

Prevalence of Pulmonary Embolism Among Emergency Department Patients With Syncope: A Multicenter Prospective Cohort Study

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Study objective: The prevalence of pulmonary embolism among patients with syncope is understudied. In accordance with a recent study with an exceptionally high pulmonary embolism prevalence, some advocate evaluating all syncope patients for pulmonary embolism, including those with another clear cause for their syncope. We seek to evaluate the pulmonary embolism prevalence among emergency department (ED) patients with syncope.

Methods: We combined data from 2 large prospective studies enrolling adults with syncope from 17 EDs in Canada and the United States. Each study collected the results of pulmonary embolism-related investigations (ie, D-dimer, ventilation-perfusion scan, or computed tomography [CT] pulmonary angiography) and 30-day adjudicated outcomes: pulmonary embolism or nonpulmonary embolism outcome (arrhythmia, myocardial infarction, serious hemorrhage, and death).

Results: Of the 9,374 patients enrolled, 9,091 (97.0%; median age 66 years, 51.9% women) with 30-day follow-up were analyzed: 547 (6.0%) were evaluated for pulmonary embolism (278 [3.1%] had D-dimer, 39 [0.4%] had ventilation-perfusion scan, and 347 [3.8%] had CT pulmonary angiography). Overall, 874 patients (9.6%) experienced 30-day serious outcomes: 818 patients (9.0%) with nonpulmonary embolism serious outcomes and 56 (prevalence 0.6%; 95% confidence interval 0.5% to 0.8%) with pulmonary embolism (including 8 [0.2%] out of 3521 patients diagnosed during the index hospitalization and 7 [0.1%] diagnosed after the index visit). Eighty-six patients (0.9%) died, and 4 deaths (0.04%) were related to pulmonary embolism. Only 11 patients (0.1%) with a nonpulmonary embolism serious condition had a concomitant pulmonary embolism.

Conclusion: The prevalence of pulmonary embolism is very low among ED patients with syncope, including those hospitalized after syncope. Although an underlying pulmonary embolism may cause syncope, clinicians should be cautious about indiscriminate investigations for pulmonary embolism. [*Ann Emerg Med.* 2019;■:1-11.]

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INTRODUCTION

Syncope is a common emergency department (ED) presenting complaint, accounting for up to 3% of visits and up to 3% of hospital admissions from the ED.^{1,2} Syncope is defined as a sudden transient loss of consciousness followed by spontaneous complete recovery.³ Although the cause of syncope is benign (eg, vasovagal syncope) among a majority of patients, a small proportion of patients have a serious underlying cause.^{4,5} These serious underlying conditions include arrhythmias (eg, ventricular tachycardia) or nonarrhythmic conditions (eg, pulmonary embolism, myocardial infarction, significant hemorrhage). The Pulmonary Embolism in Syncope Italian Trial enrolled

only patients who were hospitalized for the first episode of syncope and performed a systematic evaluation for pulmonary embolism regardless of whether alternative explanations for syncope were identified.⁶ Of the 560 hospitalized patients enrolled, 1 in 6 patients was found to have an underlying pulmonary embolism. The study did not report pulmonary embolism among patients not hospitalized or the clinical significance of the pulmonary embolism identified. However, this prevalence was strikingly higher than previously reported in smaller observational studies, raised serious questions in regard to missed pulmonary embolism, and challenged clinicians to investigate such patients for possible pulmonary embolism, including those with a clearly identified cause for their syncope.^{1,4,7-11}

*All members are listed in the [Appendix](#).

Editor's Capsule Summary*What is already known on this topic*

A large multicenter study published in 2016 reported a high proportion of pulmonary embolus diagnoses among hospitalized patients with incident syncope, contradicting the findings of previous work.

What question this study addressed

The proportion of pulmonary embolus diagnoses in greater than 9,000 emergency department (ED) syncope patients enrolled at 17 North American sites was investigated. Both admitted and discharged patients were included and assessed at 30 days.

What this study adds to our knowledge

Prevalence of pulmonary embolism was 0.6% (95% confidence interval 0.5% to 0.8%). Although evaluation for pulmonary embolism was performed at the discretion of the managing physician, even with a worst-case scenario analysis the prevalence was much lower than in the 2016 study.

How this is relevant to clinical practice

The design of the 2016 study may make its results less clinically useful for the practicing emergency physician. The current study suggests that indiscriminate evaluation for pulmonary embolism in ED syncope patients is not warranted.

Previous studies have reported that most evaluations performed for patients with syncope have low yield, expose patients to risk, increase the length of stay and ED crowding, increase costs, and contribute to the epidemic of overinvestigations.¹²⁻¹⁴ Given pulmonary embolism's frequency, routinely evaluating patients with syncope for pulmonary embolism would generate a substantial burden on any health care system.^{1,2,4,15} Yet the interpretation of the Pulmonary Embolism in Syncope Italian Trial findings requires more detailed information than previously available in regard to the true prevalence of pulmonary embolism in comparable patient populations.

Two large prospective cohort studies, one in Canada and the other in the United States, were recently conducted to characterize high-risk factors for all serious outcomes (including pulmonary embolism) after an ED presentation for syncope. The 2 groups of investigators sought to combine their collective experience to date to help contextualize the Pulmonary Embolism in Syncope Italian Trial findings, and to better characterize the prevalence of

pulmonary embolism among North American patients presenting to an ED after syncope.

The primary objective of this pragmatic study was to assess the 30-day prevalence of pulmonary embolism among patients presenting to the ED with syncope, using pooled data from 2 prospective studies. Secondary objectives were to evaluate the prevalence of pulmonary embolism among subgroups of patients comparable to those in the Pulmonary Embolism in Syncope Italian Trial; specifically, among those hospitalized for syncope and among those with an alternative nonpulmonary embolism serious underlying condition.

MATERIALS AND METHODS**Setting and Selection of Participants**

We conducted a prospective multicenter cohort study in 17 large EDs across Canada (the Risk Stratification of Emergency Department Syncope Study) and the United States (Improving Syncope Risk Stratification in Older Adults Study) to enroll patients presenting with syncope. The study sites are listed in [Appendix E1](#), available online at <http://www.annemergmed.com>. We enrolled adult patients with syncope who presented to a study site ED within 24 hours of the event. Patients who did not experience true syncope (prolonged loss of consciousness >5 minutes, change in their mental status from baseline after the syncope, or obvious witnessed seizure or head trauma causing loss of consciousness) were excluded.^{3,16} Patients who were unable to provide proper history because of alcohol intoxication, illicit drug use, or language barrier were also excluded.

The primary objective of each parent study was to identify patients with serious underlying conditions causing the syncope, and study methods were deemed sufficiently homogeneous in regard to study population, investigations, and ascertainment of the outcome of pulmonary embolism to justify data pooling.

The 2 studies differed in 3 important ways. First, the Canadian study enrolled any adult patient (≥ 16 years) presenting with syncope, whereas the US study enrolled only older patients (≥ 60 years) with syncope. Second, the Canadian study excluded patients with presyncope or near syncope (imminent sensation of passing out with loss of consciousness), whereas the US study included these patients. Third, the Canadian study collected data on history of syncope, whereas the US study collected only history of syncope in the past year. We prespecified subgroup analyses by country, age, and true syncope (excluding patients with presyncope) to test the validity of data pooling.

Data Collection and Processing

At the study sites, on-duty emergency physicians, nurses, and on-site research personnel screened consecutive patients with the presenting complaints of syncope, presyncope, fainting, blackout, loss of consciousness, fall, collapse, seizure, dizziness, or lightheadedness. Emergency physicians applied the inclusion and exclusion criteria and obtained consent before patient inclusion in the study. Potentially eligible patients with a presenting complaint suggestive of syncope who were not eligible or who were missed were identified by trained research assistants through review of all ED visits during the study period.

At the Canadian sites, the ethics committees at all the participating study sites approved the study protocol without requiring written consent. At the US sites, the institutional review boards approved the study and written consent was obtained from all participating subjects or their legally authorized representative.

We collected demographics and medical history, including active cancer, presenting vital signs, results of investigations performed in the ED, and disposition (eg, hospitalized, held in observation unit, discharged home). D-dimer test results were available only for the Canadian cohort; the local assay and cut point in use at each Canadian study site are detailed in [Appendix E1](#), available online at <http://www.annemergmed.com>. For this study, we classified the D-dimer test result according to the conventional local cut point (eg, 500 ng/mL) and did not adjust this cut point according to the patient's age. In both the Canadian and US study sites, imaging test results related to possible pulmonary embolism, including ventilation-perfusion scan or computed tomography (CT) pulmonary angiography, were retrieved, and the final interpretation on the medical record was used to classify the study result as being positive for pulmonary embolism. We also identified the timing and location of testing (ie, in the ED or outside the ED while the patient was either in the observation unit or hospitalized). Because both the Canadian and US studies were pragmatic, investigations for pulmonary embolism were performed at the discretion of the treating physician(s), as were all investigation, treatment, and disposition decisions.

Outcome Measures

The study outcome was the identification of pulmonary embolism within 30 days of the index ED visit. It had to be adjudicated as clinically relevant and the likely cause of the index syncope. Each parent study established follow-up and adjudication methods to attempt to identify any serious

underlying condition that caused the syncope and included pulmonary embolism and nonpulmonary embolism serious conditions ([Appendix E2](#), available online at <http://www.annemergmed.com>). This list of serious underlying conditions and assessment for them within 30 days of the index ED visit were considered most clinically relevant for syncope studies by an international panel of experts.¹⁶

For the Canadian study, trained chart analysts performed a structured review of all available documents in the hospital medical records related to index and subsequent visits, including consultations, hospitalizations, inpatient and outpatient testing, and hospital death records. At 30 days, a scripted telephone follow-up interview was performed to identify any other contact with the health care system, new symptoms and diagnoses, and adverse outcomes. Additionally, we reviewed health records at all local adult hospitals, and coroners' death records for patients in Ontario, Canada, and health and death records using an administrative health database (NetCare) for patients in Alberta, Canada. An adjudication committee composed of 3 physicians blinded to all the study data except the study outcomes reached consensus in regard to outcomes among the study patients, including the diagnosis of pulmonary embolism.

For patients enrolled in the United States, chart review and 30-day telephone follow-up were also performed, and hospital records at any nonstudy-site hospitals were retrieved when identified at telephone follow-up. All potential serious outcomes identified by research staff were adjudicated by a study physician. An independent review of a subset of cases by the coordinating center demonstrated a 100% sensitivity in identification of serious clinical outcomes, and interrater reliability for all other chart review items exceeded a κ of 0.8.

Primary Data Analysis

We report continuous data with median and interquartile range and categorical variables with frequency or proportion for our descriptive analysis. We conducted subgroup analyses by country, age, syncope versus presyncope, and first-time syncope. We report 95% confidence interval (CI) with the exact binomial method in cases in which the expected prevalence was less than 5, or the normal approximation method otherwise. We conducted a sensitivity analysis to report an estimate of patients with potentially missed pulmonary embolism among those not evaluated and the worst-case scenario analysis to provide the highest possible proportion of patients with pulmonary embolism in the cohort, with the assumption that all the deaths from unknown cause and all

Table 1. Demographic and clinical characteristics and ED management of patients presenting with syncope.

Characteristic	Merged Cohort, No. (%)		Canadian Cohort, No. (%)		US Cohort, No. (%)	
	All Patients, N=9,091	Evaluated for PE, N=547* (6.0%)	All Patients, N=5,415	Evaluated for PE, N=365 (6.7%)	All Patients, N=3,676	Evaluated for PE, N=182 (5.0%)
Characteristic						
Age, median (IQR), y	66 (49–77)	66 (53–77)	56 (32–74)	61 (41–76)	71 (65–79)	69 (64–77)
Women	4,715 (51.9)	257 (47.0)	2,937 (54.2)	181 (49.6)	1,778 (48.4)	76 (41.8)
Medical history						
Hypertension	4,170 (45.9)	236 (43.1)	1,743 (32.2)	128 (35.1)	2,427 (66.0)	108 (59.3)
Diabetes mellitus	1,484 (16.3)	97 (17.7)	580 (10.7)	46 (12.6)	904 (24.6)	51 (28.0)
Coronary artery disease	1,682 (18.5)	101 (18.5)	668 (12.3)	57 (15.6)	1,014 (27.6)	44 (24.2)
Atrial fibrillation or flutter	893 (8.8)	60 (11.0)	382 (7.1)	35 (9.6)	511 (13.9)	25 (13.7)
Valvular heart disease	514 (5.7)	30 (5.5)	198 (3.7)	16 (4.4)	316 (8.6)	14 (7.7)
Congestive heart failure	657 (7.2)	42 (7.7)	188 (3.5)	18 (4.9)	469 (12.8)	24 (13.2)
Active cancer	383 (4.2)	42 (7.7)	141 (2.6)	21 (5.8)	242 (6.6)	21 (11.5)
Vital signs in the ED						
Pulse rate >100 beats/min	1,159 (12.8)	114 (20.8)	861 (15.9)	89 (24.4)	298 (8.1)	25 (13.7)
Systolic blood pressure <110 mm Hg	2,957 (32.5)	212 (38.8)	2,210 (40.8)	164 (45.1)	747 (20.3)	48 (26.4)
Investigations						
ECG	8,774 (96.5)	534 (97.6)	5,165 (95.4)	357 (97.8)	3,609 (98.2)	177 (97.3)
Blood tests	8,292 (91.2)	544 (99.5)	4,637 (85.6)	362 (99.2)	3,655 (99.4)	182 (100)
VQ	39 (0.4)	39 (7.1)	31 (0.6)	31 (8.5)	8 (0.2)	8 (4.4)
CTPA	347 (3.8)	347 (63.4)	173 (3.2)	173 (47.4)	174 (4.7)	174 (95.6)
VQ or CTPA	380 (4.2)	380 (69.5)	199 (3.7)	199 (54.5)	181 (4.9)	181 (99.5)
ED disposition						
Hospitalized	3,557 (39.1)	255 (46.6)	702 (13.0)	90 (24.7)	2,855 (77.7)	165 (90.7)
Serious outcomes						
All serious outcomes (including PE)	874 (9.6)	118 (21.6)	391 (7.2)	61 (16.7)	483 (13.1)	57 (31.3)
PE	56 (0.6)	56 (10.2)	31 (0.6)	31 (8.5)	25 (0.7)	25 (13.7)
Identified in the ED	41 (0.5)	41 (7.5)	22 (0.4)	22 (6.0)	19 (0.5)	19 (10.4)
Identified in hospital	8 (0.1)	8 (0.5)	3 (0.1)	3 (0.8)	5 (0.1)	5 (2.7)
Identified after the index ED visit/hospitalization	7 (0.1)	7 (1.3)	6 (0.1)	6 (1.6)	1 (0.03)	1 (0.6)
PE leading to death	4 (0.0)	4 (0.7)	3 (0.1)	3 (0.8)	1 (0.0)	1 (0.5)
Non-PE serious outcomes	818 (9)	62 (11.3)	360 (6.6)	30 (8.2)	458 (12.5)	32 (17.6)
Total deaths not related to PE [†]	82 (0.9)	9 (1.6)	39 (0.7)	6 (1.6)	43 (1.2)	3 (1.6)
Death from unknown cause	52 (0.6)	6 (1.1)	21 (0.4)	3 (0.8)	31 (0.8)	3 (1.6)
Non-PE serious conditions[‡]						
Arrhythmias	536 (5.9)	34 (6.2)	229 (4.2)	16 (4.4)	307 (8.4)	18 (9.9)
Myocardial infarction	119 (1.3)	13 (2.4)	51 (0.9)	8 (2.2)	68 (1.8)	5 (2.7)
Serious structural heart disease	79 (0.9)	10 (1.8)	43 (0.8)	5 (1.4)	36 (1.0)	5 (2.7)
Aortic dissection	4 (0.0)	0	4 (0.1)	0	0	0
Subarachnoid hemorrhage	8 (0.1)	0	6 (0.1)	0	2 (0.1)	0
Cardiac procedural interventions	303 (3.3)	15 (2.7)	141 (2.6)	8 (2.2)	162 (4.4)	8 (4.4)
PE+another serious outcome [§]	11 (0.1)	11 (2)	8 (0.1)	8 (2.2)	3 (0.1)	3 (1.6)

PE, Pulmonary embolism; IQR, interquartile range; VQ, ventilation-perfusion scan; CTPA, CT pulmonary angiography.

*Includes 278 patients in the Canadian cohort who had D-dimer testing performed.

[†]Includes patients who experienced death because of non-PE serious conditions listed below and deaths from unknown cause.

[‡]Some patients experienced more than one serious condition.

[§]Five patients experienced arrhythmia, 3 experienced myocardial infarction, 1 received a diagnosis of aortic dissection, 1 received a diagnosis of cardiomyopathy, and 1 had pacemaker insertion.

those lost to follow-up had undiagnosed pulmonary embolism.

Because this was a secondary analysis of 2 existing cohorts, no a priori sample size calculation was conducted. A sample size of 9,000 patients, however, produces a 2-sided 95% CI with a width equal to 0.004 when the sample proportion is 0.01, using the exact Clopper-Pearson's CI formula.¹⁷ Thus, our pooled sample size across both cohorts allowed estimation of pulmonary embolism prevalence with a margin of error of 0.2%, given an anticipated prevalence estimate of 1%.

RESULTS

We enrolled 9,374 patients with syncope at the study hospitals from September 2010 to September 2016; 273 patients (2.9%) had incomplete 30-day outcome assessments and 10 (0.1%) withdrew from the study before 30-day outcome assessment, leaving 9,091 (97.0%) for analysis. There were 5,415 patients (59.6%) enrolled at the Canadian study sites and 3,676 (40.4%) enrolled at the US

sites (Table 1). The baseline demographic and clinical characteristics of the study patients are detailed in Table 1.

A total of 547 patients (6.0%; 95% CI 5.5% to 6.5%) underwent further evaluations for pulmonary embolism (Figure 1). The first modality of pulmonary embolism investigation among the study patients was as follows: 278 patients in the Canadian cohort underwent D-dimer testing; in the combined cohort, 19 patients had ventilation-perfusion scan, 249 had CT pulmonary angiography, and 1 had a confirmed pulmonary embolism on telephone follow-up (type of imaging unknown) and was treated with anticoagulation. Overall, in the study cohort 278 patients (3.1%) had D-dimer testing, 39 (0.4%) had ventilation-perfusion scan, and 347 (3.8%) had CT pulmonary angiography (several patients had more than one test). In the Canadian cohort, 199 patients (3.7%; 95% CI 3.2% to 4.2%) and in the US cohort 181 patients (4.9%; 95% CI 4.3% to 5.7%) had either one of the radiologic investigations (ventilation-perfusion scan or CT pulmonary angiography) for evaluation of pulmonary embolism.

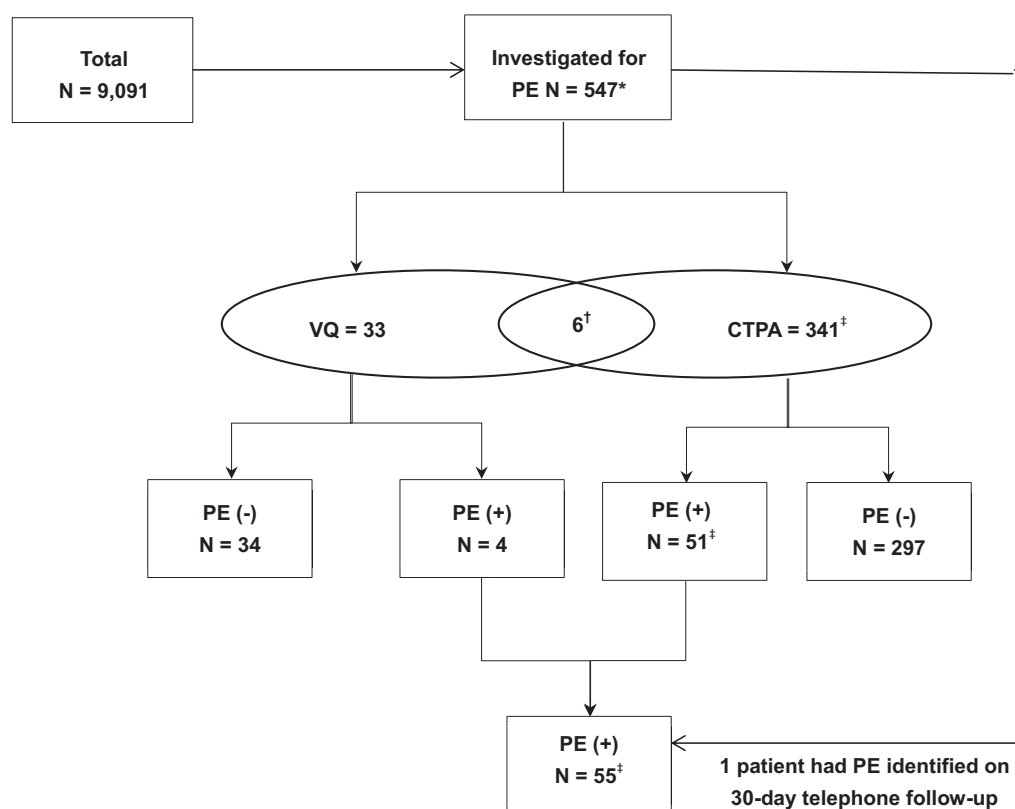


Figure 1. Patients evaluated for pulmonary embolism during the index presentation. PE+, PE identified and anticoagulation treatment offered. *Includes 278 patients in the Canadian cohort who had D-dimer testing performed. †Six patients had both VQ and CTPA performed. ‡Includes one patient who had CTPA performed on a return visit and had PE confirmed.

In the Canadian cohort (Appendix E3, available online at <http://www.annemergmed.com>), of 5,415 patients enrolled in the study, 278 (5.1%) had D-dimer testing performed, of whom 183 were classified as having negative results and 95 were classified as having positive ones. Among patients who were classified as having positive results, 16 had ventilation-perfusion scan, 76 had CT pulmonary angiography, and 3 had both. Among the 183 patients who had a negative D-dimer level, 18 had further radiologic investigations: 1 patient had ventilation-perfusion scan and 17 had CT pulmonary angiography. Additionally, 88 patients had imaging performed without D-dimer testing: 9 patients had ventilation-perfusion scan, 75 had CT pulmonary angiography, and 2 had both.

Of the 3,676 patients enrolled in the US study sites (Appendix E4, available online at <http://www.annemergmed.com>), 7 had ventilation-perfusion scan, 173 had CT pulmonary angiography, and 1 had both. The details of D-dimer testing for the patients enrolled in the US sites are not available.

Table 1 shows the comparison of patients with syncope enrolled in the 2 countries. Among those who were enrolled, 365 Canadian patients (6.7%) and 182 US patients (5.0%) were evaluated for pulmonary embolism. With the US cohort enrolling only patients aged 60 years or older, expectedly the mean age was higher and so was the presence of comorbidities. The proportion of patients with radiologic investigations for pulmonary embolism was also significantly higher in the US cohort. Among patients who underwent radiologic investigations for pulmonary embolism, the US cohort had a higher proportion of patients who had CT pulmonary angiography. Overall, the US sites hospitalized more patients than Canadian sites for all patients with syncope (77.7% versus 13.0%, difference of 64.7% [95% CI 63.0% to 66.3%]; 77.7% versus 21.6%, difference of 56.1% [95% CI 54.3% to 57.8%] for patients ≥ 60 years). Among patients evaluated for pulmonary embolism, again the US sites hospitalized more patients than the Canadian ones (90.7% versus 24.7%, difference of 66.0% [95% CI 59.1% to 71.4%]).

Of the 9,091 patients with follow-up data, 874 (9.6%) had either a serious underlying condition identified that caused the syncope or died within 30 days of their ED visit. The serious outcomes included 56 patients (0.6%) with pulmonary embolism and 818 (9.0%) with nonpulmonary embolism. Overall, 86 patients (0.9%) died within 30 days; 4 deaths were related to pulmonary embolism and 82 were not related to pulmonary embolism, and 52 patients died because of an unknown cause. The nonpulmonary embolism serious outcomes among the study patients are detailed in Table 1. Of the 1,417 patients with presyncope

in the US cohort, 179 (12.6%) experienced nonpulmonary embolism serious outcomes (some patients had more than 1 serious outcome): 119 patients (8.4%) with arrhythmias, 32 (2.3%) with myocardial infarction, 54 (3.8%) who required cardiac procedural intervention, 14 (1.0%) with serious structural heart disease, and 1 (0.1%) with subarachnoid hemorrhage.

Of the 547 patients evaluated for pulmonary embolism, 56 (10.2%; 95% CI 8.0% to 13.1%) had an underlying pulmonary embolism identified, and 63 (11.5%) had a nonpulmonary embolism serious condition or died within 30 days of syncope (some had more than 1 condition): 9 patients (1.6%) died, 34 (6.2%) had an arrhythmia, 16 (2.9%) had a cardiac procedural intervention performed, 13 (2.4%) had a myocardial infarction, and 10 (1.8%) had serious underlying structural heart disease identified.

In our study, 56 of the 380 patients who underwent ventilation-perfusion scan or CT pulmonary angiography received a diagnosis of pulmonary embolism, representing a diagnostic yield of 14.7% (95% CI 11.5% to 18.7%) for advanced radiologic investigations. In the Canadian and US cohorts, respectively, of the 199 and 181 patients who underwent ventilation-perfusion scan or CT pulmonary angiography, 31 and 25 received a diagnosis of pulmonary embolism (diagnostic yield of 15.6% [95% CI 11.2% to 21.3%] and 13.8% [95% CI 9.5% to 19.6%], respectively).

In our combined data sets, a total of 56 patients (Table 2) had underlying pulmonary embolism identified, with a prevalence of 0.6% (95% CI 0.5% to 0.8%). Of these, 41 patients (73.0%) had pulmonary embolism identified during the evaluation in the ED, of whom 36 were hospitalized and 5 were discharged home, receiving anticoagulants and thrombosis follow-up (Figure 2). Of the 56 patients who received a diagnosis of underlying pulmonary embolism, 4 died within 30 days (Table 1). Of the 3,521 patients who were hospitalized either for evaluation of syncope or for nonpulmonary embolism serious conditions identified in the ED, with no pulmonary embolism identified in the ED, 8 patients (0.2%; 95% CI 0.1% to 0.5%) had pulmonary embolism identified during their in-hospital stay. Additionally, among the 5,528 patients discharged home after no investigations for pulmonary embolism, 7 (0.1%; 95% CI 0.1% to 0.3%) had pulmonary embolism identified after their index syncope visit. There were 11 patients (0.1%; 95% CI 0.1% to 0.2%) in our study who, in addition to an underlying pulmonary embolism, had a nonpulmonary embolism serious condition identified or died within 30 days (2

Table 2. Pulmonary embolism among patients presenting with syncope.

PE	All Patients, N=9,091		Patients Evaluated for PE, N= 547	
	No. (%)	95% CI for Percentage	No. (%)	95% CI for Percentage
Overall	56 (0.6)	0.5–0.8	56 (10.2)	8.0–13.1
Identified in the ED	41 (0.5)	0.3–0.6	41 (7.5)	5.6–10.0
Identified during hospitalization	8 (0.1)	0.1–0.2	8 (1.5)	0.7–2.9
Identified on 30-day follow-up after index visit	7 (0.1)	0.0–0.2	7 (1.3)	0.6–2.6
Both PE and non-PE serious outcome*	11 (0.1)	0.1–0.2	11 (2.0)	1.1–3.6

*Non-PE serious outcomes included arrhythmia, myocardial infarction, serious structural heart disease, aortic dissection, subarachnoid hemorrhage, and cardiac procedural interventions.

patients died, 5 experienced arrhythmias, 2 had myocardial infarction, 1 patient had serious structural heart disease identified, and 1 had underlying aortic dissection).

Our subgroup analyses, stratified by country, age cutoff of 60 years, and syncope versus presyncope, showed no difference in the prevalence of pulmonary embolism among these subgroups of patients (Table 3). The prevalence of pulmonary embolism was 1% or lower in all of our predefined subgroups. In the Canadian cohort, the prevalence of pulmonary embolism among patients with first-time syncope was 0.5% (95% CI 0.3% to 0.7%); however, this information is unavailable for US patients.

In the study cohort, a total of 15 patients (0.17%; 8 of the 3,521 patients hospitalized and 7 of the 5,528 discharged directly from the ED) (Figure 2) received a

diagnosis of pulmonary embolism after the index ED evaluation. Assuming a similar misclassification rate among the 8,544 patients not evaluated for pulmonary embolism in our study, an additional 14 patients could have been identified as having an underlying pulmonary embolism. Under the worst-case scenario analysis, a total of 381 patients (4.1%; 95% CI 3.7% to 4.5%) of the 9,364 patients in the study cohort (273 patients lost to follow-up, 56 patients with confirmed pulmonary embolism, and 52 deaths because of an unknown cause) could have had an underlying pulmonary embolism.

LIMITATIONS

Our study has some limitations. The main one is that unlike the Pulmonary Embolism in Syncope Italian Trial,

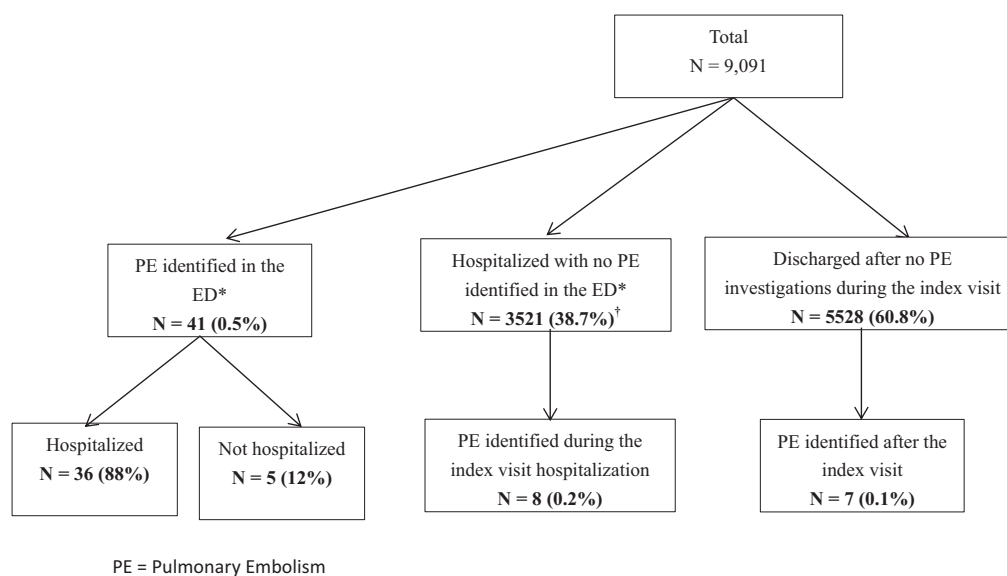


Figure 2. Location of identification of pulmonary embolism among the study patients. *Includes patients hospitalized for evaluation of syncope and with non-PE serious conditions. †Among patients hospitalized, 219 had evaluation for PE.

Table 3. Subgroup analyses by country, age, and syncope or presyncope.

PE	Canadian Cohort		US Cohort		P Value
	No. (%)	95% CI for Percentage	No. (%)	95% CI for Percentage	
Overall (N=5,415; 3,676)	31 (0.6)	(0.4–0.8)	25 (0.7)	(0.4–1.0)	.61
<60 y (N=2,987; 0)*	10 (0.3)	(0.2–0.6)	0	—†	
≥60 y (N=2,428; 3,676)	21 (0.9)	(0.6–1.3)	25 (0.7)	(0.4–1.0)	.55
True syncope (N=5,415; 2,259)	31 (0.6)	(0.4–0.8)	11 (0.5)	(0.2–0.9)	.76
Presyncope (N=0; 1,417)	—	—	14 (1.0)	(0.6–1.7)	
First-time syncope (N=4,852; 0)*	23 (0.5)	(0.3–0.7)	—	—	

*Results for the Canadian cohort only are reported because the US cohort enrolled only patients aged 60 years or older and information in regard to history of syncope was not collected for US patients. In the US cohort, of the 3,676 patients enrolled, 2,299 (62.5%) did not experience syncope in the past year, of whom 15 (0.7%; 95% CI 0.4% to 1.1%) received a diagnosis of an underlying PE.

†Dashes indicate not applicable.

our study was pragmatic, with no mandated evaluation of pulmonary embolism for all patients enrolled, and hence it was susceptible to verification bias. Also, neither parent study collected some specific pulmonary embolism risk factors such as recent immobilization or surgery. In addition to the pragmatic approach described above, the patients enrolled in the 2 countries were different. Given that the US sites recruited only patients aged 60 years or older, the median age in our study cohort was 66 years, which is older than patients in some previous studies.¹⁸ Patients enrolled in the US sites were likely to have comorbidities such as hypertension, diabetes, and active cancer. Additionally, one more major limitation of our study is that data in regard to D-dimer measurement were not collected for the US cohort. The proportion of patients undergoing radiologic investigations for pulmonary embolism and those hospitalized was also higher in the US cohort. Despite these differences, the pulmonary embolism prevalence was consistent, at less than 1% in both cohorts. Hence, notwithstanding the fact that this study included older patients with comorbidities and patients in different sites across Canada and the United States, we believe our finding of low pulmonary embolism prevalence is generalizable. Additionally, our subgroup analyses showed that the pulmonary embolism prevalence was consistently low among the subgroups, with no significant differences. Unlike the Pulmonary Embolism in Syncope Italian Trial, which enrolled first-time syncope patients, because pulmonary embolism can be the underlying cause for syncope even in patients with previous syncope, we enrolled all patients who presented to the ED with syncope irrespective of the absence of previous syncope. The prevalence of pulmonary embolism, however, was also low in the Canadian cohort among the subgroup of patients with first-time syncope (these data were not collected for

the US cohort). Our primary outcome was the adjudicated identification of pulmonary embolism that was deemed clinically relevant and the likely cause of the index syncope. In our study, we did not collect data on the location of the pulmonary embolism.

Despite the above limitations, our study has several strengths. To our knowledge, this is the largest prospective study to date with systematic and robust follow-up of a cohort of patients presenting to the ED with syncope at various sites in Canada and the United States for identification of pulmonary embolism within 30 days. Our approach was pragmatic, with the evaluation of pulmonary embolism left to the discretion of the treating physician, and our follow-up included both patients who were hospitalized and those discharged from the ED after the index syncope. Given the rigorous methods used to follow patients after ED visits, we achieved 30-day follow-up for 97% of the study patients. In our study a very low proportion of patients were lost to follow-up or withdrew from the study. Hence, our study results showing a very low pulmonary embolism prevalence is unlikely to substantially change due to loss to follow-up or withdrawals.

DISCUSSION

In this large prospective multicenter study of patients presenting to EDs across Canada and the United States who had syncope, only 1 in approximately 160 patients had an underlying pulmonary embolism identified. Similarly, the prevalence of pulmonary embolism among patients admitted to the hospital from the ED and those with nonpulmonary embolism serious conditions was also very low. The low prevalence of pulmonary embolism was consistent in both countries among younger and older patients (≥60 years) and among those

with true syncope (versus presyncope). The consistently low pulmonary embolism prevalence in both the Canadian and US cohorts is noteworthy, given the contrasts—often attributed to the prevailing medicolegal climate—between the 2 countries in regard to health care systems, access to care, thresholds for testing, and hospitalizations.

Our 30-day mortality rate was approximately 1%, consistent with that in previous studies and with other high-stakes clinical conditions in the ED such as chest pain, headache, and shortness of breath.¹⁸ The diagnostic yield of ventilation-perfusion scan or CT pulmonary angiography in our study is similar to the 15.0% that was reported by Verma et al¹⁹ in their health systems database analysis, suggesting that physicians were not reluctant to order imaging when appropriate.

With respect to the prevalence of pulmonary embolism among patients with syncope, previously published prospective studies report a less than 1% prevalence,^{4,5,11} whereas 2 smaller studies and 1 health systems database review report a pulmonary embolism prevalence of 1.2% to 2.5%.^{8,9,19} Yet these results are substantially different from those of the Pulmonary Embolism in Syncope Italian Trial by Prandoni et al,⁶ which reported a 17.1% prevalence of pulmonary embolism among patients hospitalized for syncope.

Both the Canadian and US study protocols were pragmatic in their design, with pulmonary embolism investigations performed according to the clinical context. Given that 1% to 3% of all ED visits are due to syncope and the symptom affects people of all ages, it is not feasible or appropriate to evaluate all patients for pulmonary embolism. In accordance with the principles of the Choosing Wisely campaign, investigations should be performed only if warranted and in the right clinical context. In our study, despite significantly higher proportion of US patients undergoing radiologic investigations for pulmonary embolism, we found both the diagnostic yield and the prevalence of pulmonary embolism to be similar in both cohorts. We expect that patients with clinically significant pulmonary embolism that was undetected would have likely become symptomatic within 30 days, resulting in repeated health care visits and ultimate diagnosis of pulmonary embolism. Only 1 patient in each of the 2 cohorts eventually received a diagnosis of pulmonary embolism after the index visit or hospitalization, and one cannot discount that this pulmonary embolism represented a subsequent event, falsely positive diagnosis, or incidental finding. It is of course possible that some patients died from undetected pulmonary embolism. However, with a

30-day mortality of less than 1% overall in both the Canadian and US cohorts, it is unlikely the case.

Prandoni et al⁶ reported the prevalence of pulmonary embolism among patients hospitalized with no clear criteria for hospitalization, which presumably represents a very high-risk subgroup for pulmonary embolism. Unfortunately, it is impossible to glean what factors were most helpful in generating this high-risk subgroup. This study did not report pulmonary embolism among patients discharged from the ED, rendering a direct comparison with our study difficult. However, if one estimates the prevalence of pulmonary embolism by using all eligible syncope patients in the Pulmonary Embolism in Syncope Italian Trial rather than just those selected for admission and investigation, the overall prevalence can be recalculated as being only 3.8% (97/2,584 patients).

In the Pulmonary Embolism in Syncope Italian Trial, 11.6% of the study patients had active cancer, which is substantially higher than in our cohort (4.2%) and in one previous syncope study that reported this comorbidity.²⁰ A meta-analysis by Dentali et al²¹ reported a 3.1% prevalence of incidental pulmonary embolism among cancer patients. The diagnostic interpretation of ventilation-perfusion scan findings can be challenging.²² Additionally, falsely positive CT pulmonary angiography results leading to misclassification and overdiagnosis have also been reported.^{23,24} In the Italian trial, among patients with pulmonary embolism identified by CT pulmonary angiography, 40% of the pulmonary embolisms were segmental or smaller, including 6.9% that were subsegmental, and 50% of patients with pulmonary embolism identified by ventilation-perfusion scan had a perfusion defect of 1% to 25% of the lungs. After adjusting for these effects and for evaluation bias, the true prevalence of clinically significant pulmonary embolism in the trial may be likely closer to what we observed in our study.

In a multicenter, transnational study, we found that the prevalence of pulmonary embolism is very low among patients presenting to the ED with syncope, including among those hospitalized for syncope. Although pulmonary embolism can certainly cause syncope and in the right context should be suspected and investigated diligently if clinically appropriate, caution should also be used in regard to indiscriminate or dogmatic overinvestigations for pulmonary embolism after syncope.

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Author contributions: VT, MLAS, BHR, ADM, MT, and BCS conceived the idea. All authors contributed to the study design. VT, MLAS, BHR, ADM, MM, ANY, and BCS supervised the conduct of the trial and data collection and undertook recruitment of patients. VT, MM, LH, SM, ANY, and BCS managed the data, including quality control. VT, MT, MJN, LH, and SM analyzed the data. VT drafted the article. All authors reviewed the article and contributed substantially to its revision. Dr. Thiruganasambandamoorthy (principal investigator) has full access to the Canadian data and Dr. Sun has full access to the US data. Both take responsibility for the integrity of the data and the accuracy of the data analysis for their respective data. VT takes responsibility for the paper as a whole.

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APPENDIX

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