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DOI: https://doi.org/10.1016/j.jtha.2024.04.009

Received: 31 January 2024 | Revised: 11 March 2024 | Accepted: 11 April 2024

https://doi.org/10.1016/j.jtha.2024.04.009

ORIGINAL ARTICLE

Diagnosis of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: data from a practice-based longitudinal cohort

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Abstract

Background: A large prospective multicenter cohort study with systematic follow-up recently reported a 2.3% 2-year cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after acute pulmonary embolism (PE).

Objectives: The present investigation aimed to determine the reported prevalence and incidence of CTEPH diagnosis after acute PE in real-world practice over a 12-year period.

Methods: This study was based on nationwide ambulatory billing claims and drug prescription data of all residents with public health insurance in Germany from 2010 to 2021.

Results: A total of 573 972 patients with acute PE (median age, 71 years; 57.4% women) were identified between 2010 and 2021. Prevalence of CTEPH among patients with history of PE increased during the period from 0.4% in 2010 to 0.9% in 2021. CTEPH was diagnosed in 2556 patients after acute PE, with most (17.6%) diagnoses reported within the first 3 months after the index PE event. The cumulative incidence rate after 3 months (first quarter) was calculated at 0.08% and after the first 2 years (eighth quarter) at 0.36%; it was 0.75% over the entire (90-month) follow-up period. Patients with CTEPH diagnosis during follow-up more often had right ventricular dysfunction at the index acute PE (14.9% vs 8.3%; $P < .001$).

Conclusion: The low CTEPH incidence rate after acute PE in the present analysis suggests low awareness of CTEPH. It further suggests a lack of systematic follow-up protocols for acute PE survivors in the real world. Improved implementation of existing recommendations on follow-up strategies after PE is warranted.

KEYWORDS
CTEPH, incidence, PE, real-world practice

Manuscript handled by: Saskia Middeldorp

Final decision: Saskia Middeldorp, 11 April 2024

Lukas Hobohm and Lena Marie Paschke contributed equally and share first authorship.

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1 | INTRODUCTION

Acute pulmonary embolism (PE) is a common and potentially life-threatening condition that results from acute thrombotic to fibrotic obstructions of the pulmonary arterial tree [1]. While most patients recover fully with appropriate treatment after the acute event, some may develop chronic thromboembolic pulmonary hypertension (CTEPH), a severe and underdiagnosed sequela of PE [2]. CTEPH is characterized by persistent pulmonary hypertension and progressive right heart failure due to the obstruction of the pulmonary arteries by organized chronic thrombi. Although CTEPH is a relatively rare condition, with an estimated 2-year incidence of 0.5 to 4 cases per million population, it significantly impacts patients and healthcare systems due to its high morbidity and mortality rates [3]. Reported incidence estimates of CTEPH following acute PE vary widely, from less than 1% to more than 10% [4,5]. The variability in reported incidence may be related to study design, differences among patient populations, diagnostic criteria, follow-up assessment tools, and duration of follow-up. It is recognized that the risk of CTEPH is increased in patients with underlying risk factors, such as recurrent venous thromboembolism, malignancy, or hypercoagulable disorders [6].

Early recognition and appropriate management of CTEPH are crucial to improving patient outcomes [7]. However, CTEPH is often not diagnosed, or diagnosis is delayed due to its nonspecific symptoms and the lack of awareness among healthcare providers. Optimal management of CTEPH should be initiated promptly along with CTEPH-specific treatment options including medical therapy, balloon pulmonary angioplasty, and/or pulmonary endarterectomy (PEA) [8,9]. In this analysis, we sought to investigate the prevalence and incidence of CTEPH diagnosis after acute PE in real-world practice over a 12-year time period.

2 | METHODS

2.1 | Data source

Diagnostic codes were identified using the International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10-GM). Medications were identified by Anatomical Therapeutic Chemical Classification codes. This study is based on nationwide data from outpatient claims (VDA) and drug prescriptions (AVD) for all residents with statutory health insurance in Germany from 2010 to 2021; the total population included in the database was approximately 73.3 million as of 2021. The dataset includes outpatient prescriptions, diagnoses, and patient-physician contacts of general practitioners and subspecialty physicians. Prescription data are limited to medications dispensed at a pharmacy. Because VDA data are available quarterly, once the AVD and VDA data are linked, prescriptions and diagnoses can be analyzed every quarter.

2.2 | Study population

All patients with at least 1 verified diagnosis of PE, as indicated by the ICD-10-GM code I26, were included in the analysis. To identify patients with CTEPH, verified diagnoses with the ICD-10-GM code I27.20 were utilized. To ensure that only actual cases of CTEPH were included, the diagnosis had to be coded in at least 2 out of 4 consecutive quarters.

2.3 | Prevalence and cumulative incidence

For analyses without the possibility of patient follow-up, data were available from 2010 to 2021. For this time period, the prevalence of CTEPH was calculated as the proportion of patients with diagnosed CTEPH among all patients with history of PE. A 2-year follow-up was discussed for patients with acute PE in our study analysis in order to compare with current evidence [5]; thus, patients from 2011 to 2019 were investigated regarding the diagnosis of CTEPH. To calculate the cumulative incidence of CTEPH, only patients for whom the time point of the first PE event was known were included. A diagnosis of PE was considered first diagnosis if no PE had been diagnosed previously over a period of at least 5 consecutive quarters. As neither the AVD nor the VDA data provide information on whether a patient has had continuous statutory health insurance (vs private health insurance) coverage or is a permanent resident of Germany, absence of data alone was insufficient to exclude a previous PE diagnosis. Only patients with at least 1 patient-physician contact in the 5 quarters preceding the first PE diagnosis were included to exclude patients whose diagnoses may have yet to be fully captured in the data.

Following the initial diagnosis of PE, patient data were retrieved and analyzed until CTEPH was diagnosed, the follow-up period ended, or they were considered to have died. As the data analyzed did not provide information on mortality, patients were considered to have died if they had no patient-physician contact for 4 consecutive quarters during the follow-up or postobservation period.

To avoid counting a previous CTEPH diagnosis as a first diagnostic event, diagnoses were included in the analysis only if there was no identical diagnosis in the 2 last quarters. Patients who did not develop CTEPH during follow-up were censored at death or the end of the study period.

2.4 | Patient characteristics, comorbidities, and comedication

Patient characteristics and comorbidities were analyzed separately for PE patients who were diagnosed with and those who were not diagnosed with CTEPH during the study period. Definitions of the characteristics and comorbidities assessed are shown in Tables 1 to 3. Comorbidities were analyzed in the year before the initial diagnosis of PE. PE-specific conditions were evaluated in the same quarter as the

TABLE 1 Analyzed patient characteristics.

General characteristics	Values
Sex	Female, male
Age (y)	18-108

initial PE diagnosis. Comedication was analyzed 2 quarters before and in the same quarter as the first PE diagnosis.

Since prolonged anticoagulation treatment, or lack thereof, may affect the development of CTEPH, we also captured data on anticoagulant therapy in the patients with PE. Vitamin K antagonist and direct oral anticoagulant prescriptions were analyzed according to the Anatomical Therapeutic Chemical Classification codes listed in Table 4. This prescription analysis included patients with new-onset PE from 2012 to 2018. The inclusion criteria were the same as those for the cumulative incidence analysis, and for visualization purposes, these results were presented in years.

3 | RESULTS

3.1 | Baseline characteristics and comorbidities of patients with PE

A total of 573 972 patients with acute PE were identified to fulfill inclusion criteria in the German ambulatory healthcare system between 2010 and 2021. Of these, 57.4% were women with a median age of 71 years (Table 5). Cardiovascular risk factors and comorbidities were common in this patient population: 19.9% had a history of coronary artery disease, 24.8% had diabetes, 30.1% had malignancy, 21.1% were obese, and 61.8% had arterial hypertension. In most patients, the index event of PE was reportedly not accompanied by signs of right ventricular dysfunction (94.4%; Table 5).

3.2 | Risk factors predisposing to CTEPH

Risk factors for CTEPH after PE have been described previously in the literature. Of these known risk factors, L-thyroxin treatment was present in 18.9% of all PE cases in our study population. Further risk factors were not frequently diagnosed. Overall, 1.5% were diagnosed with inflammatory bowel disease, 0.13% had a diagnosis of splenectomy, and 0.03% patients had a cerebrospinal fluid drainage device placed (Table 5).

3.3 | Prevalence and cumulative incidence of CTEPH after PE

Among patients with history of PE, prevalence of CTEPH increased during the 12-year observation period from 0.5% in 2010 to 0.9% in

TABLE 2 Diagnosis codes used for the evaluation of risk factors and comorbidities.

Comorbidities	ICD-10-GM code
Endocrine and metabolic disorders	
Obesity	E66.-
Diabetes	E10-E14
Hyperlipidemia	E78
Hypothyroidism	E02.-, E03.-
Cardiovascular disorders	
Coronary heart disease	I25.-
Heart failure	I50.-
Left heart failure	I50.1-
NYHA1	I50.11
NYHA2	I50.12
NYHA3	I50.13
NYHA4	I50.14
Right heart failure	I50.0-
Atrial fibrillation	I48.-
Other disorders	
Chronic obstructive pulmonary disease	J44.-
Hypertension	I10.-
Chronic kidney disease	N18.3-, N18.83, N18.84, N18.4-, N18.5-
Thrombophilia	D68.5-, D68.6-
Hyposplenism	D73.0-
Inflammatory bowel disease	K50.-, K51.-
Presence of cerebrospinal fluid drainage device	Z98.2-
Malignant neoplasm of:	C00-C97
Specified site	C00-C75
Lymphoid, hematopoietic and related tissues	C81-C96
Unspecified sites	C76-C80, C97.-
PE-specific conditions	
Phlebitis and thrombophlebitis	I80.-
PE with acute cor pulmonale	I26.0-
PE without acute cor pulmonale	I26.9-

ICD-10-GM, International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification; NYHA, New York Heart Association; PE, pulmonary embolism.

TABLE 3 Anatomical Therapeutic Chemical Classification codes used for the evaluation of chronic thromboembolic pulmonary hypertension (CTEPH) risk and comorbidities, including medications directly altering CTEPH risk or indicating diseases with altered CTEPH risk.

Comedication	ATC code
Levothyroxine sodium	H03AA01
Acetylsalicylic acid	B01AC06, N02BA01, A01AD05

ATC, Anatomical Therapeutic Chemical Classification.

2021 (Figure 1). Overall, 2556 (0.4%) patients were diagnosed with CTEPH after acute PE during a follow-up of 30 quarters (90 months). The quarter following the index PE event was the quarter with the highest proportion of CTEPH diagnoses (17.7%). CTEPH was diagnosed at a median of 4.5 quarters after the index PE. The cumulative incidence rate after 3 months (first quarter) was calculated at 0.08% and after the first 2 years (eighth quarter) at 0.36%; it was 0.75% over the entire (90-month) follow-up period (Figure 2).

3.4 | Specific characteristics of patients with CTEPH during follow-up

Patients subsequently diagnosed with CTEPH were older at the time of the index PE event compared with those without a CTEPH diagnosis (median 72 vs 71; absolute risk reduction [ARR] + 1%; Table 5). Patients with CTEPH during follow-up were more often likely to be female (62.4% vs 57.4%; ARR + 4.98%) and obese (23.6% vs 21.0%; ARR + 2.59%) and more frequently had a history of chronic obstructive pulmonary disease (19.8% vs 14.9%; ARR + 4.89%) and arterial hypertension (67.4% vs 61.8%; ARR + 5.66%) compared with patients without CTEPH during follow-up. Patients with CTEPH diagnosis during the follow-up period had considerably more often signs of right ventricular dysfunction than those without CTEPH (14.9% vs 8.3%; ARR + 6.67%; Table 5).

Prescriptions for oral anticoagulants changed in the opposite direction: in 2018, direct oral anticoagulants were predominantly prescribed, while vitamin K oral antagonists accounted for only a small proportion of prescriptions (Figure 3).

TABLE 4 Treatment classification.

Treatment label	Treatment	ATC code
VKA	Phenprocoumon	B01AA04
	Warfarin	B01AA03
DOAC	Dabigatran	B01AE07
	Rivaroxaban	B01AF01
	Apixaban	B01AF02
	Edoxaban	B01AF03

ATC, Anatomical Therapeutic Chemical Classification; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

4 | DISCUSSION

In the present study, we retrospectively investigated a large population of 573 972 unselected patients with acute PE for the diagnosis of CTEPH over a 12-year period. The key findings can be summarized as follows: (I) the estimated cumulative incidence of CTEPH was 0.36% after 2 years and 0.75% after 7.5 years (90 months); (II) the quarter following the index PE event was the quarter with the highest proportion of CTEPH diagnoses (17.7%), and CTEPH was diagnosed at a median of 4.5 quarters after the index PE; (III) prevalence of CTEPH among survivors of acute PE increased from 0.5% in 2010 to 0.9% in the year 2021; and (IV) patients with right ventricular dysfunction at the initial PE event had a higher probability of CTEPH diagnosis during the 12-year period.

CTEPH is considered a rare but severe sequela after acute PE, with a high mortality rate and poor prognosis if not detected early and managed inappropriately [10]. CTEPH is potentially curable if surgical PEA is performed [7,8]. In patients in whom PEA is not feasible, medical therapy and/or percutaneous balloon pulmonary angioplasty may be alternative treatment options [9]. Therefore, the awareness of CTEPH should be high. The possibility of CTEPH should be carefully considered in all patients with persistent symptoms after acute PE, leading to functional limitation, and in patients who may claim to be asymptomatic but have predisposing risk factors for CTEPH [3,11]. Persistent dyspnea and functional limitation along with imaging and/or laboratory abnormalities may result in further diagnostic work-up, such as ventilation/perfusion lung scintigraphy, for assessment of CTEPH. If imaging yields ventilation-perfusion mismatch, right heart catheterization is required to confirm the diagnosis of CTEPH [3]. In the present study, patients with CTEPH diagnosis more often had right ventricular dysfunction (14.9% vs 8.3%; ARR + 6.67%) at the index acute PE event, suggesting that patients with right ventricular dysfunction may have an elevated risk of developing CTEPH or that it may be a sign of preexisting CTEPH.

Predisposing factors for CTEPH, such as permanent intravascular devices, inflammatory bowel disease, splenectomy, thrombophilia, high-dose thyroid hormone replacement therapy, and malignancy, may increase the probability of CTEPH either in the presence or in the absence of functional limitation after acute PE [3,12]. The most common predisposing risk factor in our study population was hypothyroidism with consecutive levothyroxine substitution, which was more often present in PE patients with CTEPH diagnosis during the follow-up period (ARR + 2.11%). Thyroid disease and dysfunction have numerous effects on organs and tissues, including alterations of the coagulation cascade [13]. High levels of free thyroxine can increase the risk of venous thromboembolism by elevating the plasma concentration of von Willebrand factor and factor VIII [14]. Studies suggest that thyroid dysfunction affects hemodynamic status and long-term survival [15]. It has been reported that cancer patients are at higher risk of first and recurrent venous thromboembolism events, and almost 20% of PE occurs in patients with malignancy [16]. Our data revealed that malignancy was less frequently present in patients with CTEPH as opposed to

TABLE 5 General characteristics, comorbidities, and comedications of the study population.

General characteristics		All patients	With diagnosed CTEPH	Without diagnosed CTEPH	Difference
No. of patients	*N*	573 972	2556	571 416	−568 860
	%	100	0.4	99.6	−99.1
Female sex	%	57.44	62.4	57.42	4.98
Age	Mean ± SD	66.9 ± 16.1	68.1 ± 14.1	66.9 ± 16.1	1.2
	Median	71	72	71	1
Comorbidities %					
Endocrine and metabolic disorders					
Obesity		21.05	23.63	21.04	2.59
Diabetes		24.83	22.54	24.84	−2.3
Hyperlipidemia		37.45	37.09	37.45	−0.36
Hypothyroidism		8.73	9.04	8.73	0.31
Cardiovascular disorders					
Coronary heart disease		19.92	19.21	19.92	−0.71
Heart failure		14.18	19.21	14.15	5.06
Left heart failure		4.97	7.75	4.95	2.8
NYHA class I		0.42	0.67	0.42	0.25
NYHA class II		1.75	2.58	1.75	0.83
NYHA class III		1.54	2.66	1.54	1.12
NYHA class IV		0.4	0.39	0.4	−0.01
Right heart failure		1.69	3.25	1.69	1.56
Atrial fibrillation		9.3	9.12	9.3	−0.18
Other disorders					
Chronic obstructive pulmonary disease		14.93	19.8	14.91	4.89
Hypertension		61.77	67.41	61.75	5.66
Chronic kidney disease		4.89	5.48	4.89	0.59
Thrombophilia		0.93	1.29	0.93	0.36
Hyposplenism		0.13	0.2	0.13	0.07
Inflammatory bowel disease		1.45	1.49	1.45	0.04
Presence of cerebrospinal fluid drainage device		0.03	0.2	0.02	0.18
Malignant neoplasm of:					
Specified site		22.61	18.31	22.63	−4.32
Lymphoid hematopoietic and related tissues		2.01	1.88	2.01	−0.13
Unspecified sites		5.47	1.88	5.49	−3.61
PE-specific conditions					
Phlebitis and thrombophlebitis		28.53	29.42	28.52	0.9
PE with acute cor pulmonale		8.31	14.95	8.28	6.67
PE without acute cor pulmonale		94.44	92.61	94.45	−1.84

Comedication %	All patients	With CTEPH	Without CTEPH	Difference
Levothyroxine sodium	16.8	18.9	16.79	2.11
Acetylsalicylic acid	10.92	8.53	10.93	−2.4

CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association; PE, pulmonary embolism.

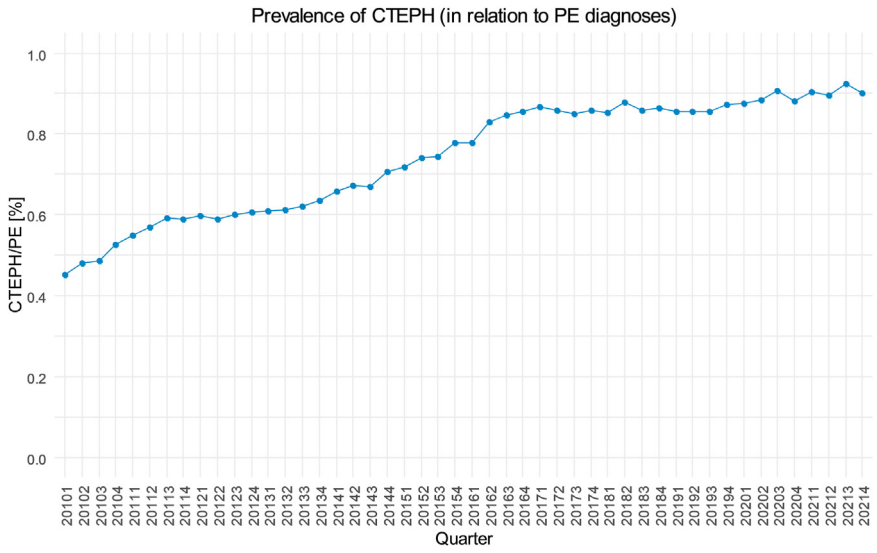

FIGURE 1 Prevalence of chronic thromboembolic pulmonary hypertension (CTEPH) diagnosis after acute pulmonary embolism (PE).

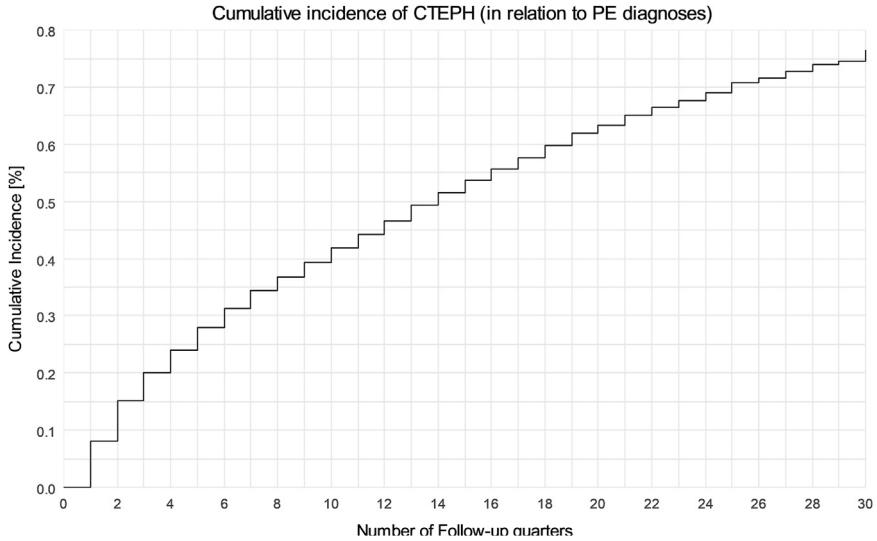

FIGURE 2 Cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after acute pulmonary embolism (PE).

those without CTEPH. These findings suggest the lack of search for CTEPH in patients with malignancy, perhaps also the lack of search for malignancy in patients with diagnosed CTEPH [17]. Other reported risk factors predisposing to CTEPH, such as thrombophilia, inflammatory bowel disease, or permanent drainage devices, were not significantly different in PE patients with vs without CTEPH in our study [6,12].

The increased incidence and prevalence of CTEPH reported in the last few years may relate to a higher level of awareness, leading to stricter screening protocols for patients with imaging abnormalities and/or functional limitations [18–20]. The recently published results of the FOCUS study yielded a 2-year cumulative CTEPH incidence of 2.3% (1.2%-4.4%). That prospective multicenter observational cohort study followed patients with acute symptomatic PE with a standardized, systematic assessment plan and predefined visits. In fact, the 2019 European Society of Cardiology guidelines for diagnosing and managing acute PE recommended specific strategies for patient follow-up after PE [11]. In our study population reflecting real-world practice from 2010 to 2021, an increasing prevalence and cumulative incidence of diagnosed CTEPH after acute PE was observed. However, this is still only a small fraction of the expected incidence rate as expected based on the FOCUS study. Thus, the diagnosis of CTEPH may have been missed in more than 13 000 patients with acute PE. In addition to the implications for the patients' lives and health status, the economic consequences of missing early CTEPH diagnosis after acute PE need to be taken into consideration [21]. A recent study demonstrated a substantial health gain when CTEPH was diagnosed promptly and managed early [22].

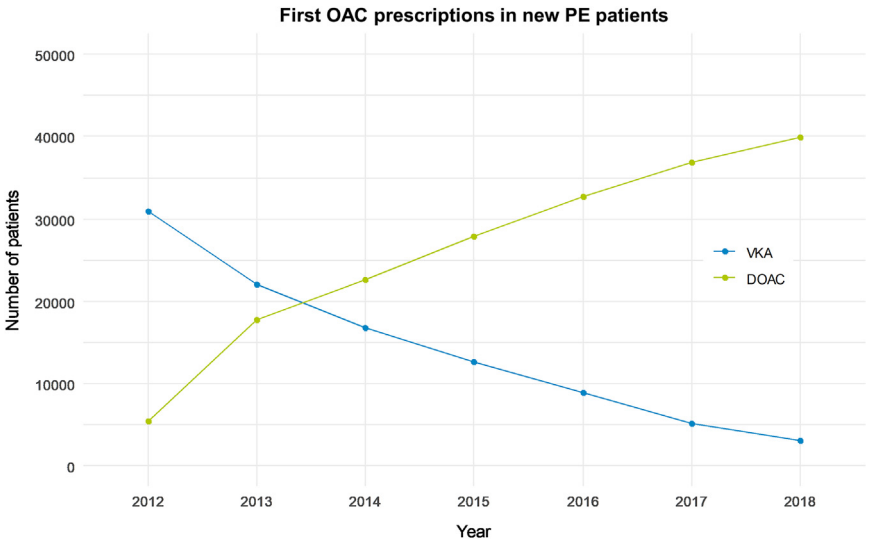

FIGURE 3 Prescriptions of oral anticoagulants in patients with acute pulmonary embolism (PE). DOAC, direct oral anticoagulant; OAC, oral anticoagulants; VKA, vitamin K antagonist.

Some limitations of our study need to be kept in mind. Since our results are based on administrative data and the original charts could not be directly verified, we must include code misclassification or missed diagnoses of other complications. Additionally, the data are restricted to outpatient diagnoses and do not incorporate information from the inpatient sector. As a result, patients who require hospitalization can only be identified once an outpatient physician documents the diagnosis. This may result in an actual duration between PE and CTEPH being different from that calculated based on our data. Furthermore, patients who die in the hospital after being hospitalized for new-onset PE or CTEPH can only be recognized as deaths. Additionally, a PE event is often not recognized in patients with CTEPH due to the fact that PE can also occur asymptomatically. Thus, the PE diagnosis that caused hospitalization was not available, leading to some underestimation of the actual number of events.

In conclusion, the present study provides an estimate of the incidence of CTEPH after acute PE as diagnosed in the "real world" of the German healthcare system. The low rate of CTEPH incidence, compared with that in prospective cohort studies employing systematic follow-up protocols, suggests a low level of awareness of late PE sequelae and considerable underdiagnosis of CTEPH in Germany. Our results thus support the need for improved implementation and possibly further optimization of follow-up strategies after acute PE.

AUTHOR CONTRIBUTIONS

Conceptualization, L.H. and K.K.; Methodology, L.H., L.M.P., K.K., and M.B.; Software, L.M.P. and M.B.; Validation, L.H., L.M.P., K.K., and M.B.; Formal analysis, L.M.P. and M.B.; Investigation, L.H., L.M.P., K.K., and M.B.; Resources, L.M.P. and M.B.; Data curation, L.M.P. and M.B.; Writing—original draft preparation, L.H., L.M.P., I.T.F., K.K., and M.B.; Writing—review and editing, L.H., L.M.P., I.T.F., S.B., S.P., T.M., S.K., K.K., and M.B.; Visualization, L.M.P. and M.B.; Supervision, L.H., L.M.P., K.K., and M.B.; Project administration, L.M.P. and M.B. All authors had full access to the data and have read and agreed to the published version of the manuscript.

DECLARATION OF COMPETING INTERESTS

L.H. received lecture/consultant fees from Johnson & Johnson, Inari Medical, MSD, and Boston Scientific, outside the submitted work. L.M.P. reports no conflict of interest. I.F. declares no conflict of interest. S.B. received lecture/consultant fees from Bayer HealthCare, Concept Medical, BTG Pharmaceuticals, INARI, Boston Scientific, and LeoPharma; institutional grants from Boston Scientific, Bentley, Bayer HealthCare, INARI, Medtronic, Concept Medical, Bard, and Sanofi; and economic support for travel/congress costs from Daiichi Sankyo, BTG Pharmaceuticals, and Bayer HealthCare, outside the submitted work. S.P. reports no conflict of interest. T.M. reports no conflict of interest. S.K. reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol-Myers Squibb/Pfizer. K.K. reports no conflict of interest. M.B. reports no conflict of interest.

DATA AVAILABILITY

The dataset generated and/or analyzed during the current study is available from the corresponding author on reasonable request.

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REFERENCES

[1] Keller K, Hobohm L, Ebner M, Kresoja KP, Münzel T, Konstantinides SV, Lankeit M. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. *Eur Heart J*. 2020;41:522–9.

[2] 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.

[3] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43:3618–731.

[4] Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, Delcroix M, Pruszczyk P, Mairuhu AT, Huisman MV, Klok FA. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49:1601792.

[5] Valerio L, Mavromanoli AC, Barco S, Abele C, Becker D, Bruch L, Ewert R, Faehling M, Fistera D, Gerhardt F, Ghofrani HA, Grgic A, Grünig E, Halank M, Held M, Hobohm L, Hoeper MM, Klok FA, Lankeit M, Leuchte HH, et al. Chronic thromboembolic pulmonary hypertension and impairment after pulmonary embolism: the FOCUS study. *Eur Heart J*. 2022;43:3387–98.

[6] Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. *Eur Respir J*. 2013;41:462–8.

[7] Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jaïs X, Ambroz D, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *Circulation*. 2016;133:859–71.

[8] Hobohm L, Keller K, Munzel T, Konstantinides SV, Lankeit M. Time trends of pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension. *Pulm Circ*. 2021;11:20458940211008069.

[9] Jais X, Brenot P, Bouvaist H, Jevnikar M, Canuet M, Chabanne C, Chaouat A, Cottin V, De Groote P, Favrolt N, Horeau-Langlard D, Magro P, Savale L, Prévot G, Renard S, Sitbon O, Parent F, Trésorier R, Tromeur C, Piedvache C, et al. Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study. *Lancet Respir Med*. 2022;10:961–71.

[10] Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest*. 1982;81:151–8.

[11] Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2019;40:3453–5.

[12] Bonderman D, Wilkens H, Wakounig S, Schäfers HJ, Jansa P, Lindner J, Simkova I, Martischnig AM, Dudczak J, Sadushi R, Skoro-Sajer N, Klepetko W, Lang IM. Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2009;33:325–31.

[13] Krieg VJ, Hobohm L, Liebetrau C, Guth S, Kölmel S, Troidl C, Mayer E, Konstantinides SV, Wiedenroth CB, Lankeit M. Risk factors for chronic thromboembolic pulmonary hypertension - Importance of thyroid disease and function. *Thromb Res*. 2020;185:20–6.

[14] Debeij J, van Zaane B, Dekkers OM, Doggen CJ, Smit JW, van Zanten AP, Brandjes DP, Büller HR, Gerdes VE, Rosendaal FR, Cannegieter SC. High levels of procoagulant factors mediate the association between free thyroxine and the risk of venous thrombosis: the MEGA study. *J Thromb Haemost*. 2014;12:839–46.

[15] Pohl KR, Hobohm L, Krieg VJ, Sentler C, Rogge NIJ, Steimke L, Ebner M, Lerchbaumer M, Hasenfuß G, Konstantinides S, Lankeit M, Keller K. Impact of thyroid dysfunction on short-term outcomes and long-term mortality in patients with pulmonary embolism. *Thromb Res*. 2022;211:70–8.

[16] Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122:1712–23.

[17] Catella-Chatron J, Merah A, De Magalhaes E, Moulin N, Accassat S, Duvillard C, Mismetti P, Bertoletti L. Chronic thromboembolic pulmonary hypertension suspicion after pulmonary embolism in cancer patients. *Respir Med Res*. 2019;76:34–7.

[18] 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.

[19] Delcroix M, Torbicki A, Gopalan D, Sitbon O, Klok FA, Lang I, Jenkins D, Kim NH, Humbert M, Jais X, Vonk Noordegraaf A, Pepke-Zaba J, Brénot P, Dorfmuller P, Fadel E, Ghofrani HA, Hoeper MM, Jansa P, Madani M, Matsubara H, et al. ERS statement on chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2021;57:2002828.

[20] Kramm T, Wilkens H, Fuge J, Schäfers 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.

[21] Farmakis IT, Keller K, Barco S, Konstantinides SV, Hobohm L. From acute pulmonary embolism to post-pulmonary embolism sequelae. *Vasa*. 2023;52:29–37.

[22] Boon G, van den Hout WB, Barco S, Bogaard HJ, Delcroix M, Huisman MV, Konstantinides SV, Meijboom LJ, Nossent EJ, Symersky P, Vonk Noordegraaf A, Klok FA. A model for estimating the health economic impact of earlier diagnosis of chronic thromboembolic pulmonary hypertension. *ERJ Open Res*. 2021;7:00719–2020.

SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.jtha.2024.04.009.