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Prevalence of Pulmonary Embolism in Patients With Syncope

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IMPORTANCE Sparse data and conflicting evidence exist on the prevalence of pulmonary embolism (PE) in patients with syncope.

OBJECTIVE To estimate the prevalence of PE among patients presenting to the emergency department (ED) for evaluation of syncope.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, observational study analyzed longitudinal administrative data from 5 databases in 4 different countries (Canada, Denmark, Italy, and the United States). Data from all adult patients (aged ≥18 years) who presented to the ED were screened to identify those with syncope codes at discharge. Data were collected from January 1, 2000, through September 30, 2016.

MAIN OUTCOMES AND MEASURES The prevalence of PE at ED and hospital discharge, identified using codes from the *International Classification of Diseases*, was considered the primary outcome. Two sensitivity analyses considering prevalence of PE at 90 days of follow-up and prevalence of venous thromboembolism were performed.

RESULTS A total of 1 671 944 unselected adults who presented to the ED for syncope were included. The prevalence of PE, according to administrative data, ranged from 0.06% (95% CI, 0.05%-0.06%) to 0.55% (95% CI, 0.50%-0.61%) for all patients and from 0.15% (95% CI, 0.14%-0.16%) to 2.10% (95% CI, 1.84%-2.39%) for hospitalized patients. The prevalence of PE at 90 days of follow-up ranged from 0.14% (95% CI, 0.13%-0.14%) to 0.83% (95% CI, 0.80%-0.86%) for all patients and from 0.35% (95% CI, 0.34%-0.37%) to 2.63% (95% CI, 2.34%-2.95%) for hospitalized patients. Finally, the prevalence of venous thromboembolism at 90 days ranged from 0.30% (95% CI, 0.29%-0.31%) to 1.37% (95% CI, 1.33%-1.41%) for all patients and from 0.75% (95% CI, 0.73%-0.78%) to 3.86% (95% CI, 3.51%-4.24%) for hospitalized patients.

CONCLUSIONS AND RELEVANCE Pulmonary embolism was rarely identified in patients with syncope. Although PE should be considered in every patient, not all patients should undergo evaluation for PE.

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Syncope is a common symptom that occurs in 1 of 4 people during their lifetime.[1] Pulmonary embolism (PE) has long been recognized as an important and serious cause of syncope. Data on its prevalence are scanty. Several prospective studies enrolling patients with syncope in the emergency department (ED) reported a prevalence of less than 1.5%.[2-11] These observational studies provided good follow-up on patients but did not follow a structured algorithm for the assessment of PE. A recent study (Pulmonary Embolism in Syncope Italian Trial [PESIT])[12] aiming at evaluation of PE prevalence by using a standardized algorithm in hospitalized patients after a first syncope episode found a prevalence of PE in hospitalized patients as high as 17%. PESIT enrolled all patients hospitalized for a first episode of syncope and adopted a validated algorithm that was based on pretest clinical probability and the result of the D-dimer assay. Any patient with positive D-dimer findings or high pretest PE probability, according to the Wells score, underwent computed tomography or ventilation perfusion lung scanning.[12] Verma et al[13] tried to replicate this study by analyzing data from all patients admitted for syncope in 4 Canadian hospitals and found a much lower prevalence of PE and venous thrombosis. Both studies considered only hospitalized patients, which can make the data less generalizable because the decision to admit a patient relies on multiple factors and the characteristics and admission rates are very heterogeneous among different countries and health care systems.[6,14] Estimating PE prevalence in unselected patients with syncope presenting to the ED would be more informative because it would guide the decision as to whether a systematic protocol for ruling out PE is warranted.[15-19]

Large prospective studies from different health care systems could help solve this problem. However, these studies would be expensive, time-consuming, and difficult to conduct. Therefore, administrative databases are an alternative option to determine the prevalence of PE. The aim of the present study was to determine the prevalence of PE in patients with syncope using several international administrative databases.

Key Points

Question What is the estimated prevalence of pulmonary embolism in patients who present to the emergency department with syncope?

Findings In this study of 5 administrative databases that included more than 1.5 million people from 4 different countries, pulmonary embolism was identified in less than 1% of patients with syncope.

Meaning Although pulmonary embolism should be considered at first evaluation in every patient with syncope, not all patients warrant a diagnostic algorithm to exclude it, and the algorithm may increase false-positive results and overtreatment, resulting in more adverse events.

Methods

Study Setting and Sources of Data

This retrospective, observational study used 5 longitudinal administrative databases from Canada, Denmark, Italy, and the United States. The databases analyzed included (1) all inhabitants of the province of Alberta, Canada; (2) all inhabitants of Denmark; (3) all inhabitants of the metropolitan area of Milan, Italy; (4) data from the US Healthcare Cost and Utilization Project; and (5) data from a large US national insurance provider (Clinformatics Data Mart database; OptumInsight). Data were collected from January 1, 2000, through September 30, 2016. The characteristics of each database are described in the **Box**. The Alberta Ministry of Health, Agency for Health Protection of the Province of Milan, and Agency for Healthcare Research and Quality gave permission to use deidentifed data for the present study; no ethics approval is required for registry studies in Denmark. The University of Alberta institutional review board, the Danish Data Protection Agency, and the Agency for Health Protection of the Province of Milan approved the study. The institutional review boards of Massachusetts General Hospital and Stanford University determined that the project was exempt from formal review.

Study Cohort

We applied uniform inclusion criteria to all data sets to identify all adult patients (aged ≥18 years) who presented to the ED for evaluation of syncope. We used discharge codes in any diagnosis field from the *International Classification of Diseases, Ninth Revision* (*ICD-9*) (code 780.2) or the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) (code R55), where appropriate, to identify adult patients who presented to the ED with syncope.

Outcome

The prevalence of PE at ED and hospital discharge as defined by *ICD-9* and *ICD-10* codes was considered as the primary outcome. The presence of PE was determined at the first ED evaluation or immediate hospitalization using discharge codes 415 from the *ICD-9* and I26 from the *ICD-10*.

Statistical Analysis

For each patient with multiple ED visits for syncope, only the first visit was considered the index evaluation for our analysis. Data were reported as medians (interquartile range) and counts (percentages) for descriptive purposes. The prevalences of the primary outcome were reported as proportions with 95% CIs.

We performed 2 sensitivity analyses. First, we considered all PE identified within 90 days of follow-up as being present also at the index ED presentation. This time frame was chosen because 90 days is considered an appropriate follow-up to clinically assess the presence or absence of PE.[20-22] Second, we considered as the worst-case scenario all identified venous thromboembolism as PE. For this analysis, we considered *ICD-9* codes 415, 453.4, 453.5, 453.8, and 453.9 and *ICD-10* codes I26, I801-I803, I808, I809, I821-I823, I828, and I829.

Box. Characteristics of the Analyzed Databases

Canada

Data from all the inhabitants of Alberta, the fourth largest province in western Canada with a population of approximately 4.2 million, were retrieved. The following databases, maintained by the Alberta Ministry of Health, were linked: (1) the Ambulatory Care Classification System Database, which records all visits to hospital-based physician offices or emergency departments (EDs) and includes as many as 10 diagnosis fields; (2) the inpatient Discharge Abstract Database that records information for all acute care hospitalizations (dates, principal diagnosis, and ≤24 other diagnoses, procedures, length of stay, and discharge status); (3) the Alberta Health Care Insurance Plan, the population registry that records basic demographic and geographic information for all residents; and (4) the Alberta Vital Statistics database, which records all deaths in the province. The codification system is based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*). Each patient has a unique personal identifier that allows linkage of patient information across the databases. The period considered was April 1, 2006, through December 31, 2013. As many as 10 diagnosis fields were permitted in the ED, whereas up to 25 were permitted in the hospitalization database.

Denmark

Data from all inhabitants of Denmark, with a population of approximately 5.5 million, were retrieved. All *ICD* discharge codes from the ED and hospital are maintained by the National Health System using *ICD-10* codes. Each patient has a unique personal identifier, and admission rate has been calculated as patients discharged from the ED and admitted in hospital in the same day. The period considered for the analysis was January 1, 2000, through September 30, 2012.

Italy

Data from all the inhabitants of the metropolitan area of Milan, with a population of approximately 3.2 million, were retrieved. The following databases, maintained by the Health Information System of the Health Protection Agency, were linked: (1) ED visits (coded in *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]); (2) hospitalizations (coded in *ICD-9-CM*); (3) and the Nominative Causes of Death Registry (coded in *ICD-10*). These sources covered all direct medical costs attributable to the Italian National Health Service and all deaths that occurred at the population level. Each patient has a unique personal identifier allowing linkage of patient information across the databases. The period considered was January 1, 2014, through September 30, 2016. As many as 2 diagnosis fields were permitted in the ED, whereas up to 5 were permitted in the hospitalization database.

US Healthcare Cost and Utilization Project

The population-based data from the Healthcare Cost and Utilization Project (HCUP) State Emergency Department Databases and State Inpatient Databases of 5 US states—California, Florida, Nebraska, New York, and Utah—were used. The HCUP is a family of health care databases developed through a federal-state-industry partnership and sponsored by the Agency for Healthcare Research and Quality. The State Emergency Department Databases includes all treat-and-release and transfer ED visits from short-term, acute-care, nonfederal hospitals in participating states. The State Inpatient Databases includes all inpatient discharges from short-term, acute-care, nonfederal, general, and other specialty hospitals, including those admitted from the ED. Taken together, we identified all ED visits regardless of disposition and all hospitalizations regardless of the source. The period considered was January 1, 2007, through December 31, 2011. The *ICD-9-CM* code has been used. The number of residents, derived from the US Census in 2010, was approximately 80 million. The number of diagnosis fields varied from 9 to 31 according to the analyzed states.

US National Insurance Provider Database

A large national insurance provider maintained a deidentified database (ClinformaticsTM Data Mart Database; OptumInsight). The entire database involves 58 million unique members representing 50 states. The database contains 12 to 14 million members each year, of whom 2.5 to 3.5 million are Medicare beneficiaries. Of these members, 78% are continually insured for 6 months, and members compare favorably to most US population benchmarks, although African American persons and those of lower socioeconomic status are underrepresented in the private insurer market and also in this database. ED visits for syncope were retrieved from claims data using the *ICD-9* and *ICD-10* codes. Each patient has a unique personal identifier allowing linkage of patient information across the databases. The period considered was January 1, 2004, through December 31, 2015. As many as 5 diagnosis fields were permitted.

All analyses were performed for patients who presented in the ED with syncope and in the subgroup of patients hospitalized for syncope. The analyses were conducted for each cohort separately using SAS statistical software (version 9.4; SAS Institute, Inc).

Results

The combined database included 1 671 944 adult patients presenting to the ED for syncope from 4 different countries. Descriptive characteristics of the databases are reported in **Table 1**. The rate of PE diagnosis ranged from 0.06% (95% CI, 0.05%-0.06%) to 0.55% (95% CI, 0.50%-0.61%) of all patients who presented in the ED for syncope, according to administrative data. When considering the subgroup of hospitalized patients, PE diagnosis ranged from 0.15% (95% CI, 0.14%-0.16%) to 2.10% (95% CI, 1.84%-2.39%).

Sensitivity Analyses

Diagnoses of PE within 90 days of follow-up, according to administrative data, ranged from 0.14% (95% CI, 0.13%-0.14%) to 0.83% (95% CI, 0.80%-0.86%) for all patients and from 0.35% (95% CI, 0.34%-0.37%) to 2.63% (95% CI, 2.34%-2.95%) for hospitalized patients. Finally, the identification of venous thromboembolism within 90 days ranged from 0.30% (95% CI, 0.29%-0.31%) to 1.37% (95% CI, 1.33%-1.41%) for all patients and from 0.75% (95% CI, 0.73%-0.78%) to 3.86% (95% CI, 3.51%-4.24%) in the subgroup of hospitalized patients. Details of the results of each database are reported in **Table 2** and **Table 3**.

Table 1. Characteristics of the 5 Syncope Cohorts[a]

Country	Resident Population by 1 Million	Study Period Considered	No. of ED Visits	ED Visits Coded as Syncope, No. (%)	No. of Patients Evaluated for Syncope in the ED[b]	Admission Rate for Syncope, No. (%)	Patients Presenting to the ED for Syncope		Patients Hospitalized for Syncope	
							Age, Median (IQR), y	No. (%) Male	Age, Median (IQR), y	No. (%) Male
Canada	4.2	Apr 1, 2006, to Dec 31, 2013	11 887 797	80 369 (0.7)	67 243	11 087 (16.5)	53 (32-73)	31 009 (46.1)	74 (60-83)	5850 (52.8)
Denmark	5.5	Jan 1, 2000, to Sep 30, 2012	7 981 129	58 805 (0.7)	57 500	24 144 (42.0)	60 (39-76)	26 617 (46.3)	66 (47-79)	12 440 (51.5)
Italy	3.2	Jan 1, 2014, to Sep 30, 2016	3 260 721	31 735 (1.0)	29 543	5598 (18.9)	70 (48-81)	13 633 (46.1)	79 (71-85)	2812 (50.2)
United States (HCUP)	80	Jan 1, 2007, to Dec 31, 2011	128 078 887	1 362 903 (10.6)	1 190 621	362 793 (30.5)	58 (38-77)	497 324 (41.8)	73 (58-83)	160 757 (44.3)
United States (national insurance provider)	58[c]	Jan 1, 2004, to Dec 31, 2015	54 476 678	497 250 (0.9)	327 037	118 842 (36.3)	74 (66-81)	142 190 (43.5)	77 (69-82)	54 647 (46.0)

Abbreviations: ED, emergency department; HCUP, Healthcare Cost and Utilization Project; IQR, interquartile range.

[a] All data except for resident population refer to adult patients (aged ≥18 years).

[b] Patients with multiple visits have been considered only the first time.

[c] Because this database from a large national insurance provider (Clinformatics Data Mart database; OptumInsight) is deidentified, the number refers to lives covered during the study period.

Discussion

Our results, based on administrative data, show that PE was identified in less than 1% of all patients with syncope and in less than 3% of hospitalized patients with syncope. Pulmonary embolism has always been considered an uncommon cause of syncope. Several prospective cohort studies enrolling consecutive patients with syncope in the ED[4,5,9,14,19] have reported a PE prevalence of less than 1% at 7 to 30 days of follow-up. Retrospective data from the United States[23] confirmed such results. The recently published PESIT[12] was specifically aimed at evaluating PE prevalence in syncope by applying a standardized diagnostic protocol for all the patients admitted to the hospital for their first episode of syncope. According to the investigators, the prevalence of PE can be as high as 17% in patients hospitalized for first syncope and as high as 3.7% in all patients presenting to the ED with syncope. Verma et al[13] retrospectively applied the PESIT inclusion criteria in Canada and reported a prevalence of PE and/or deep venous thrombosis of 1.4%. These conflicting results leave physicians uncertain as to whether they should follow a structured diagnostic pathway to rule out PE in all patients with syncope, with the risks being overdiagnosis and overtreatment.[15-19,23] The results of the present study, an international collaboration of 5 groups, considered different administrative databases from 4 different countries, involved more than 1.5 million patients, and confirmed that PE prevalence in patients with syncope is low.[13,22]

Because the admission rates are known to be very heterogeneous, as confirmed by the present study, we decided to consider hospitalized and nonhospitalized patients separately to increase the generalizability of the results.[6-8,24] Because PESIT used a structured algorithm to assess for the presence of PE, one could hypothesize that previous studies, as well as clinical practice, might have underestimated PE prevalence. Even in the present study, some PE diagnoses could have been missed because they were not suspected, and therefore no information relevant to PE was reported in the administrative data. However, to identify all possible cases of unrecognized PE, we performed a sensitivity analysis in which all events diagnosed within 90 days as syncope-related PE were considered.[20-22,25] Even in this case, PE was identified in less than 1% of patients, suggesting that, even if some PE had been missed at first evaluation, most were not clinically relevant.

Our results are consistent with those of most single studies recruiting patients with syncope in the ED and assessing them within different time frames,[2-5,13] which reported a PE prevalence of less than 1.5%. Moreover, meta-analyses of these studies[24,26,27] reported the same prevalence. Although we used the same inclusion criteria, we observed some variation in PE identification among the countries and databases we used. This variation is not surprising given the difference in health care systems, the population enrolled, physician incentives to investigate, and variations of insurance coverage and type among all the data sets (Box). This high variability was expected as a con-

Table 2. PE Identification in All Patients Presenting to the ED for Syncope, According to Administrative Databases

Country	PE At First Evaluation[a]		PE Within 90 d		VTE Within 90 d	
	Prevalence, % (95% CI)	No./No. Undergoing Evaluation	Prevalence, % (95% CI)	No./No. Undergoing Evaluation	Prevalence, % (95% CI)	No./No. Undergoing Evaluation
Canada	0.55 (0.50-0.61)	370/67 243	0.80 (0.73-0.87)	538/67 243	1.24 (1.15-1.32)	831/67 243
Denmark	0.25 (0.21-0.29)	142/57 500	0.37 (0.32-0.42)	212/57 500	0.55 (0.49-0.61)	315/57 500
Italy	0.19 (0.14-0.24)	55/29 543	0.28 (0.23-0.35)	84/29 543	0.34 (0.28-0.41)	100/29 543
United States (HCUP)	0.06 (0.05-0.06)	684/1 190 621	0.14 (0.13-0.14)	1621/1 190 621	0.30 (0.29-0.31)	3574/1 190 621
United States (national insurance provider)	0.55 (0.52-0.58)	1798/327 037	0.83 (0.80-0.86)	2706/327 037	1.37 (1.33-1.41)	4467/327 037

Abbreviations: ED, emergency department; HCUP, Healthcare Cost and Utilization Project; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Considered to occur during the first presentation in the ED for syncope and/or immediate hospitalization.

Table 3. PE Identification in the Subgroup of Patients Hospitalized for Syncope After the First ED Evaluation, According to Administrative Databases

Country	PE at First Evaluation[a]		PE Within 90 Days		VTE Within 90 Days	
	Prevalence, % (95% CI)	No./No. Undergoing Evaluation	Prevalence, % (95% CI)	No./No. Undergoing Evaluation	Prevalence, % (95% CI)	No./No. Undergoing Evaluation
Canada	2.10 (1.84-2.39)	233/11 087	2.63 (2.34-2.95)	292/11 087	3.86 (3.51-4.24)	428/11 087
Denmark	0.58 (0.48-0.68)	139/24 144	0.75 (0.64-0.87)	181/24 144	0.99 (0.87-1.12)	239/24 144
Italy	0.84 (0.62-1.11)	47/5598	1.05 (0.80-1.36)	59/5598	1.23 (0.96-1.56)	69/5598
United States (HCUP)	0.15 (0.14-0.16)	563/362 793	0.35 (0.34-0.37)	1286/362 793	0.75 (0.73-0.78)	2731/362 793
United States (national insurance provider)	1.46 (1.40-1.53)	1739/118 842	1.89 (1.82-1.97)	2251/118 842	2.99 (2.90-3.09)	3559/118 842

Abbreviations: ED, emergency department; HCUP, Healthcare Cost and Utilization Project; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Considered to occur during the first presentation in the ED for syncope and/or immediate hospitalization.

sequence of our decision to include heterogeneous contexts. However, despite this variation, the rate of identification of PE is low and significantly lower than that reported in PESIT regardless of the data set considered. Different hypotheses could be proposed to explain the higher PE prevalence found in the PESIT study. First, using a structured algorithm to assess PE might have led to an increase in the use of computed tomography and scintigraphy. This method might have led to an increase in the identification of subsegmental PE, for which clinical relevance is debated, and false-positive results.[16] Finally, the design of the PESIT study, which enrolled only hospitalized patients, might have led to the inclusion of patients at higher PE risk.

Our study has relevant clinical implications; our findings discourage the adoption of a routine protocol for excluding PE in all patients presenting to the ED with syncope. The unnecessary exposure to radiation and the risk of contrast allergy is significant. Furthermore, the false-positive rate of tests, such as the D-dimer assay and computed tomographic pulmonary angiograms, is high, leading to more tests and overdiagnosis and including risks of unnecessary anticoagulation.[13,16-18,23,28,29] Beyond the risks, these tests are expensive and time consuming. We do not advocate that physicians should disregard the presence of PE in patients with syncope. The decision to pursue further investigations should be determined by the risk of the patient for that outcome and the incidence of the outcome in the population considered.[30] Our study shows that PE diagnosis in patients with syncope is too low to justify a standardized diagnostic algorithm for PE in every patient.

Limitations

The main limitation of our study is the use of administrative databases to identify patients with syncope and PE. Although the sensitivity and specificity of *ICD-9* and *ICD-10* codes for PE are higher than 90%, the validation of the codes for syncope resulted in a high specificity and positive predictive value but moderate sensitivity.[31,32] Therefore, some patients were likely missed. However, because few patients with syncope receive a PE diagnosis in the ED, our prevalence should not have been substantially affected.[6-8] Moreover, most of the missed patients with syncope were those with an established diagnosis reached in the ED in whom syncope has been considered only the consequence of the primary diagnosis. For this reason, other discharge codes instead of the ones for syncope could have been used. Use of these codes could lead to the overrepresentation of patients with indeterminate syncope. Indeed, in the clinical setting, the main interest of clinicians is to exclude PE in patients with indeterminate syncope rather than in patients who already have an etiologic diagnosis of syncope.[33]

We have not assessed the influence of some patient characteristics, such as sex, age, and comorbidities, on the diagnosis of venous thromboembolism. In addition, we have not analyzed the trend of venous thromboembolism identification through time. However, we decided to focus the present study on the prevalence of PE in patients with syncope. Finally, some patients could have been included in both US databases. Because data are deidentified, we cannot adjust for this overlap. Considering the small degree of overlap, we decided to keep both databases and to analyze them separately.

Conclusions

The results of the present study confirm that PE is rarely identified in patients presenting to the ED with syncope. Although PE should be considered as a differential diagnosis in every patient, not all patients warrant an evaluation for it. Otherwise, evaluation could lead to false-positive results and overtreatment, thereby increasing adverse events and health care costs.

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