients were 89.6% (86.4; 92.1), 79.1% (75.0; 82.5), and 53.3% (47.7; 58.6), respectively. The most common cause of death among all patients was underlying disease (33.0%), followed by ischemic heart disease (13.7%). Of the 26 patients who died within 6 months of PEA, the reasons for death included: underlying disease (65.4%), heart failure (11.5%), infection (7.7%), other (7.7%), arrhythmia (3.8%), and renal failure (3.8%). Overall, patients diagnosed with CTEPH between 2006 and 2016 had a 2.37-fold higher mortality rate compared with the general population of the same age and sex (SMR [95% CI]: 2.37 [1.98; 2.76]). For operated and not-operated patients, this rate was 1.91 (1.41; 2.42) and 2.80 (2.21; 3.40), respectively.

DISCUSSION

This study provides insights into the epidemiology of CTEPH in the Czech Republic between 2003 and 2016, using the unique national expert center that systematically records all CTEPH cases in the country. Over this time, 453 patients were diagnosed and 236 (52.1%) patients underwent PEA, with 71 (34.1%) having residual PH following surgery. Hospitalization rates and survival were observed during a period in which PEA was predominantly the only targeted treatment option (until 2015) and grouped according to operability status. Five-year survival probability was highest for operated patients without residual PH (95.3%), followed by operated patients with residual PH (86.3%), and was lowest for patients who were not-operated (61.2% overall).

The outcomes described herein were observed in a centralized model of PH care, which is in line with the guideline recommendations to refer all patients with suspected CTEPH to expert centers.[3,4,9] As a result, all patients receive a confirmed diagnosis and are able to discuss treatment options with a multidisciplinary team consisting of a PEA surgeon, PH specialist, cardiac anesthesiologist, and a radiologist with expertise in CTEPH. This ensures a robust clinical assessment, allowing all patients who could benefit from PEA to undergo the operation.[3,4,9] This study observed a median time from diagnosis to PEA of 2.9 (IQR: 2.0; 4.7) months, which is similar to or shorter than reports from other countries. In the United Kingdom (2018/2019 PH audit), the median wait-time between initial CTEPH diagnosis and PEA was approximately 6 months,[29] and in the International registry, wait-time ranged from less than 1 month up to almost 4 months.[7]

It should be noted that medical therapy was used for very few patients in the present study, and the initiation of medication can sometimes delay PEA,[30,31] hence this could possibly be part of the reason for the relatively short wait-time reported here. Altogether, study findings are broadly in line with previous reports that found centralized CTEPH care to be associated with better outcomes than a decentralized system.[32,33] Further investigation into the optimal healthcare model is needed.

Importantly, the centralized management of CTEPH in the Czech Republic provides the rare advantage of complete national coverage and thus accurate epidemiology estimates. The 2006–2016 incidence rate (95% CI) of CTEPH was 4.47 (4.05; 4.91) ppm per year and the prevalence of CTEPH in 2016 was 37.43 (33.47; 41.73) ppm. These findings are consistent with estimates from other European registries with similar designs, namely national registries with systematic enrollment of patients in a country with a centralized healthcare system.[2] This includes the United Kingdom and Swedish registries, which estimate annual incidence to be 3.1–6.0 ppm and prevalence to be 25.8–38.4 ppm.[2] This study, therefore, adds to the authoritative epidemiology estimates provided by "systematic" registries with national coverage.[2] The prevalence of CTEPH reported in this study is still likely to be a conservative estimate, given the evidence that CTEPH is often mistaken for PE,[8,34,35] and therefore, not all cases may reach the expert center for diagnosis. While further efforts are required to better characterize patients at risk of CTEPH and identify suspected CTEPH cases, the epidemiological estimates from systematic registries remain the most reliable estimates available.[2]

Clinical characteristics at diagnosis were also generally consistent with those from previous studies. For example, the percentage of patients with a history of PE or deep vein thrombosis (DVT) was 78.1% and 41.9%, respectively, which is similar to the findings of an international CTEPH registry.[7] Operated patients were younger than the not-operated group (median: 62.2 vs. 69.9 years), had a higher percentage of males (62.3% vs. 46.1%), and a higher median pulmonary arterial pressure (48.0 vs. 43.0 mmHg). These demographic data at diagnosis are also in line with the first international registry findings in operable and nonoperable patients (median age of 61 vs. 67 years, and 53.4% vs. 44.5% males).[7] The present study reported that 43.2% of women underwent PEA compared with 59.5% of men. The reasons for not being operated were similar for women (60.7% technically and 39.3% medically inoperable) and men (58.0% technically inoperable and 42.0% medically inoperable). A European registry has also reported similar findings: 54% of women underwent PEA compared with 65% of men and the reasons for not being operated did not differ between the sexes.[36] Further research would be to understand the reasons for fewer women undergoing PEA.

In terms of anticoagulant use, very few patients diagnosed with CTEPH in the Czech Republic between 2003 and 2016 were using NOACs. This is in contrast to a 2016 German study that reported patients with CTEPH were prescribed NOACs more frequently than traditional vitamin K antagonists.[37] Research into the effect of NOACs in patients with CTEPH is required, as they could be associated with a higher risk of recurrent thromboembolic events in specific clinical situations.[8]

In total, 236 (52.1%) patients underwent PEA and 22 (4.9%) patients (in the not-operated group) underwent BPA during the 2003–2018 observation period. The BPA procedure was not routinely used in the Czech Republic until 2017, hence the low prevalence of this procedure. Compared with the present study, a slightly higher percentage of patients underwent PEA in the international CTEPH registry (60% of patients diagnosed between 2007 and 2009 in 27 centers across Europe and Canada, and followed up until 2012),[6] whereas reports from a German registry were similar (50.3% in 2016), and figures reported from Spain and Poland were lower (34.3% of patients diagnosed between 2007 and 2018 in Spain; 23.3% of patients being managed at participating Polish centers between March 2018 and August 2019).[33,37,38] The percentage of patients undergoing PEA in the present study being among the highest figures reported reflects the center's expertise, amassed since the introduction of the PEA program to this high-volume expert center in 2004. Expertise in PEA enables this surgery to be performed on all patients who could benefit from it, thereby improving patient outcomes.

Residual PH was assessed in 208 patients at 6 months post-PEA and detected in 71 (34.1%) patients. Other

studies, including a recent meta-analysis,[39] have reported residual PH occurring in between 17% and up to one-third of patients.[40,41] It is difficult to compare the prevalence of residual PH between studies, as not all centers or studies systematically investigate for the presence of residual PH at 6 months. Comparisons are further impeded by the lack of consensus on the definition of residual PH.[8] This study defined residual PH as detection of pulmonary artery systolic pressure ≥40 mmHg by echocardiography 6 months post-PEA with subsequent confirmation by right heart catheterization. However, other studies use a range of thresholds for mean pulmonary arterial pressure (25–30 mmHg) and PVR (400–500 dyn/s/cm^5),[42] and some use *either* right heart catheterization *or* echocardiographic assessments to assess for residual PH.[41] Agreement on a universal definition of residual PH is a current aim in the field and will help standardize optimal care for operated patients.

There is little information published on the predictors for residual PH. In this study, among operated patients, patients with residual PH were older (median age: 66.2 vs. 58.6 years), had a higher percentage of female patients (50.7% vs. 32.1%), and a longer time to CTEPH diagnosis after first PE occurrence than patients with no residual PH (median time: 3.5 vs. 1.5 years). At diagnosis, NYHA FC was similar for both groups, while the median 6-min walk distance (6MWD) was lower for those with residual PH (313.5 m) compared with those who had no residual PH (359.5 m). The trend for female preponderance in patients with residual PH is in line with findings from a previous study, which identified female sex as a risk factor for residual PH.[43] The relationship between preoperative hemodynamics and clinical worsening post-PEA is currently not well-defined. The present study found that hemodynamic profiles at baseline were similar for those with and without residual PH. This is in alignment with a prospective UK study of patients undergoing PEA between 1997 and 2007 which reported that the only significant preoperative difference between patients with residual PH and those without residual PH was 6MWD, which was significantly lower in those with residual PH. Preoperative hemodynamic profiles were similar in both groups.[44] However, this is in contrast to a previous large UK cohort study which found that in patients with CTEPH, baseline hemodynamic factors such as mean pulmonary artery pressure and PVR were correlated with the need for treatment initiation following PEA.[45] Similarly, another study investigating outcomes in patients with residual PH following PEA reported that elevated PVR and mean pulmonary artery pressure at baseline were associated with clinical worsening and poor survival post-PEA.[46] These findings suggest that preoperative hemodynamic factors may be used to predict patients at risk of residual PH, but further research is needed.

This study analyzed outcomes by operability status, sourcing data from the IHIS CR, which provides a comprehensive record of hospitalizations and vital status of the Czech Republic population. The rate of CTEPH-related hospitalizations, per 100 person-years (95% CI), was 28.4 (26.5; 30.4), with 24.4 (22.1; 26.9) for operated and 34.2 (30.9; 37.7) for not-operated. The five-year survival probabilities were also lower for not-operated patients: 82.2% for operated and 61.2% for not-operated, which is aligned with contemporary estimates from the United Kingdom and Sweden (5-year survival rates of 85% and 88% for operated patients compared with 54% and 59% for not-operated patients).[29,47] It is important to repeat the slight difference in age at diagnosis between these two groups, as this could partly contribute to the differences in outcomes. This age difference is not unexpected, given that older patients are more likely to have comorbidities that could preclude them from having surgery. The SMR (95% CI) for all patients diagnosed between 2006 and 2016 indicates that the risk of death is more than double for patients with CTEPH compared with the general population of the Czech Republic with same age and sex (2.37 [1.98; 2.76]). The risk was even greater for not-operated patients (2.80 [2.21; 3.40]).

Altogether, these data demonstrate the high burden of disease, particularly for the not-operated patients. Among the not-operated group, five-year survival probability was worse for patients who were not operated upon due to comorbidities or patient refusal (i.e., the medically inoperable group; 55.2%) than the technically inoperable group (65.3%). This study also identified an unmet need for operated patients with residual PH. The survival outcomes for operated patient subgroups in this study are in agreement with a long-term outcomes study, which found that freedom from CTEPH-related death (defined as cardiac death, respiratory failure, hemorrhagic stroke, and death from an unknown cause) at 10 years post-PEA was lower in patients with normal mean pulmonary arterial pressure (89.0%) compared with those with residual PH (67.9%).[48]

These outcome data should be interpreted in the historical context of the study: the usage of BPA and medical therapies in the Czech Republic was confined to the very end of this study's observation period. This allows for the observation of the natural history of CTEPH and the impact of PEA alone on survival, thus providing a point of reference against which future studies can measure the impact of new treatment options. Multimodal management of CTEPH is now recommended by the guidelines and is likely to improve survival outcomes in CTEPH patients.[5,8,10,16,33,49] BPA has been performed

routinely in the Czech Republic since 2017 and a recent study that included 25 patients with CTEPH who completed their series of BPA procedures between 2013 and 2019 reported significant improvements in their NYHA FC, 6MWD, PVR and quality of life following the procedure (median of 4 months [95% CI: 2.0; 14.0] after the last BPA).[25]

The strengths of this study are the national coverage afforded by the single national expert center, the use of comprehensive data from the national databases (IHIS CR), and the ability of the study to provide a basis for future studies by virtue of being conducted when PEA was the only treatment option. In this study, survival was estimated since diagnosis for all groups. This could have led to an immortal-time bias when reporting the survival in the group "operated" as, per definition, patients who were categorized as operated could not have died in the time period between diagnosis and PEA surgery, whereas not-operated patients may have died any time since diagnosis. Therefore, the survival outcomes in the operated and not-operated populations should be compared with caution, though it is not believed to have a major impact on the substantial difference observed between these two groups due to the limited time reported between diagnosis and surgery.

In conclusion, this historical cohort study is a comprehensive and robust description of the epidemiology and outcomes of CTEPH in the Czech Republic, during a time period in which there was access to PEA surgery but limited use of BPA and medical treatment options. As such, it indicates that there is an unmet need for the treatment of not-operated patients and operated patients with residual PH. Future studies are needed to ascertain the extent to which multimodal management of the disease can address this unmet need, using these data as a historical reference.

ACKNOWLEDGMENTS

Medical writing and editorial support for the development of this manuscript, under the direction of the authors, were provided by Carrie Fielden, MSc, Malgorzata Urbacz, MSc, and Rosalind Perrett, BA, of Ashfield MedComms, an Ashfield Health company, and was funded by Actelion Pharmaceuticals Ltd., Allschwil, Switzerland, a Janssen Pharmaceutical company of Johnson and Johnson.

CONFLICT OF INTERESTS

Pavel Jansa has received fees and grants from Janssen Pharmaceutical Companies of Johnson and Johnson, AOP Orphan, and MSD. Audrey Muller and Virginie Gressin are employees of, and have shares in Janssen, a pharmaceutical company of Johnson and Johnson. Ci Song was an employee of Janssen, a pharmaceutical company of Johnson and Johnson, at the time of data collection and manuscript development. The remaining authors declare that there are no conflict of interests.

ETHICS STATEMENT

The study was approved by the Prague General University Hospital's research ethics committee.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study, analysis and interpretation of the data, and critical revision of the manuscript.

ORCID

Pavel Jansa http://orcid.org/0000-0002-3711-7064

REFERENCES

1. Simonneau G, Torbicki A, Dorfmuller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26:160112.
2. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. Pulm Circ. 2021;11: 2045894020977300–12.
3. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: ehe Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015(46):903–75.
4. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Noordegraaf AV, Beghetti M, Ghofrani A, Sanchez MAG, Hansmann G, Klepetko W, Lancellotti, P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2015;46(4):903–75.
5. Ghofrani HA, D'Armini AM, Kim NH, Mayer E, Simonneau G. Interventional and pharmacological management of chronic thromboembolic pulmonary hypertension. Respir Med. 2021; 177:106293.
6. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J,

Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jais X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevelle P, Mayer E, Simonneau G. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an International Prospective Registry. Circulation. 2016; 133(9):859–71.

7. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barbera JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jais X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973–81.
8. Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, Jenkins D, Kim NH, Humbert M, Jais X, Noordegraaf AV, Pepke-Zaba J, Brénot P, Dorfmuller P, Fadel E, Ghofrani HA, Hoeper MH, Jansa P, Madani M, Matsubara H, Ogo T, Grünig E, D'Armini A, Galie N, Meyer B, Corkery P, Meszaros G, Mayer E, Simonneau G. ERS statement on chronic thromboembolic pulmonary hypertension. Eur Respir J. 2020;57(6):2002828.
9. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53:1801915.
10. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013;369:319–29.
11. Siennicka A, Darocha S, Banaszkiewicz M, Kedzierski P, Dobosiewicz A, Błaszczak P, Peregud-Pogorzelska M, Kasprzak JD, Tomaszewski M, Mroczek E, Zieba B, Karasek D, Ptaszynska-Kopczynska K, Mizia-Stec K, Mularek-Kubzdela T, Doboszynska A, Lewicka E, Ruchała M, Lewandowski M, Łukasik S, Chrzanowski Ł, Zielinski D, Torbicki A, Kurzyna M. Treatment of chronic thromboembolic pulmonary hypertension in a multidisciplinary team. Ther Adv Respir Dis. 2019;13:1753466619891529.
12. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, Olsson KM, Meyer K, Vizza CD, Vonk-Noordegraaf A, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Huscher D, Pittrow D, Rosenkranz S, Grunig E. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017;50:1700740.
13. Brenot P, Jais X, Taniguchi Y, Garcia Alonso C, Gerardin B, Mussot S, Mercier O, Fabre D, Parent F, Jevnikar M, Montani D, Savale L, Sitbon O, Fadel E, Humbert M, Simonneau G. French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53:1802095.
14. Chausheva S, Naito A, Ogawa A, Seidl V, Winter MP, Sharma S, Sadushi-Kolici R, Campean IA, Taghavi S, Moser B, Klepetko W, Ishida K, Matsubara H, Sakao S, Lang IM. Chronic thromboembolic pulmonary hypertension in Austria and Japan. J Thorac Cardiovasc Surg. 2019;158(2):602–14.
15. Olsson KM, Wiedenroth CB, Kamp JC, Breithecker A, Fuge J, Krombach GA, Haas M, Hamm C, Kramm T, Guth S, Ghofrani HA, Hinrichs JB, Cebotari S, Meyer K, Hoeper MM, Mayer E, Liebetrau C, Meyer BC. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Respir J. 2017;49:1602409.
16. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv. 2012;5:748–55.
17. Jin Q, Zhao ZH, Luo Q, Zhao Q, Yan L, Zhang Y, Li X, Yang T, Zeng QX, Xiong CM, Liu ZH. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: state of the art. World J Clin Cases. 2020;8:2679–702.
18. Hoole SP, Coghlan JG, Cannon JE, Taboada D, Toshner M, Sheares K, Fletcher AJ, Martinez G, Ruggiero A, Screaton N, Jenkins D, Pepke-Zaba J. Balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: the UK experience. Open Heart. 2020;7:e001144.
19. EMA SmPC: Trepulmix. https://www.ema.europa.eu/en/documents/assessment-report/trepulmix-epar-public-assessment-report_en.pdf. Accessed August 2020.
20. EMA authorisation details: Adempas. https://www.ema.europa.eu/en/medicines/human/EPAR/adempas#authorisation-details-section. Accessed August 2020.
21. FDA prescribing information: ADEMPAS (riociguat) tablets. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204819s006lbl.pdf. Accessed August 2020.
22. Hoeper MM. Pharmacological therapy for patients with chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2015;24:272–82.
23. Sadushi-Kolici R, Jansa P, Kopec G, Torbicki A, Skoro-Sajer N, Campean IA, Halank M, Simkova I, Karlocai K, Steringer-Mascherbauer R, Samarzija M, Salobir B, Klepetko W, Lindner J, Lang IM. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med. 2019;7: 239–48.
24. Lindner J, Jansa P, Kunstyr J, Mayer E, Blaha J, Palecek T, Aschermann M, Grus T, Ambroz D, Tosovsky J, Vitkova I. Implementation of a new programme for the surgical treatment of CTEPH in the Czech Republic—pulmonary endarterectomy. Thorac Cardiovasc Surg. 2006;54:528–31.
25. Jansa P, Heller S, Svoboda M, Pad'our M, Ambroz D, Dytrych V, Siranec M, Kovarnik T, Felsoci M, Hutyra M, Linhart A, Lindner J, Aschermann M. Balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension: impact on clinical and hemodynamic parameters, quality of life and risk profile. J Clin Med. 2020;9: 3608.
26. Institute of Health Information and Statistics. https://www.uzis.cz/index-en.php. Accessed January 2020.
27. Czech Statistical Office Database Life Tables. https://www.czso.cz/csu/czso/life-tables-for-the-czech-republic-cohesion-regions-and-regions-npw84ucnon. Accessed January 2020.
28. Czech Statistical Office Database Population and Vital Statistics. https://vdb.czso.cz/vdbvo2/faces/en/index.jsf?page=

vystup-objekt%26pvo=DEM05%26z=T%26f=TABULKA%26skupId=546%26katalog=30845%26pvo=DEM05%26str=v94. Accessed January 2021.
29. NHS. National Audit of Pulmonary Hypertension, 10th Annual Report. https://digital.nhs.uk/data-and-information/publications/statistical/national-pulmonary-hypertension-audit/2019. Accessed July 2020.
30. Jensen KW, Kerr KM, Fedullo PF, Kim NH, Test VJ, Ben-Yehuda O, Auger WR. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. Circulation. 2009;120:1248–54.
31. Castro MA, Piloto B, Dos Santos Fernandes CJC, Jardim C, Filho WS, Oleas FG, Alves JL, Morinaga LTK, Hoette S, Filho MT, Filho OF, Jatene FB, Souza R. Use of medical therapies before pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension patients with severe hemodynamic impairment. PLOS One. 2020;15:e0233063.
32. Escribano-Subias P, Blanco I, Lopez-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, Castillo-Palma MJ, Segovia J, Gomez-Sanchez MA, Barbera JA. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. Eur Respir J. 2012;40:596–603.
33. Martínez-Santos P, Velázquez-Martín MT, Barberá JA, Fernández Pérez C, López-Meseguer M, López-Reyes R, Martínez-Meñaca A, Lara-Padrón A, Domingo-Morera JA, Blanco I, Escribano-Subías P, REHAP investigators. Chronic thromboembolic pulmonary hypertension in Spain: a decade of change. Rev Esp Cardiol (Engl Ed). 2020;74(5):384–92.
34. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA. Europe and Japan. 2017;26:160121.
35. Guerin L, Couturaud F, Parent F, Revel MP, Gillaizeau F, Planquette B, Pontal D, Guegan M, Simonneau G, Meyer G, Sanchez O. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Prevalence of CTEPH after pulmonary embolism. Thromb Haemost. 2014;112:598–605.
36. Barco S, Klok FA, Konstantinides SV, Dartevelle P, Fadel E, Jenkins D, Kim NH, Madani M, Matsubara H, Mayer E, Pepke-Zaba J, Simonneau G, Delcroix M, Lang IM. Sex-specific differences in chronic thromboembolic pulmonary hypertension. Results from the European CTEPH registry. J Thromb Haemost. 2020;18:151–61.
37. Kramm T, Wilkens H, Fuge J, Schafers HJ, Guth S, Wiedenroth CB, Weingard B, Huscher D, Pittrow D, Cebotari S, Hoeper MM, Mayer E, Olsson KM. Incidence and characteristics of chronic thromboembolic pulmonary hypertension in Germany. Clin Res Cardiol. 2018;107:548–53.
38. Kopeć G, Dzikowska-Diduch O, Mroczek E, Mularek-Kubzdela T, Chrzanowski Ł, Skoczylas I, Tomaszewski M, Peregud-Pogorzelska M, Karasek D, Lewicka E, Jacheć W, Gąsior Z, Błaszczak P, Ptaszyńska-Kopczyńska K, Mizia-Stec K, Biederman A, Zieliński D, Przybylski R, Kędzierski P, Waligóra M, Roik M, Grabka M, Orłowska J, Araszkiewicz A, Banaszkiewicz M, Sławek-Szmyt S, Darocha S, Magoń W, Dąbrowska-Kugacka A, Stępniewski J, Jonas K, Kamiński K, Kasprzak JD, Podolec P, Pruszczyk P, Torbicki A, Kurzyna M. Characteristics and outcomes of patients with chronic thromboembolic pulmonary hypertension in the era of modern therapeutic approaches: data from the Polish multicenter registry (BNP-PL). Ther Adv Chronic Dis. 2021;12:20406223211002961.
39. Hsieh WC, Jansa P, Huang WC, Niznansky M, Omara M, Lindner J. Residual pulmonary hypertension after pulmonary endarterectomy: a meta-analysis. J Thorac Cardiovasc Surg. 2018;156:1275–87.
40. Jenkins D, Madani M, Fadel E, D'Armini AM, Mayer E. Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26:160111.
41. Mayer E, Jenkins D, Lindner J, D'Armini A, Kloek J, Meyns B, Ilkjaer LB, Klepetko W, Delcroix M, Lang I, Pepke-Zaba J, Simonneau G, Dartevelle P. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. J Thorac Cardiovasc Surg. 2011;141:702–10.
42. Hoeper MM. Residual pulmonary hypertension after pulmonary endarterectomy: the fog is clearing. Circulation. 2016;133:1731–33.
43. de Perrot M, Thenganatt J, McRae K, Moric J, Mercier O, Pierre A, Mak S, Granton J. Pulmonary endarterectomy in severe chronic thromboembolic pulmonary hypertension. J Heart Lung Transplant. 2015;34:369–75.
44. Freed DH, Thomson BM, Berman M, Tsui SSL, Dunning J, Sheares KK, Pepke-Zaba J, Jenkins DP. Survival after pulmonary thromboendarterectomy: effect of residual pulmonary hypertension. J Thorac Cardiovasc Surg. 2011;141:383–7.
45. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, Treacy C, Ponnaberanam A, Condliffe R, Sheares K, Taboada D, Dunning J, Tsui S, Ng C, Gopalan D, Screaton N, Elliot C, Gibbs S, Howard L, Corris P, Lordan J, Johnson M, Peacock A, MacKenzie-Ross R, Schreiber B, Coghlan G, Dimopoulos K, Wort SJ, Gaine S, Moledina S, Jenkins DP, Pepke-Zaba J. Dynamic risk stratification of patient long-term outcome after pulmonary endarterectomy: results from the united kingdom national cohort. Circulation. 2016;133:1761–71.
46. Ghio S, Klersy C, Corsico A, Gamba SL, Monterosso C, Masiglat J, Borrelli E, Scelsi L, Greco A, Piloni D, Visconti LO, D'Armini AM. Risk stratification in patients with residual pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol. 2021;334:116–22.
47. Sandqvist A, Kylhammar D, Bartfay SE, Hesselstrand R, Hjalmarsson C, Kavianipour M, Nisell M, Radegran G, Wikstrom G, Kjellstrom B, Soderberg S. Risk stratification in chronic thromboembolic pulmonary hypertension predicts survival. Scand Cardiovasc J. 2021;55:43–9.
48. Miyahara S, Schröder TA, Wilkens H, Karliova I, Langer F, Kunihara T, Schäfers HJ. Long-term outcomes after pulmonary endarterectomy in 499 patients over a 20-year period. Ann Thorac Surg. 2021;111(5):1585–2.
49. Jansa P, Ambroz D, Kuchar J, Dytrych V, Lindner J, Linhart A. The impact of riociguat on clinical parameters and quality of life in patients with chronic thromboembolic pulmonary hypertension—results of a retrospective clinical registry. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2020;165(2):157–61.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Jansa P, Ambrož D, Kuhn M, Dytrych V, Aschermann M, Černý V, Gressin V, Heller S, Kunstýř J, Širanec M, Song C, Linhart A, Lindner J, Muller A. Epidemiology of chronic thromboembolic pulmonary hypertension (CTEPH) in the Czech Republic. Pulm Circ. 2022;12:e12038. https://doi.org/10.1002/pul2.12038