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Original Research

Symptoms Suggestive of Postpulmonary Embolism Syndrome and Utilization of Diagnostic Testing

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ABSTRACT

Background: Persistent symptoms of chest pain, dyspnea, fatigue, lightheadedness, and/or syncope more than 3 months after an acute pulmonary embolism (PE) are collectively classified as postpulmonary embolism syndrome (PPES). Although PPES is increasingly recognized as an important long-term sequel of acute PE, its contemporary incidence is unclear. Furthermore, the utilization of diagnostic testing for further phenotypic characterization of these patients is unknown. This study aimed to define the incidence of PPES and evaluate the utilization of diagnostic tests among a national cohort of patients with PE.

Methods: Retrospective cohort study was performed using the national administrative database, Clinformatics DataMart Database (Optum Insight), and included adult patients (18 years or older) with no history of acute PE or pulmonary hypertension, diagnosed with acute PE between October 1, 2016, and December 31, 2018. With acute PE event as the exposure, the incidence of symptoms consistent with PPES and diagnostic test utilization among patients with PPES were evaluated.

Results: Of 21,297 incident patients with acute PE, 11,969 (56.2%) showed ≥1 symptom of PPES, which was new since their pre-PE baseline. New dyspnea was the most common and noted in 3268/15,203 (21.5%) patients, followed by new malaise or fatigue in 2894/15,643 (18.5%) patients. Among the 11,969 patients with PPES, 5128 (42.8%) received ≥1 diagnostic test, with 3242 (27%) receiving a computed tomography pulmonary angiogram, 2997 (25%) receiving an echocardiogram, and 325 (2.7%) received a ventilation-perfusion scan within 3-12 months after PE. Significantly lower use of diagnostic testing was noted in patients older than 65 years (adjusted odds ratio, 0.89; 95% CI, 0.81-0.98).

Conclusions: Symptoms consistent with PPES are common after acute PE, occurring in more than half of the patients. Diagnostic imaging for further phenotypic characterization is used in less than half of such patients with PPES.

Introduction

Acute pulmonary embolism (PE) is a leading cause of cardiovascular morbidity and mortality worldwide.[1–3] It accounts for ~100,000 deaths annually in the United States and is directly related to 5%-10% of all in-hospital deaths.[4–6] Although inpatient mortality after acute PE continues to be a significant concern, recent studies have emphasized postdischarge sequelae such as persistent symptoms, complications, and increased mortality.[7] New awareness of the long-term consequences of acute PE is

Abbreviations: CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; ICD, international classification of diseases; PE, acute pulmonary embolism; PPES, postpulmonary embolism syndrome; RPVO, residual pulmonary vascular obstruction; V/Q, ventilation-perfusion.

Keywords: chronic thromboembolic disease; chronic thromboembolic pulmonary hypertension; pulmonary embolism; pulmonary hypertension; post-PE syndrome; residual pulmonary vascular obstruction.

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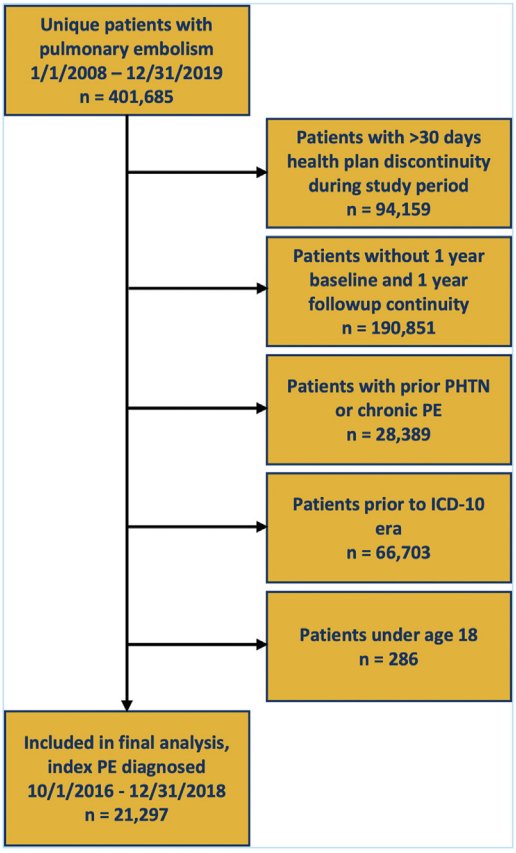


Figure 1.
Patient selection and study flow. ICD, International Classification of Diseases; PE, pulmonary embolism; PHTN, pulmonary hypertension.

important, given the previous perception that most of the patients experience full restoration of normal hemodynamics and gas exchange in the setting of nearly complete resolution of thromboemboli within 90 days.[8] The developing concept of PE as an acute event followed by potential long-term sequelae requires both deeper investigation and increased awareness.[9] For example, it is widely known that recurrent PE is a potential complication of acute PE.[3,10,11] Less well characterized is the postpulmonary embolism syndrome (PPES),[12–19] which can include symptoms such as new dyspnea, chest pain, fatigue, lightheadedness, syncope, exercise intolerance, and/or impaired functional or mental status after ≥3 months of adequate anticoagulation.[19,20] Importantly, this is a heterogeneous population and patients with PPES may experience symptoms ranging from deconditioning and no cardiopulmonary dysfunction to chronic thromboembolic pulmonary hypertension (CTEPH) with significant cardiopulmonary dysfunction.[21]

Early identification of patients with PPES is of great importance, and professional organizations have issued guideline recommendations for testing in symptomatic patients with suspected PPES, such as the use of echocardiography, 6-minute walk testing, and/or ventilation-perfusion (V/Q) scan.[22–26] Despite this growing awareness and a commitment to altering the natural history of PPES, the overall incidence of this syndrome and the utilization of diagnostic testing for its early detection remain relatively uncertain. Previous work has highlighted the concerning lack of diagnostic testing for symptomatic patients with a history of PE; however, the study design was not able to consider any symptoms preceding PE.[27]

In this study, we sought to identify the incidence of new symptoms suggestive of PPES in a contemporary, US-based, national cohort of patients with a history of acute PE. We also assessed the utilization pattern of currently recommended diagnostic tests in this cohort as suggested by guidelines from professional organizations.

Methods

Study population

This study used the national administrative database, Clinformatics DataMart Database (Optum Insight). This database includes privately insured enrollees who have enrollment with both medical and pharmacy plans that are commercially insured or purchased through a Medicare Advantage plan (part C). Ensured beneficiaries' service utilization includes emergency department, outpatient, and inpatient encounters representing billable services. This study was deemed exempt by the University of Michigan institutional review board.

All adults aged 18 years or older with an acute PE diagnosis from October 1, 2016, to December 31, 2018, were eligible for the analysis. Patients recorded ≥12 continuous months of enrollment without evidence of a previous diagnosis of acute PE to represent incident cases. In addition, 12 months of continuous enrollment after diagnosis of acute PE was required to ensure adequate capture of follow-up data. Because patients can move in and out of their insurance plans, we limited our study population to those patients continuously enrolled with no plan changes or transient plan changes no longer than 30-day gaps in coverage during the study period. Patients with acute PE with an evidence of a previous diagnosis of pulmonary hypertension or chronic pulmonary embolism were excluded. All diagnoses of acute PE were identified using the International Classification of Diseases (ICD), 10th Revision, diagnostic codes (Supplemental Table S1). Because we created a 1-year "look-back" period, we included acute PE cases starting after October 1, 2016, as ICD-10 was initiated on October 1, 2015. Primary discharge codes were used for this identification. Patients in the earlier ICD-9 era were excluded to focus on a contemporary population at a time when literature had started to recognize PPES. At-risk patients are defined as patients with no previous symptoms suggestive of PPES before their diagnosis of acute PE.

Symptoms and comorbidities

Comorbidities were also identified using ICD-10 diagnoses in the 12 months before the index PE. These included hypertension, ischemic heart disease, cerebrovascular disease, diseases of the peripheral arteries, pneumonia and flu, and chronic obstructive pulmonary disease (Supplemental Table S1). Symptoms associated with the acute PE cases were identified using ICD-10 diagnosis codes in the 3 to 12 months after PE (not including the index PE episode). Because acute PE symptoms could occur immediately after index PE, identification of symptoms suggestive of PPES was assessed 3 months post-PE, consistent with the definition of PPES. Symptoms included syncope, malaise and fatigue, dyspnea, unspecified chest pain, dizziness, and/or vertigo.

Identification of diagnostic testing procedures

Utilization of diagnostic tests was assessed in the same period of 3 to 12 months after the acute PE event using Current Procedure Terminology codes with both evidence of billable services in these timeframes and the number of diagnostic testing procedures performed within those timeframes (Supplemental Table S2). Diagnostic testing

Table 1. Baseline characteristics of study population.

Baseline characteristics	Full cohort, N = 21,297	PPES present, n = 11,969	PPES absent, n = 9328	*P*
Demographics				
Age, y	67.9 ± 14.2	67.7 ± 14.43	68.1 ± 14.0	.04
Male sex	9641 (45.3)	5483 (45.8)	4158 (44.6)	.08
Race				
White	14,194 (66.7)	8016 (67.0)	6178 (66.2)	.25
Black	2475 (11.6)	1444 (12.1)	1031 (11.1)	.02
Hispanic	1632 (7.7)	907 (7.6)	725 (7.8)	.60
Asian	365 (1.7)	196 (1.6)	169 (1.8)	.33
Household income, $				
<40,000	4938 (23.2)	2756 (23.0)	2182 (23.4)	.53
40,000-49,000	1423 (6.7)	816 (6.8)	607 (6.5)	.37
50,000-59,000	1547 (7.3)	844 (7.1)	703 (7.5)	.18
60,000-74,000	2055 (9.7)	1200 (10.0)	855 (9.2)	.04
75,000-99,000	2735 (12.8)	1591 (13.3)	1144 (12.3)	.03
100,000+	4255 (20.0)	2373 (19.8)	1882 (20.2)	.53
Missing	1992 (9.4)	1047 (8.7)	945 (10.1)	<.01
Unknown	2352 (11.0)	1342 (11.2)	1010 (10.8)	.37
Comorbid conditions before PE diagnosis				
Hypertension	15,345 (72.1)	8560 (71.5)	6785 (72.7)	.05
Ischemic heart disease	4417 (20.7)	2345 (19.6)	2072 (22.2)	<.01
Cerebrovascular disease	2717 (12.8)	1397 (11.7)	1320 (14.2)	<.01
Peripheral arterial disease	4915 (23.1)	2598 (21.7)	2317 (24.8)	<.01
Pneumonia	4137 (19.4)	2195 (18.3)	1942 (20.8)	<.01
Chronic obstructive pulmonary disease	6854 (32.2)	3727 (31.1)	3127 (33.5)	<.01
Symptoms in 12 mo preceding index PE				
Syncope	1325 (6.2)	481 (4.0)	844 (9.0)	<.01
Malaise and fatigue	5654 (26.5)	1851 (15.5)	3803 (40.8)	<.01
Dyspnea	6094 (28.6)	2015 (16.8)	4079 (43.7)	<.01
Hemoptysis	209 (1.0)	68 (0.6)	141 (1.5)	<.01
Chest pain, unspecified	5236 (24.6)	1744 (14.6)	3492 (37.4)	<.01
Dizziness	2396 (11.3)	862 (7.2)	1534 (16.4)	<.01

Values are mean ± SD or n (%).
PE, pulmonary embolism; PPES, postpulmonary embolism syndrome.

included echocardiogram, V/Q scan, and computed tomography pulmonary angiography (CTPA).

Statistical analysis

For the initial descriptive analysis, the study cohort was divided into 2 subgroups. The first group reflected patients that reported 1 or more new symptoms in the 3- to 12-month period after acute PE. A symptom was considered "new" if that concern was not noted in the year before PE. This first group was considered to have PPES owing to the presence of ≥1 new symptom. Patients who did not develop any new post-PE symptom were included in the second group and were considered to not have PPES.

A bivariate analysis of symptom and comorbidity rates and counts for patients with acute PE were calculated. Imaging rates were calculated for 3 to 12 months after the acute PE event. To examine associations between PPES symptom status groups and imaging studies, multivariable logistic regression models were fitted to estimate the unadjusted odds of a diagnostic testing procedure being used after PE. An adjusted analysis involved fitting models adjusted for age, sex, race, income level, education, and comorbidities as previously defined to enable adjusted odds of the exposure.

To further our methodology, ICD-10 codes used in this analysis were queried in the Data Direct online tool at our institution (Michigan Medicine). This was reviewed and approved by University of Michigan institutional review board (HUM 00132118). We identified 25 consecutive patients with primary discharge code of acute PE from January 1, 2022, to December 31, 2022. On a chart review, 24 of 25 were noted to present with acute PE as primary discharge diagnosis. New chest pain was identified in 8 (30%) patients, new shortness of breath was identified in 10 (41.7%) patients at the 3- to 12-month follow-up. On the chart review, these symptoms were confirmed and noted in each patient as identified by the ICD-10 code.

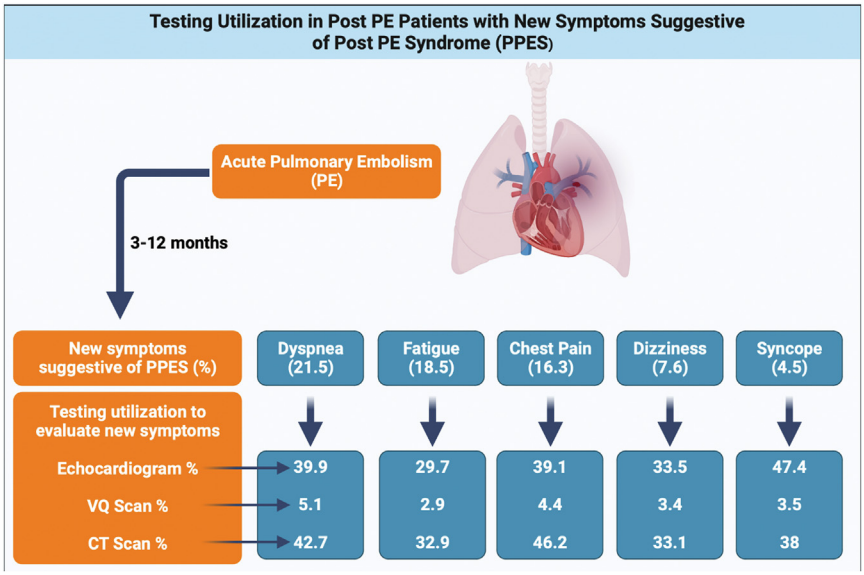
Results

A total of 21,297 patients met our study inclusion criteria (Figure 1). The average age at incident acute PE was 67.9 years; 9641 (45.3%) were men and 14,194 (66.7%) were Whites. PPES cohort was younger and more likely to be African American. These demographic differences were statistically significant ($P < .05$) but clinically insignificant. There were no other significant demographic differences between patients who developed PPES and those who did not. Table 1 includes other demographic and clinical variables analyzed at baseline for the comprehensive cohort and the subgroups with and without PPES. However, patients with symptoms suggestive of PPES were also

Table 2. Rates of new symptoms 3-12 months after index PE.

Symptom	n/N[a]	%
Dyspnea	3268/15,203	21.5
Malaise and fatigue	2894/15,643	18.5
Chest pain, unspecified	2615/16,061	16.3
Dizziness and/or vertigo	1440/18,901	7.6
Syncope	892/19,972	4.5

PE, pulmonary embolism.
[a] Percentage reflects the number of patients with a new symptom after PE whereas being free from that given symptom before PE.



Central Illustration.
Testing utilization in patients after PE with new symptoms suggestive of PPES. CT, computed tomography; PE, pulmonary embolism; PPES, postpulmonary embolism syndrome; V/Q, ventilation-perfusion.

less likely to present with hypertension, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, chronic obstructive pulmonary disease, and pneumonia at baseline.

At least 1 new symptom suggestive of PPES was noted in 11,969 (56.2%) of the 21,297 patients. New dyspnea was noted in 3268 of 15,203 at-risk patients (21.5%), followed by new malaise and fatigue in 2894 of 15,643 at-risk patients (18.5%), and new chest pain in 2615 of 16,061 at-risk patients (16.3%). Table 2 reports these crude incidence rates of all PPES symptoms analyzed in this cohort.

Next, the utilization of diagnostic testing among the PPES cohort was evaluated. At least one diagnostic test was ordered in 5128 (42.8%) of the 11,969 patients with ≥1 new symptom of PPES. Moreover, 3242 (27%) of the patients with PPES received a CTPA, 2997 (25%) received an echocardiogram, and 325 (2.7%) underwent a V/Q scan in the 3- to 12-month follow-up period after an acute PE diagnosis (Central Illustration). In addition to evaluating diagnostic test utilization in the entire PPES subgroup, utilization was also evaluated for each new symptom. Table 3 demonstrates the number of each test ordered among patients with the specified new symptom. Figures 2-4 show the rate of a new symptom among patients who did not experience the symptom preceding PE and rates of diagnostic testing ordered for each symptom. On the multivariable analysis, significantly lower use of diagnostic testing was noted in patients older than 65 years (adjusted odds ratio, 0.89; 95% CI, 0.81-0.98).

Discussion

This analysis suggests that PPES is common in a large proportion of patients with PE who are symptomatic 3 months after an acute PE. Our findings also identified a lower than expected use of tests that may have resulted in a better understanding of the etiology of the residual symptoms and may have led to potential treatment interventions for these symptomatic patients. Appropriate use of these tests play an important role in the characterization of PPES phenotypes such as asymptomatic residual pulmonary vascular obstruction (RPVO), RPVO associated with symptoms, and CTEPH manifested by RPVO and pulmonary hypertension.

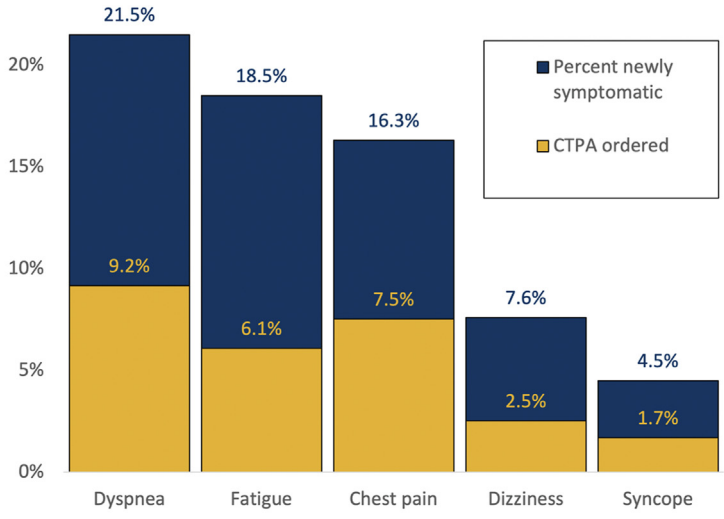
It is important to note that although V/Q scanning has a sensitivity of >96% and a specificity of 90%-95% for RPVO identification in PPES, it was performed in <5% of patients with PPES in this cohort.[28] It is concerning that a similar underutilization of V/Q scanning in the evaluation of possible pulmonary arterial hypertension or CTEPH was recognized in a previous study involving a cohort of patients evaluated in the period from 2005 through 2007.[29] The underutilization of V/Q scans identified by 2 studies performed >10 years apart identifies a critical need for educating providers regarding the importance of this testing modality. The utilization of V/Q scan in patients with post–acute PE not only assists with the early diagnosis of RPVO and CTEPH but is also a powerful predictor of future thromboembolic events. The SCOPE study, a multicenter study in Italy, recruited 647 patients who experienced an acute symptomatic PE and demonstrated that the presence of RPVO was an independent predictor of recurrent venous thromboembolic events and/or CTEPH.[30]

Echocardiography provides valuable prognostic and diagnostic information by evaluating right ventricular function and structure and an estimation of right systolic pressure, after acute PE. A post

Table 3. Number of tests ordered for patients with each new symptom.

	Echocardiography ordered		V/Q ordered		CT ordered	
	n/N[a]	%	n/N[a]	%	n/N[a]	%
Dyspnea	1305/3268	39.9	168/3268	5.1	1395/3268	42.7
Malaise and fatigue	860/2894	29.7	83/2894	2.9	953/2894	32.9
Chest pain unspecified	1023/2615	39.1	116/2615	4.4	1209/2615	46.2
Dizziness and/or vertigo	483/1440	33.5	49/1440	3.4	477/1440	33.1
Syncope	423/892	47.4	31/892	3.5	339/892	38.0

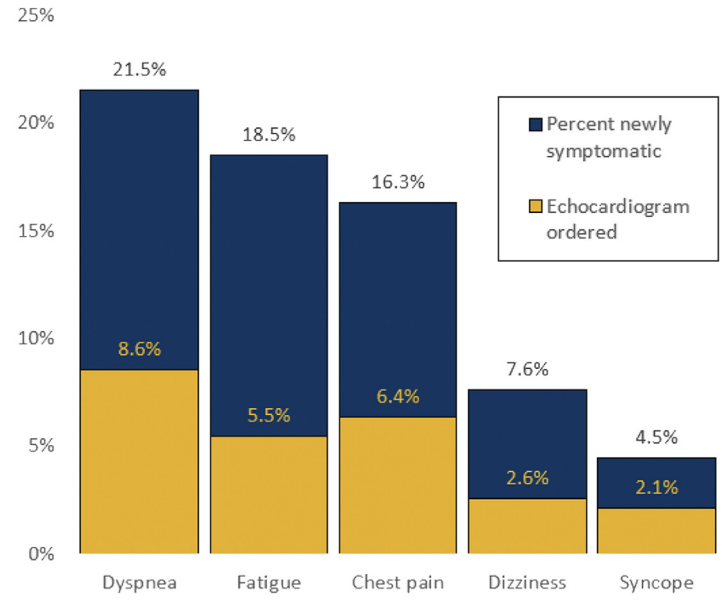
CT, computed tomography; PE, pulmonary embolism; V/Q, ventilation-perfusion.
[a] No. of study ordered/no. of patients with specified new symptom.



	Dyspnea	Fatigue	Chest pain	Dizziness	Syncope
Patients without symptoms before PE	15203	15643	16061	18901	19972
Patients with new symptoms after PE	3268	2894	2615	1440	892
Patients with new symptoms getting tested (CTPA)	1395	953	1209	477	339

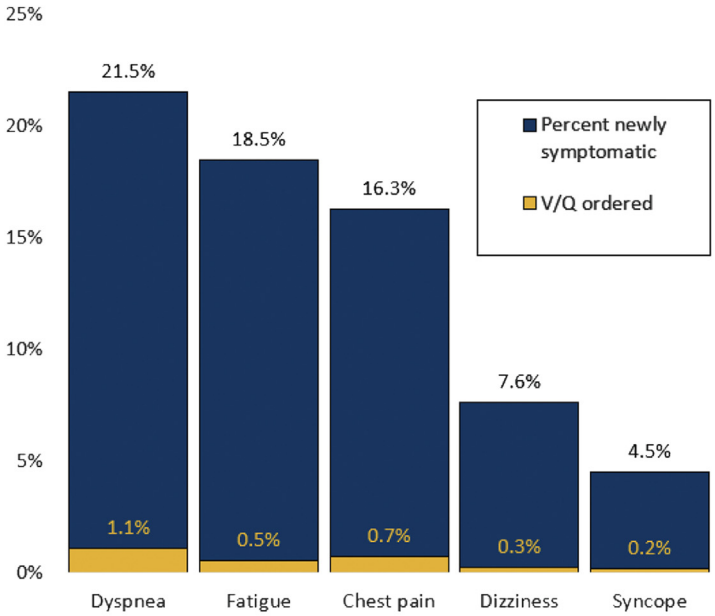
Figure 2.
Rates of computed tomography angiogram testing in patients with new symptoms after PE. CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

hoc analysis from the Pulmonary Embolism Thrombolysis trial indicated that nonrecovery of right ventricular function at 6 months was predictive of CTEPH or functional impairment at a median of 3 years follow-up.[31] However, echocardiogram may be inconclusive or even normal in early stages of CTEPH,[22] emphasizing the importance of a multimodality approach to the evaluation of PPES. Nonetheless, even echocardiogram was performed in only 25% of patients with PPES in our cohort.



	Dyspnea	Fatigue	Chest pain	Dizziness	Syncope
Patients without symptoms before PE	15203	15643	16061	18901	19972
Patients with new symptoms after PE	3268	2894	2615	1440	892
Patients with new symptoms getting tested (Echocardiogram)	1305	860	1023	483	423

Figure 3.
Rates of echocardiogram testing in patients with new symptoms after PE. PE, pulmonary embolism.



	Dyspnea	Fatigue	Chest pain	Dizziness	Syncope
Patients without symptoms before PE	15203	15643	16061	18901	19972
Patients with new symptoms after PE	3268	2894	2615	1440	892
Patients with new symptoms getting tested (V/Q)	168	83	116	49	31

Figure 4.
Rates of V/Q scan testing in patients with new symptoms after PE. PE, pulmonary embolism; V/Q, ventilation-perfusion.

However, the study most frequently performed in patients with suspected PPES was a CTPA. Although CTPA is the gold standard diagnostic testing for evaluation of acute PE, it has a low sensitivity to detect chronic PE or RPVO. Tunariu et al[28] reported that V/Q scan had a sensitivity > 95% for the diagnosis of CTEPH, whereas the sensitivity of CTPA was 51%. A negative-result CTPA in a patient with PPES may give the clinician a false reassurance that the persistent symptoms are not from RPVO, leading to a delay in a time-sensitive diagnosis such as CTEPH.

Maintaining a high index of suspicion for possible PPES in patients who remain symptomatic 3 months after PE combined with a formalized, guideline-based approach to the evaluation of such patients is necessary for the diagnosis and phenotyping of RPVO. For example, RPVO with exercise limitation, also known as chronic thromboembolic disease without pulmonary hypertension, is an important RPVO subgroup because it may reduce right ventricular contractile reserve and exercise capacity.[32] Further research is needed to better define the consequences of RPVO on recurrent PE events and functional limitations. An understanding of the effect of long-term anticoagulation on RPVO is also needed.

A better understanding of the PPES spectrum of phenotypes has the potential to improve outcomes by providing tailored therapies. For example, patients with PPES and no RPVO may have symptoms related to skeletal muscle deconditioning amenable to treatment with cardiopulmonary rehabilitation.[33] This intervention has the potential to improve functional status in many patients with PPES, and must be further evaluated in prospective studies. The consequences of underused diagnostic testing in our cohort is beyond the scope of our study. However, our concern is that undertesting may contribute to delays in CTEPH diagnosis at its earliest stage because a growing body of evidence supports the likelihood of acute PE triggering the cascade of events that first leads to chronic thromboembolic disease and eventually results in CTEPH.[34,35] Establishing dedicated PE clinics may be a way to address this gap in guideline-driven multimodality PPES evaluation. The establishment of coordinated, multidisciplinary, inpatient PE response teams has resulted in improvement in care quality for acute PE.

Our study should be interpreted in context of the following limitations. This is a retrospective study using an administrative claims database. Symptom and diagnostic codes in these databases may be driven by reimbursement concerns or "rule-out diagnoses"; thus, it is possible that non-PE cases were included in the cohort.[36] However, we believe this is unlikely to have been a major confounder given the substantial magnitude of symptom incidence and testing underutilization. We are also unable to rule out whether the testing was performed for another alternate diagnosis. Symptoms of PPES could also occur from other alternate cardiopulmonary diagnosis that occurred in the peri-incident acute PE event. From a symptom evaluation status, we also were limited to the binary presence or absence of a symptom and were unable to measure worsening of preexisting symptoms as markers of PPES. This may have underestimated the true incidence of PPES because our definition required a new symptom to have developed. Using this methodology, we essentially excluded anyone with a previous symptom of dyspnea/chest pain/fatigue/syncope as developing PPES in the follow-up period after acute PE. This likely lead to us also observing lower baseline comorbidity burden in PPES cohort. Finally, these findings are relevant for this insured population and may not reflect either the incidence of PPES or diagnostic testing in other populations.

In summary, we demonstrate that PPES is common and may affect most of the acute PE patients in the 3- to 12-month follow-up window after their acute event. The historical belief that patients with acute PE experience complete recovery with anticoagulation needs to be reevaluated, and future work should focus on enhancing our understanding of PPES. Finally, there is suggestion that recommended diagnostic testing for characterization of PPES may be underused in identifying these patients.

Declaration of competing interest

Geoffrey Barnes is a consultant for Pfizer, Bristol-Myers Squibb, Janssen, Abbott Vascular, and Boston Scientific and reports grant funding from Boston Scientific. Victor Moles reports funding provided to the University of Michigan to perform research from Acceleron Pharma and Janssen. Kenneth Rosenfield is a consultant and a member of the scientific advisory board, Abbott Vascular, Althea Medical, Angiodynamics, Auxetics, Becton-Dickinson, Boston Scientific, Contego, Crossliner, Innova Vascular, InspireMD, Janssen/Johnson & Johnson, Magneto, Mayo Clinic, MedAlliance, Neptune Medical, Penumbra, Philips, Surmodics, Terumo, Thrombolex, Truvic, Vasorum, and Vumedi; receives institutional research grants from the National Institutes of Health, Abiomed, Boston Scientific, Novo Nordisk, Penumbra, and Getinge-Atrium; reports equity interest in Accolade, Access Vascular, Aerami, Althea Medical, Auxetics, Contego, Crossliner, Cruzar Systems, Embolitech, Endospan, Imperative Care/Truvic, Innova Vascular, InspireMD, JanaCare, Magneto, MedAlliance, Neptune Medical, Orchestra, PQ Bypass, Prosomnus, Shockwave, Skydance, Summa Therapeutics, Thrombolex, Valcare, Vasorum, and Vumedi; and is a board member and founder of The PERT Consortium. All other authors have no relevant relationships to disclose.

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Ethics statement and patient consent

This research was conducted according to the ethical standard of the University of Michigan institutional review board (HUM00132118).

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.101063.

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