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Original Research

Association between depression, anxiety and long-term healthcare resource utilization in patients with pulmonary embolism

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ABSTRACT

Background: To date, the utilization of healthcare resources for complications associated with acute pulmonary embolism (PE) have received no attention. This study aimed to explore healthcare utilization and its association with depression and anxiety up to 2 years after in-patient treatment for PE.
Methods: Data from the German 'Lungenembolie Augsburg (LEA)' cohort study was used. Baseline characteristics of the adult patients with PE were collected through an interview during hospital stay and via chart review. Participants completed postal questionnaires 3, 6, 12, and 24 months after their PE event containing questions on healthcare utilization. Depression and anxiety were assessed using the Hospital Anxiety and Depression scale (HADS-D). Negative binomial mixed models were used to investigate the associations between depression and anxiety scores (exposures) and the number of hospitalizations, hospital outpatient clinic visits, general practitioner consultations and medical specialist visits with outcomes adjusted for potential confounders.
Results: Out of 569 patients (55 % male, mean age 63.0 ± 14.5 years), 18.3 % had at least mild symptoms of depression and 21.3 % had at least mild symptoms of anxiety at the initial hospitalization. During the first 3 months after hospital discharge, 28.1 % of the patients had at least one hospital readmission. Higher HADS-D depression scores were significantly associated with more hospitalizations ($p = 0.0063$), hospital outpatient clinic visits ($p = 0.0009$) and visits to general practitioners ($p = 0.0434$). Higher HADS-D anxiety scores were significantly associated with more hospitalizations ($p = 0.0413$) and visits to medical experts ($p = 0.0268$).
Conclusions: Depression and anxiety were significantly associated with increased healthcare utilization in patients with PE.

1. Background

Venous thromboembolism (VTE), clinically presenting as deep vein thrombosis (DVT) or pulmonary embolism (PE), is the third most common cardiovascular syndrome after myocardial infarction and stroke [1]. PE imposes a substantial burden not only on the affected individuals but also on the healthcare systems [2–4]. Although mortality rates in management of acute PE have decreased overtime, the overall incidence of PE is rising in ageing societies [5–11]. Thus, it can be expected that the number of survivors of acute PE who require long-term healthcare will substantially increase in the future. The course of PE after the acute phase is often characterized by frequent hospital readmissions and prevalent persisting functional impairments, clinical symptoms such as dyspnea, poor health-related quality of life, and mental health problems such as depression or anxiety [12–18]. Fischer et al. [14] reported that between 18 % and 24 % of patients with PE had Hospital Anxiety and Depression Scale scores indicating depression, and 19 %–29 % had scores indicating anxiety, 3–24 months after the acute PE event.

To improve long-term healthcare for patients with acute PE and to control its costs, it is important to know, which healthcare resources are utilized, what are the characteristics of the users, and which factors impose a high healthcare utilization. Besides clinical characteristics,

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mental health conditions such as depression or anxiety were reported to influence healthcare resource use. For instance, individuals with a cardiovascular disorder and a high risk of depression had increased healthcare expenditures and a higher odds for resource utilization compared with those with a low depression risk [19]. Similarly, in patients with heart failure, depression independently predicted an increase in the use of healthcare resources and in rehospitalizations [20,21]. Associations between depression and increased healthcare utilization were also found in other health conditions, such as cancer [22,23], spinal cord injury [24], Parkinson's disease [25], and osteoarthritis [26]. Less consistent results are available for the association between anxiety and healthcare utilization. While Curcio et al. [27] and Wu et al. [23] found that patients after cardiac surgery and patients with cervical cancer with higher anxiety scores had significantly more medical service utilization than patients scoring lower, Sansone et al. [28] found no association between anxiety symptoms and healthcare utilization in outpatients of an internal medicine clinic.

However, in patients with PE, data on long-term healthcare resource utilization and its associated factors is lacking so far. Hence, the objective of the present study was to characterize healthcare resource utilization of patients with PE up to 2 years after hospital discharge and to investigate the association of depression and anxiety with healthcare resource utilization.

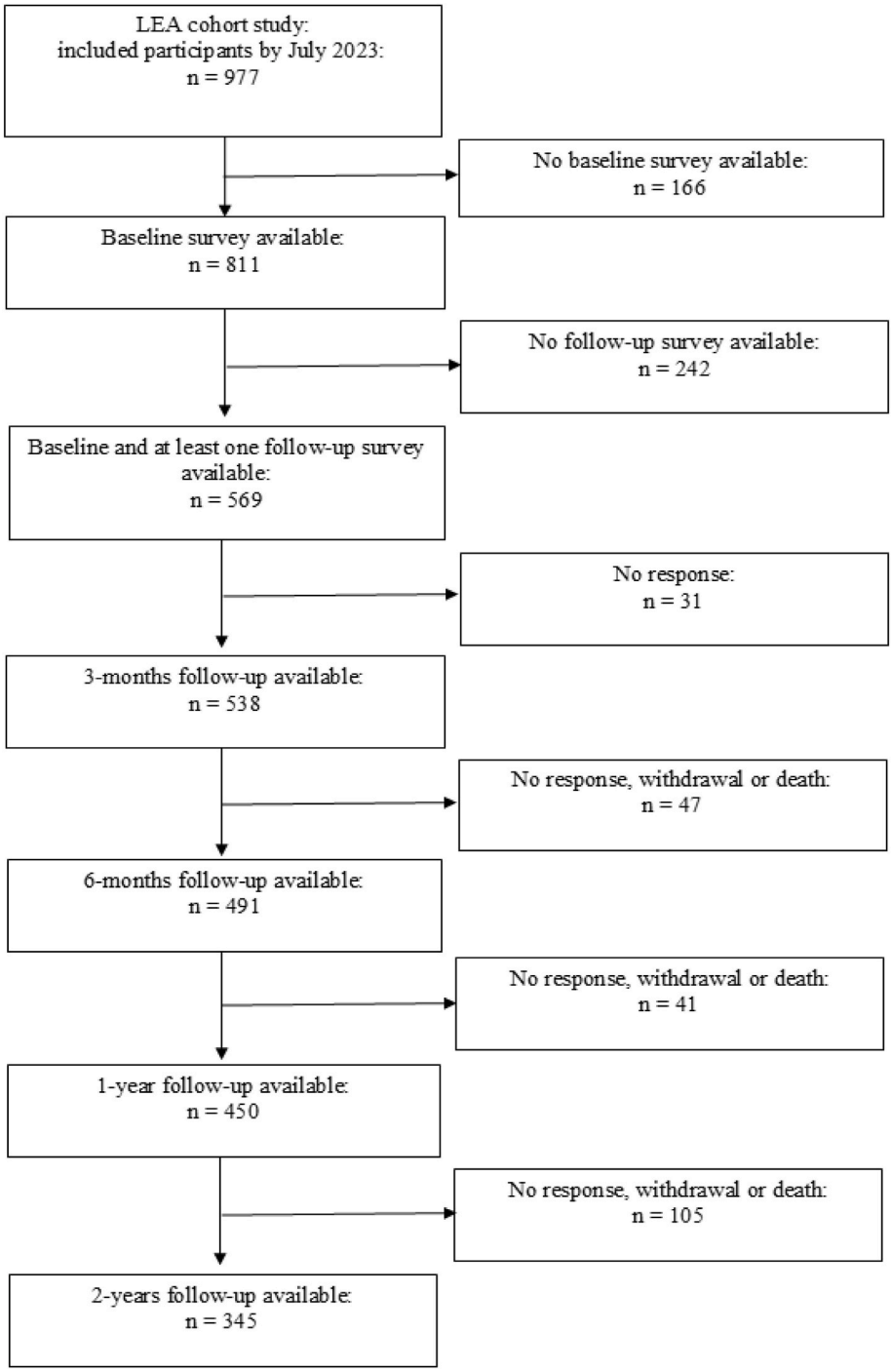

Fig. 1. Flow chart of the study.

2. Methods

2.1. Design and study population

The study sample consisted of participants of the 'Lungenembolie Augsburg' (LEA) study. The LEA study is a long-term observational cohort study including adult patients with incident or recurrent confirmed PE diagnosis based on multidetector CT pulmonary angiography or ventilation–perfusion lung scanning who were treated at the University Hospital Augsburg, Germany. The study design has been described in detail by Meisinger et al. [29].

Clinical characteristics of the study participants were extracted from the medical records. Socio-demographics (e.g. education, marital status, nationality), risk factors (e.g. smoking, alcohol use), and comorbidities (e.g. pulmonary conditions, cardiovascular conditions, depression) were obtained from personal interviews conducted by study nurses during the hospital stay. After discharge, study participants were requested to complete postal questionnaires after 3, 6, and 12 months in the first year, thereafter in yearly intervals up to 60 months.

In total, 977 patients were included in the study between July 2017 and July 2023. The present analyses are based on data up to 24 months post PE. Fig. 1 shows the flow chart of the study.

2.2. Survey data

The postal follow-up assessments included questions on healthcare utilization (rehospitalizations and visits to different medical specialists and clinics), recurrent PE events, newly diagnosed health conditions, surgeries, major bleeding complications, current medication and treatment. In addition, standardized questionnaires were used to assess mental health and dyspnea.

Symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS-D), a self-administered and validated German version of the HADS [30–32]. It consists of two subscales with seven items each on depression and anxiety. The subscale scores can be classified into four categories: 0–7 (no depression or anxiety), 8–10 (mild depression or anxiety), 11–14 (moderate depression or anxiety) and 15–21 (severe depression or anxiety). A dichotomous cut-off threshold of 8 points was shown to be appropriate in several studies [30].

Dyspnea was assessed using the 5-item dyspnea subscale of the self-administered Chronic Respiratory Questionnaire (CRQ). Higher scores indicate less impairment due to respiratory disease [33].

2.3. Data analysis

For the analysis, self-reported data on comorbidities were only considered if the information was not available from the medical records. The number of respiratory conditions was calculated as the sum of lifetime diagnoses of asthma, chronic obstructive pulmonary disease, pulmonary emphysema, pneumonia, sleep apnea and interstitial lung disease. The Simplified Pulmonary Embolism Severity Index (sPESI) was calculated based on the patient's age, history of cancer, chronic cardiopulmonary disease, heart rate, systolic blood pressure and arterial oxygen saturation to classify patients into high ($\geq$1) or low (0) PE-related risk of death [34]. HADS-D scores were dichotomized for uni- and bivariate analyses with scores less than 8 classified as "no depression/anxiety" and scores equal or above 8 indicating the presence of depression or anxiety. In the multivariable regression models the continuous HADS-D scores were used. The total number of visits at medical specialists was calculated from the sum of visits to internists, ophthalmologists, gynecologists, dermatologists, otolaryngologists, neurologists, orthopedists, urologists, and physicians with other specializations. School and professional education were classified according to the International Standard Classification of Education (ISCED) system into the levels 1 (lowest level) to 5 (highest level) [35]. For the multivariable analyses ISCED categories 1 and 2 as well as the categories 4 and 5 were collapsed.

Differences between patients with or without depression/anxiety were tested using Chi square test, Fisher's exact test, or Mann-Whitney-U-test, depending on the nature of the outcome variable. Multivariable mixed models were used to investigate the association between depression and anxiety (independent variables) and number of hospitalizations, visits to hospital outpatient clinics, visits to the general practitioner, and visits at medical specialists (dependent variables) adjusted for sociodemographic and clinical confounding variables and the follow-up time point. Due to the count nature of the outcome variables and overdispersion, negative binomial models with random intercepts were fitted. Interaction effects between depression/anxiety and follow-up time points were tested in the full models but were not significant and therefore not included in the final models. The confounding variables were selected based on a directed acyclic graph [36]. For statistical tests an alpha level of 0.05 was defined. Due to the explorative study approach no adjustment for multiple testing was applied. Statistical analyses were performed using SAS Version 9.4.

3. Results

3.1. Sample characteristics

The demographic and clinical characteristics of the participants are shown in Table 1. The mean age of the 569 enrolled participants at the time of the PE event was 63.0 $\pm$ 14.5 years with 55 % men and 45 % women. During hospitalization for PE, 9.5 % of the patients had mild symptoms of depression, 5.5 % moderate symptoms and 3.3 % severe symptoms, respectively. Mild symptoms of anxiety were reported by 13.2 % of the patients, moderate symptoms by 6.7 % and severe symptoms by 1.4 %, respectively. Additional file 1 demonstrates that these proportions remained almost stable within the 2-year follow-up period.

Some demographic and clinical characteristics were significantly different in patients with symptoms of depression or anxiety during hospitalization compared with patients without symptoms of depression or anxiety. Patients with symptoms of depression were significantly more often employed, more often diagnosed for a depressive disorder and had less often a history of varicosis than patients without symptoms of depression (see Table 1). Patients with symptoms of anxiety had significantly more often an autoimmune disease, a diagnosis of a depressive disorder in the past and had worse sPESI scores than patients without anxiety.

Compared with 242 participants who were lost to follow-up, the analyzed sample was significantly younger with more men, married persons, persons not living alone, and persons with higher educational levels (see additional file 2). Moreover, the patients included in the present analyses had significantly less past diagnoses of other conditions (COPD, heart failure, diabetes, neuromuscular diseases, cancer, depression), were less often treated at the intensive care unit for their acute PE, had better sPESI scores and a shorter hospitalization than individuals lost to follow-up.

3.2. Healthcare utilization

During the first 3 months after discharge, 28.1 % of the patients had at least one hospital readmission (see Table 2). General practitioners were consulted most often with 17.6 % of the patients with one and 65.0 % with multiple consultations. Among the medical experts, internists were most often consulted, with 24.6 % of the patients having one and 14.3 % having multiple consultations. Patients with depression were significantly more likely to have a hospital readmission (38.8 %) than patients without depression (25.4 %). In addition, patients with depression had a significantly larger number of visits to hospital outpatient clinics, general practitioners and neurologists, compared

Table 1
Sample characteristics at baseline (n = 569). Significant differences ($p < 0.05$)[1] between patients with or without depression/anxiety are highlighted in bold type.

		Total sample (n = 569)	Depression (yes) (n = 104)	Depression (no) (n = 465)	Anxiety (yes) (n = 121)	Anxiety (no) (n = 448)
	N total	Mean ± SD Median, 25./75. Quantile				
Age (years)	567	63.0 ± 14.5 64, 55/74	61.9 ± 14.8 63, 53/74	63.2 ± 14.4 64, 55/74	61.2 ± 14.2 63, 53/72.5	63.4 ± 14.5 65, 55/75
Days hospitalization	565	12.7 ± 24.12 9, 6/13	15.7 ± 36.9 9, 6/14	12.0 ± 20.2 9, 6/12	14.8 ± 35.6 8, 6/13	12.1 ± 20.0 9, 6/13
		N (%)				
Male sex	569	313 (55.0)	59 (56.7)	254 (54.6)	64 (54.9)	249 (55.6)
Education	563					
ISCED 1		5 (0.9)	2 (2.0)	2 (0.4)	1 (0.9)	3 (0.7)
ISCED 2		50 (8.9)	6 (6.1)	33 (7.3)	6 (5.2)	33 (7.6)
ISCED 3		345 (61.3)	62 (62.6)	283 (62.8)	79 (68.1)	266 (61.3)
ISCED 4		45 (7.9)	10 (10.1)	34 (7.5)	10 (8.6)	34 (7.8)
ISCED 5		118 (21.0)	19 (19.2)	99 (22.0)	20 (17.2)	98 (22.6)
Currently employed	556	241 (43.3)	**46 (45.1)**	**189 (41.0)**	53 (44.5)	182 (41.0)
Marital status	564					
Married		364 (64.6)	63 (61.2)	301 (65.3)	74 (62.2)	290 (65.2)
Single		74 (13.1)	17 (16.5)	57 (12.4)	19 (16.0)	55 (12.4)
Divorced		52 (9.2)	8 (7.8)	44 (9.5)	12 (10.1)	40 (9.0)
Widowed		74 (13.1)	15 (14.6)	59 (12.8)	14 (11.8)	60 (13.5)
Living alone	561	185 (32.8)	34 (33.3)	151 (32.8)	36 (30.5)	149 (33.5)
Prior pulmonary embolism	569	56 (9.8)	13 (12.5)	43 (9.3)	8 (6.6)	48 (10.7)
Respiratory diseases (ever diagnosed)						
Asthma	569	65 (11.4)	7 (6.7)	58 (12.5)	13 (10.7)	52 (11.6)
COPD	569	40 (7.0)	7 (6.7)	33 (7.1)	9 (7.4)	31 (6.9)
Pulmonary emphysema	569	13 (2.3)	4 (3.9)	9 (1.9)	5 (4.1)	8 (1.8)
Pneumonia	568	126 (22.2)	24 (23.3)	102 (21.9)	27 (22.5)	99 (22.1)
Sleep apnea	569	76 (13.4)	14 (13.5)	62 (13.3)	22 (18.2)	54 (12.0)
Interstitial lung disease	569	9 (1.6)	2 (1.9)	7 (1.5)	2 (1.7)	7 (1.6)
Other conditions (ever diagnosed)						
Hypertension	569	305 (53.6)	51 (49.0)	254 (54.6)	68 (56.2)	237 (52.9)
Heart failure	569	50 (8.8)	12 (11.5)	38 (8.2)	16 (13.2)	34 (7.6)
Diabetes	569	70 (12.3)	15 (14.4)	55 (11.8)	17 (14.1)	53 (11.8)
Inflammatory bowel disease	569	17 (3.0)	2 (1.9)	15 (3.2)	3 (2.5)	14 (3.1)
Neuromuscular disease	569	27 (4.8)	7 (6.7)	20 (4.3)	7 (5.8)	20 (4.5)
Autoimmune disease	569	54 (9.5)	13 (12.5)	41 (8.8)	**19 (15.7)**	**35 (7.8)**
Chronic hepatitis	569	6 (1.1)	0 (0.0)	6 (1.3)	1 (0.8)	5 (1.1)
Chronic kidney disease	569	46 (8.1)	11 (10.6)	35 (7.5)	13 (10.7)	33 (7.4)
Depression	569	73 (12.8)	**22 (21.2)**	**51 (11.0)**	**26 (21.5)**	**47 (10.5)**
Thrombophilia	569	20 (3.5)	2 (1.9)	18 (3.9)	2 (1.7)	18 (4.0)
Varicosis	566	149 (26.3)	**19 (18.3)**	**130 (28.1)**	24 (19.8)	125 (28.1)
Cancer treatment in the past 12 months	569	85 (14.9)	20 (19.2)	65 (14.0)	18 (14.9)	67 (15.0)
Smoking status	560					
Smoker		48 (8.6)	9 (8.7)	39 (8.5)	9 (7.6)	39 (8.8)
Ex-Smoker		222 (39.6)	42 (40.8)	180 (39.1)	50 (42.0)	172 (38.7)
Never smoker		290 (51.8)	52 (50.5)	238 (51.6)	59 (50.0)	231 (51.9)
sPESI score	528					
0		234 (44.3)	42 (43.3)	192 (44.6)	**47 (42.8)**	**187 (45.0)**
1		182 (34.5)	27 (27.8)	155 (36.0)	**31 (27.7)**	**151 (36.3)**
2		83 (15.7)	20 (20.6)	63 (14.6)	**28 (25.0)**	**55 (13.2)**
3		26 (4.9)	8 (8.3)	18 (4.2)	**6 (5.4)**	**20 (4.8)**
4		3 (0.6)	0 (0.0)	3 (0.7)	**0 (0.0)**	**3 (0.7)**
Treatment						
Intensive Care Unit	565	220 (38.8)	39 (37.5)	181 (39.1)	51 (42.5)	169 (37.8)
Ventilation	565	39 (6.0)	6 (5.8)	33 (7.1)	9 (7.5)	30 (6.7)
Anticoagulation	564	554 (98.2)	101 (97.1)	453 (97.8)	117 (97.5)	437 (97.8)
Embolectomy	566	3 (0.5)	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.7)
Antibiotics	564	263 (46.6)	54 (51.9)	209 (45.1)	57 (47.5)	206 (46.1)
Thrombolysis	567	38 (6.7)	6 (5.8)	32 (6.9)	9 (7.5)	29 (6.5)
Depression[2]	569					
No		465 (81.7)				
Mild		54 (9.5)				
Moderate		31 (5.5)				
Severe		19 (3.3)				
Anxiety[2]	569					
No		448 (78.7)				
Mild		75 (13.2)				
Moderate		38 (6.7)				
Severe		8 (1.4)				

ISCED: International Standard Classification of Education; sPESI: Simplified Pulmonary Embolism Severity Index; [1]Chi square test, Fisher's exact test or Mann-Whitney-U-Test used as appropriate; [2]Hospital Anxiety and Depression Scale.

Table 2
Number of hospitalizations and visits to physicians [n (%)] during the first 3 months after hospital discharge for pulmonary embolism. Significant differences ($p < 0.05$) between patients with or without depression/anxiety are highlighted in bold type.

Number of visits	N total	Total sample (n = 538)	Depression (yes) (n = 109)	Depression (no) (n = 429)	Anxiety (yes) (n = 104)	Anxiety (no) (n = 434)
Hospitalizations	516					
0		371 (71.9)	**63 (61.2)**	**308 (74.6)**	65 (65.7)	306 (73.4)
1		90 (17.4)	**19 (18.5)**	**71 (17.2)**	22 (22.2)	68 (16.3)
>1		55 (10.7)	**21 (20.3)**	**34 (8.2)**	12 (12.1)	43 (10.3)
Hospital outpatient clinic	504					
0		413 (81.9)	**76 (73.8)**	**337 (84.0)**	74 (78.8)	339 (82.7)
1		40 (7.9)	**7 (6.8)**	**33 (8.3)**	10 (10.6)	30 (7.3)
>1		51 (10.2)	**20 (19.4)**	**31 (7.7)**	10 (10.6)	41 (10.0)
General practitioner	505					
0		88 (17.4)	**13 (12.6)**	**75 (18.7)**	**11 (11.1)**	**77 (19.0)**
1		89 (17.6)	**10 (9.7)**	**79 (19.7)**	**9 (9.1)**	**80 (19.7)**
>1		328 (65.0)	**80 (77.7)**	**248 (61.6)**	**79 (79.8)**	**249 (61.3)**
Internist	512					
0		313 (61.1)	66 (64.1)	247 (60.4)	53 (53.0)	260 (63.1)
1		126 (24.6)	22 (21.4)	104 (25.4)	26 (26.0)	100 (24.3)
>1		73 (14.3)	15 (14.5)	58 (14.2)	21 (21.0)	52 (12.6)
Ophtalmologist	515					
0		443 (86.0)	93 (89.4)	350 (85.2)	82 (82.0)	361 (87.0)
1		52 (10.1)	8 (7.7)	44 (10.7)	12 (12.0)	40 (9.6)
>1		20 (3.9)	3 (2.9)	17 (4.1)	6 (6.0)	14 (3.4)
Gynecologist	513					
0		462 (90.1)	95 (91.4)	367 (89.7)	90 (90.0)	372 (90.1)
1		41 (8.0)	8 (7.7)	33 (8.1)	10 (10.0)	31 (7.5)
>1		10 (1.9)	1 (0.9)	9 (2.2)	0 (0.0)	19 (2.4)
Dermatologist	510					
0		455 (89.2)	**86 (83.5)**	**369 (90.7)**	85 (86.7)	370 (89.8)
1		29 (5.7)	**11 (10.7)**	**18 (4.4)**	9 (9.2)	20 (4.9)
>1		26 (5.1)	**6 (5.8)**	**20 (4.9)**	4 (4.1)	22 (5.3)
Otolaryngologist	514					
0		484 (94.2)	96 (93.2)	388 (94.4)	91 (91.0)	393 (94.9)
1		20 (3.9)	6 (5.8)	14 (3.4)	6 (6.0)	14 (3.4)
>1		10 (1.9)	1 (1.0)	9 (2.2)	3 (3.0)	7 (1.7)
Neurologist	514					
0		475 (92.4)	**87 (84.5)**	**388 (94.4)**	91 (91.0)	384 (92.8)
1		30 (5.8)	**11 (10.7)**	**19 (4.6)**	6 (6.0)	24 (5.8)
>1		9 (1.8)	**5 (4.9)**	**4 (1.0)**	3 (3.0)	6 (1.4)
Orthopedist	512					
0		427 (83.4)	90 (87.4)	337 (82.4)	77 (77.8)	350 (84.8)
1		36 (7.0)	3 (2.9)	33 (8.1)	8 (8.1)	28 (6.8)
>1		49 (9.6)	10 (9.7)	39 (9.4)	14 (14.1)	35 (8.4)
Urologist	515					
0		448 (87.0)	**80 (76.2)**	**368 (89.8)**	82 (82.0)	366 (88.2)
1		47 (9.1)	**16 (15.2)**	**31 (7.6)**	14 (14.0)	33 (8.0)
>1		20 (3.9)	**9 (8.6)**	**11 (2.7)**	4 (4.0)	16 (3.8)
Other specialists	510					
0		409 (80.2)	77 (74.8)	332 (81.6)	75 (75.8)	334 (81.3)
1		51 (10.0)	10 (9.7)	42 (10.1)	8 (8.1)	43 (10.5)
>1		50 (9.8)	16 (15.5)	34 (8.3)	16 (16.1)	34 (8.3)

[1]Chi square test or Fisher's exact test used.

with patients without depression. Patients with anxiety showed a significantly larger number of visits to the general practitioner compared with patients without anxiety.

At 24 months after hospital discharge, patients with depression continue to have significantly more frequent rehospitalizations and visits to neurologists than patients without depression (see additional files 3 to 5).

3.3. Association between depression and anxiety, and healthcare utilization

The results of the mixed models showed that within 2 years after hospital discharge, higher HADS-D depression scores were significantly associated with more frequent hospitalizations (estimate 0.05, 95 % confidence interval (CI) 0.01–0.09, p = 0.0063), hospital outpatient clinic visits (estimate 0.08, 95 % CI 0.03–0.13, p = 0.0009) and visits at general practitioners (estimate 0.02, 95 % CI 0.0005–0.03, p = 0.0434) (see Table 3). Moreover, higher HADS-D anxiety scores were significantly associated with more frequent hospitalizations (estimate 0.04, 95 % CI 0.002–0.08, p = 0.0413) and visits at medical experts (estimate 0.02, 95 % CI 0.002–0.04, p = 0.0268) (see Table 4). Most important confounding variables which also showed significant associations with healthcare utilization were prior respiratory diseases, current dyspnea, higher sPESI score at hospital admission and history of cancer.

4. Discussion

Overall, this study found a large number (28 %) of rehospitalizations in patients after acute PE, specifically in the first three months after hospital discharge. This number is considerably higher than in the study of Farmakis et al. [37], who reported a readmission rate of 9 % among 326 German patients with low-risk PE and early discharge, but these differences may be explained by the different PE severity in both study samples. Similarly, the results from Willich et al. [38] who investigated healthcare resource utilization of 1399 patients (mean age 62 years)

Table 3
Association between depressive symptoms and healthcare utilization: results of the mixed models (n = 503).

	Hospitalizations (1497 observations)		Hospital outpatient clinic (1484 observations)		General practitioner (1447 observations)		Specialized physicians (1478 observations)	
	Estimate (95 % CI)	p-value	Estimate (95 % CI)	p-value	Estimate (95 % CI)	p-value	Estimate (95 % CI)	p-value
Depressive symptoms[1]	0.05 (0.01; 0.09)	**0.0063**	0.08 (0.03; 0.13)	**0.0009**	0.02 (0.0005; 0.03)	**0.0434**	0.02 (−0.0005; 0.04)	0.0567
Female gender[2]	−0.33 (−0.62; −0.03)	**0.0286**	−0.09 (−0.50; 0.33)	0.6876	0.14 (0.003; 0.28)	**0.0456**	0.12 (−0.05; 0.28)	0.1650
Age	0.007 (−0.004; 0.02)	0.2116	−0.01 (−0.03; 0.003)	0.1056	−0.003 (−0.008; 0.002)	0.2718	0.004 (−0.002; 0.009)	0.1868
Education[3]								
ISCED 3	0.18 (−0.38; 0.74)	0.5246	0.72 (−0.16; 1.60)	0.1071	0.15 (−0.12; 0.42)	0.2747	0.23 (−0.09; 0.54)	0.1576
ISCED 4,5	0.48 (−0.13; 1.09)	0.1215	0.73 (−0.21; 1.67)	0.1273	0.03 (−0.12; 0.42)	0.8293	0.35 (0.01; 0.69)	**0.0439**
Follow-up[4]								
6 months	−0.66 (−1.00; −0.37)	**<0.0001**	−0.05 (−0.38; 0.29)	0.7777	−0.20 (−0.31; −0.08)	**0.0008**	−0.04 (−0.16; 0.09)	0.5515
12 months	−1.10 (−1.45; −0.75)	**<0.0001**	−0.54 (−0.91; −0.17)	**0.0048**	−0.26 (−0.38; −0.14)	**<0.0001**	−0.06 (−0.19; 0.07)	0.3980
24 months	−1.12 (−1.51 -0.73)	**<0.0001**	−0.49 (−0.91; −0.06)	**0.0261**	−0.41 (−0.55; −0.27)	**<0.0001**	−0.08 (−0.22; 0.07)	0.3063
Sum of respiratory diseases	0.24 (0.02; 0.46)	**0.0344**	−0.18 (−0.51; 0.16)	0.3056	0.08 (−0.03; 0.18)	0.1696	0.13 (0.009; 0.25)	**0.0353**
Dyspnea[5]	−0.14 (−0.26; −0.03)	**0.0130**	−0.07 (−0.22; 0.08)	0.3584	−0.11 (−0.16; −0.06)	**<0.0001**	−0.09 (−0.15; −0.04)	**0.0014**
History of cancer	1.36 (0.97; 1.75)	**<0.0001**	1.16 (0.63; 1.69)	**<0.0001**	0.11 (−0.13; 0.35)	0.3649	0.44 (0.19; 0.69)	**0.0005**
History of diabetes	−0.11 (−0.64; 0.43)	0.7001	0.01 (−0.69; 0.71)	0.9772	0.01 (−0.22; 0.24)	0.9327	−0.28 (−0.54; −0.01)	**0.0403**
History of depression	0.32 (−0.17; 0.80)	0.2030	−0.24 (−0.96; 0.49)	0.5237	0.29 (0.05; 0.52)	**0.0166**	0.31 (0.05; 0.57)	**0.0214**
Prior pulmonary embolism	1.13 (0.51; 1.75)	**0.0003**	−0.36 (−1.50; 0.79)	0.5427	0.28 (−0.08; 0.64)	0.1301	−0.07 (−0.48; 0.33)	0.7194
Duration hospitalization	0.01 (−0.002; 0.02)	0.1138	0.01 (−0.007; 0.03)	0.2028	0.006 (−0.0004; 0.01)	0.0639	0.002 (−0.006; 0.01)	0.6609
sPESI score ≥1[6]	0.40 (0.09; 0.71)	**0.0107**	0.68 (0.25; 1.11)	**0.0020**	0.06 (−0.08; 0.20)	0.3850	0.20 (0.04; 0.37)	**0.0157**

CI: confidence interval; ISCED: International Standard Classification of Education; sPESI: Simplified Pulmonary Embolism Severity Index; [1]Hospital Anxiety and Depression Scale continuous score; [2]Reference: men; [3]Reference: ISCED 1,2; [4]Reference: 3-months follow-up; [5]Chronic Respiratory Questionnaire, [6]Reference: sPESI score = 0.

Table 4
Association between anxiety symptoms and healthcare utilization: results of the mixed models (n = 499).

	Hospitalizations (1501 observations)		Hospital outpatient clinic (1488 observations)		General practitioner (1454 observations)		Specialized physicians (1485 observations)	
	Estimate (95 % CI)	p-value	Estimate (95 % CI)	p-value	Estimate (95 % CI)	p-value	Estimate (95 % CI)	p-value
Anxiety symptoms[1]	0.04 (0.002; 0.08)	**0.0413**	0.002 (−0.04; 0.04)	0.9304	0.02 (−0.002; 0.03)	0.0833	0.02 (0.002; 0.04)	**0.0268**
Female gender[2]	−0.36 (−0.65; −0.06)	**0.0190**	−0.14 (−0.58; 0.29)	0.5126	0.14 (0.003; 0.28)	0.0505	0.11 (−0.05; 0.27)	0.1703
Age	0.009 (−0.002; 0.02)	0.1185	−0.01 (−0.02; 0.006)	0.2136	−0.002 (−0.007; 0.003)	0.4344	0.005 (−0.0004; 0.01)	**0.0682**
Education[3]								
ISCED 3	0.16 (−0.40; 0.72)	0.5847	0.80 (−0.11; 1.70)	0.0830	0.17 (−0.10; 0.44)	0.2101	0.25 (−0.06; 0.56)	0.1146
ISCED 4,5	0.47 (−0.15; 1.08)	0.1360	0.73 (−0.24; 1.69)	0.1415	0.06 (−0.23; 0.35)	0.6927	0.38 (0.05; 0.72)	**0.0260**
Follow-up[4]								
6 months	−0.65 (−0.94; −0.35)	**<0.0001**	0.14 (−0.07; 0.35)	0.1778	−0.19 (−0.30; −0.08)	**0.0008**	−0.04 (−0.17; 0.08)	0.4915
12 months	−1.11 (−1.47; −0.76)	**<0.0001**	−0.52 (−0.77; −0.28)	**<0.0001**	−0.26 (−0.38; −0.14)	**<0.0001**	−0.06 (−0.19; 0.07)	0.3506
24 months	−1.13 (−1.52 -0.73)	**<0.0001**	−0.29 (−0.57; −0.0002)	**0.0498**	−0.41 (−0.54; −0.27)	**<0.0001**	−0.08 (−0.22; 0.07)	0.3007
Sum of respiratory diseases	0.23 (0.007; 0.46)	**0.0434**	−0.32 (−0.58; 0.06)	**0.0155**	0.07 (−0.03; 0.18)	0.1720	0.14 (0.02; 0.26)	**0.0227**
Dyspnea[5]	−0.16 (−0.27; −0.04)	**0.0071**	−0.23 (−0.36; 0.11)	**0.0002**	−0.11 (−0.16; −0.06)	**<0.0001**	−0.10 (−0.15; −0.04)	**0.0009**
History of cancer	1.36 (0.96; 1.75)	**<0.0001**	0.50 (0.16; 0.83)	**0.0036**	0.14 (−0.10; 0.37)	0.2548	0.47 (0.22; 0.72)	**0.0002**
History of diabetes	−0.07 (−0.61; 0.48)	0.8087	0.53 (0.14; 0.91)	**0.0080**	0.01 (−0.22; 0.25)	0.9121	−0.26 (−0.53; −0.004)	**0.0469**
History of depression	0.31 (−0.20; 0.81)	0.2294	−0.32 (−0.87; 0.24)	0.2667	0.29 (0.05; 0.52)	**0.0167**	0.30 (0.04; 0.57)	**0.0242**
Prior pulmonary embolism	1.13 (0.51; 1.75)	**0.0003**	−0.33 (−1.28; 0.61)	0.4900	0.29 (−0.07; 0.65)	0.1129	−0.07 (−0.47; 0.34)	0.7436
Duration hospitalization	0.01 (−0.0008; 0.03)	**0.0378**	0.01 (−0.009; 0.03)	0.2666	0.008 (0.001; 0.01)	**0.0242**	0.004 (−0.004; 0.01)	0.3186
sPESI score ≥1[6]	0.42 (0.11; 0.73)	**0.0086**	0.77 (0.33; 1.21)	**0.0006**	0.06 (−0.08; 0.20)	0.3922	0.20 (0.04; 0.36)	**0.0160**

CI: confidence interval; ISCED: International Standard Classification of Education; sPESI: Simplified Pulmonary Embolism Severity Index; [1]Hospital Anxiety and Depression Scale continuous score; [2]Reference: men; [3]Reference: ISCED 1,2; [4]Reference: 3-months follow-up; [5]Chronic Respiratory Questionnaire, [6]Reference: sPESI score = 0.

with PE in 5 European countries (thereof 241 from Germany, Austria and Switzerland) are not exactly comparable with the present study. They reported a VTE-related rehospitalization rate of 24.1 % in the German-speaking countries within the first year post-PE. In addition, Mohr et al. [39] recently published results from a German multicentre cohort study (n = 1017, median age 64 years) with a follow-up of one year. Overall, 23.6 % of the patients with PE were re-hospitalized at least once, and this proportion is again lower than in in the present study.

The results of the present study suggest that the presence of a depression or anxiety symptomatology significantly increases the risk of being re-hospitalized, regardless of important clinical confounders such as PE severity and concomitant conditions (e.g. cancer), and the time point within the 2-year follow-up interval. This finding is new for patients with PE, however, the association of depression and healthcare utilization has been reported in a number of studies with other health conditions such as cardiovascular disorders [19,20], cancer [22,23,40], spinal cord injury [24], Parkinson's disease [25], and osteoarthritis [26].

Less evidence is available in terms of the association between anxiety and healthcare utilization. For instance, Sansone et al. [28] found no association between anxiety symptoms and healthcare utilization in outpatients of an internal medicine clinic. Conversely, Curcio et al. [27] showed that patients after cardiac surgery with higher HADS anxiety scores had significantly more outpatient visits within 1 year after discharge than patients without anxiety. In contrast to studies on other health conditions, the present study on patients with PE also found a significant and independent association between anxiety and rehospitalization besides a significant increase of visits at medical experts with increasing anxiety scores.

Overall, the results indicate the need for a post-PE screening for depression and anxiety. Until recently, mental health problems in patients with PE have been neglected in the research on this condition, even though PE is the third most common cardiovascular disorder with rising incidence rates [1,5–11]. Currently, the guidelines of the European Society of Cardiology for diagnosis and management of acute PE still do not address mental health problems in patients with PE [41]. However, recent studies identified a considerable proportion of patients with PE experiencing mental problems such as depression and anxiety [14,15]. The present study has investigated one of the potential consequences of depression and anxiety, namely altered healthcare utilization. The identified increased rate of outpatient visits may be due to higher rates of somatization, increased awareness of bodily symptoms and their interpretation as potentially threatful [42,43]. Also, lacking information about PE and its consequences and poor health literacy may increase the number of outpatient visits [44–46]. Furthermore, depression and anxiety are known to influence patient behaviors and may result in increased smoking and alcohol abuse, poor diet, physical inactivity, and poor medication adherence [47]. These risk factors of cardiovascular health could also contribute to an increased rate of outpatient visits and rehospitalizations in depressed or anxious patients with PE [47].

Several effective approaches are available for treating depression and anxiety in patients with coronary artery disease, which may also be applied in patients with PE. These include cardiac rehabilitation, collaborative care, stress management and stress reduction techniques, cognitive behavioral therapy, and antidepressant and anxiolytic medication [48–51]. Whether treatment will also be able to reduce healthcare utilization in cardiovascular diseases including PE still remains unclear and has been studied in other populations with conflicting results [52,53].

To our knowledge the present study is the first which investigated the association of mental health and healthcare utilization in patients with PE. Further strengths of the present cohort study include the long-term follow-up over two years after PE and the inclusion of merely patients with PE, instead of VTE in general.

However, some limitations should be considered. The HADS-D is a patient-reported assessment of symptoms of depression and anxiety but does not provide a clinical diagnosis of depression and anxiety disorders. Although a large number of confounders was included in the regression models, potentially relevant confounders such as health literacy, were not assessed. Patients were recruited from a single university hospital in southern Germany which may restrict external validity. Since participants who were lost to follow-up and therefore not included in the analysis, were more severely ill, we cannot exclude an attrition bias resulting in an underestimation of healthcare utilization. Furthermore, a recall bias might have influenced the reports of healthcare utilization. Finally, due to the study design, no causal effects can be derived from the results.

5. Conclusions

In conclusion, the present study found that depression and anxiety significantly increase healthcare utilization of patients with PE. Post-PE screening for depression and anxiety in clinical practice may be a useful approach to identify affected individuals. Further studies are needed to examine whether depression and anxiety can be effectively treated in patients with PE and whether treatment-related improvements of depression and anxiety are associated with reduced healthcare utilization and costs, while improving health outcomes.

CRediT authorship contribution statement

Inge Kirchberger: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Simone Fischer:** Writing – review & editing, Methodology, Formal analysis. **Thomas M. Berghaus:** Writing – review & editing, Resources, Investigation, Funding acquisition, Conceptualization. **Jakob Linseisen:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Christine Meisinger:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (Date of approval: August 1, 2017. Reference number: 17–378). The study is performed according to the Declaration of Helsinki. Written informed consent is obtained from each study participant.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available due to data protection aspects but are available in an anonymized form from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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