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Original Contribution

Prevalence of pulmonary embolism in patients presenting with syncope. A systematic review and meta-analysis

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ABSTRACT

Background: Syncope is a common clinical presentation and establishing an etiology is often challenging. Pulmonary embolism (PE) has been thought to be an uncommon cause but a recent report suggested otherwise.
Objective: To establish the prevalence of PE in patients presenting with syncope to the emergency department (ED) and in hospitalized patients.
Methods: We systematically searched Medline, CINAHL, EMBASE, LILACS and Web of Science with relevant keywords and MeSH headings for syncope and PE. Inclusion criteria were patients presenting with syncope to ED or hospitalized due to syncope, and etiologies including PE.
Results: Of 1329 titles and abstracts, 12 (other than Prandoni et al.) met inclusion criteria. Nine studies included 6608 ED patients and 3 included 975 hospitalized patients. The mean age was 62 (95% CI 54–69) for ED patients and 67 (95% CI 64–70) for hospitalized. The pooled estimate of PE prevalence in ED syncope patients was 0.8% (95% CI 0.5–1.3%, $I^2 = 0\%$). The pooled estimate of PE prevalence in hospitalized patients was 1.0% (95% CI 0.5–1.9%, $I^2 = 0$). In contrast, the prevalence of PE in Prandoni et al. were 3.8% and 17.3% for ED and hospitalized patients respectively, both significantly higher than in other relevant studies ($p < 0.0001$).
Conclusion: The estimated prevalence of PE in patients presenting with syncope is low. The Prandoni et al. estimates are significantly higher, suggesting a possible site effect, accrual bias, or investigation strategy. These and the prognostic impact of higher PE prevalence require understanding before changes in practice.

1. Introduction

Syncope is a common clinical problem accounting for 1% to 6% of hospital admissions and 1% to 3% of emergency department (ED) visits [1-4]. There are numerous causes of syncope, some potentially lethal but most relatively benign, and establishing an accurate diagnosis is a common and expensive problem [2,5]. Effective and efficient clinical management of syncope requires knowing the pretest probability of a diagnosis, the diagnostic accuracy of a test, and the impact on clinical outcome.

Among the many possible causes of syncope are pulmonary emboli (PE), which can be associated with recurrences and not infrequently death [6]. Until recently pulmonary emboli were thought to be an uncommon cause, but a recent study by Prandoni et al. [7] reported a much higher prevalence than previously suspected. This prompted us to conduct a systematic review and meta-analysis to determine the prevalence of pulmonary embolism in patients presenting with syncope to the emergency department and in hospitalized patients.

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2. Methods

Details of the protocol for this systematic review were registered on PROSPERO CRD42017056798 [8].

2.1. Search strategy (Appendix A)

We systematically searched Medline, CINAHL, EMBASE, LILACS and Web of Science databases. Search terms combined relevant keywords of fainting, unconsciousness, drop attack, thromboembolism, pulmonary infarction and MeSH headings for the concepts: 1) syncope and 2) pulmonary embolism. This was followed by a hand search in references of included studies for other potential studies.

2.2. Eligibility criteria

Studies that included patients presenting with syncope and reported on etiologies including pulmonary embolism were eligible for inclusion. We included all age categories. There were no language, time or patient setting limitations. There was no prior meta-analysis identified and review articles were excluded.

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2.3. Methods of review

The titles and abstracts of potential papers were independently reviewed by two authors. Full text articles were obtained when there was uncertainty in the studies. Data extraction and assessment of validity were also performed by both reviewers and confirmed by a third reviewer. Fig. 1 shows the PRISMA diagram.

2.4. Quality assessment

The quality of the studies was evaluated independently by two reviewers. Neither the Newcastle-Ottawa Scale [9] nor the Quality Assessment of Diagnostic Accuracy Studies [10] tools were suitable for application to this study. Therefore, we modified an existing scale [11] and summarized the methodological quality of the studies with a series of descriptors. (Supplementary Tables S2 and S3).

2.5. Statistical analysis

Data were analyzed using Comprehensive Meta-Analysis software version 3 (Biostat Inc. Englewood, NJ). The studies were divided into two cohorts: 1) patients presenting with syncope to the emergency department, 2) hospitalized patients with syncope. Pooled odds ratios were calculated using a random-effects model. A two sample z-test of proportions was used to compare the pooled prevalence of the selected studies to Prandoni et al. [7] Heterogeneity was estimated using the I^2 statistic in a random effect analysis [12]. The data of Prandoni et al. [7] were not included in the meta-analyses.

3. Results

3.1. Study selection and characteristics

The initial search yielded 1902 articles, and after removing duplicates 1329 articles were assessed for titles and abstracts. Fifty-three full text articles were accessed and of these, 38 were excluded due to wrong population involving patients who presented with confirmed PE, 3 were review articles and 12 (other than Prandoni et al. [7]) met the eligibility criteria. There were no randomized controlled trials.

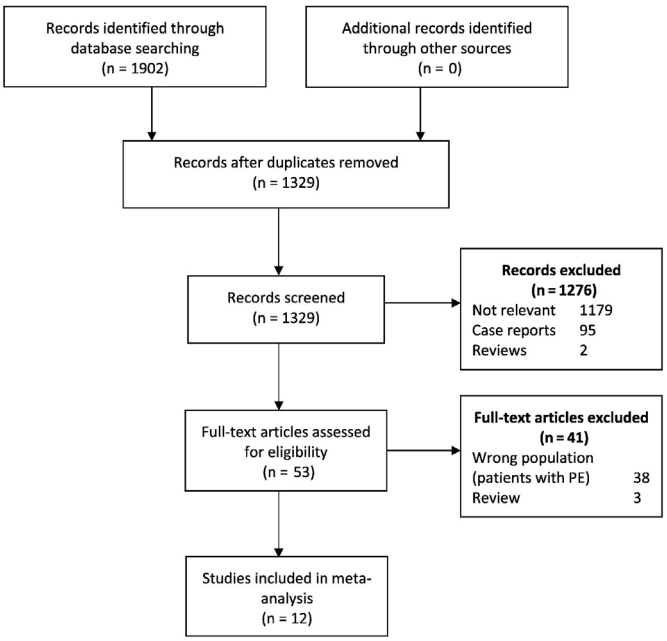

Fig. 1. PRISMA diagram for systematic literature search.

3.2. Study participants

The sample sizes ranged from 117 to 2871 patients with a mean study size of 660 (standard deviation (SD) = 721, standard error of mean (SEM) = 200). The weighted mean age of ED patients was 61.5 (95% CI 54.4–68.7, SEM = 3.6) and 49% (SD = 4.8%, SEM = 1.6) were male. The hospitalized cohort was older with weighted mean age of 67.1 (95% CI 63.6–70.1, SEM = 1.8) and 48.5% (SD = 10.9%, SEM = 4.9) were male.

3.3. Study characteristics (Table 1)

There were nine studies involving 6608 ED patients and three studies involving 975 hospitalized patients. Only 4/12 studies reported on the specific methods of diagnosing PE. Vanbrabant et al. [13] performed 13 computed tomography (CT) scans of the chest in patients suspected of having PE and confirmed PE in 3 patients. Neither the reason for ordering the CT scans nor the clinical presentations of the patients was reported. Sarasin et al. [14] reported on 67/650 patients with unknown causes of syncope, of whom 11/67 were suspected to have a PE and 8/11 were confirmed using lower limb venous compression ultrasound, plasma D-dimer measurement, and CT scan. Neither whether the 11 patients underwent all these tests, nor the reasons for ordering the CT scans were reported. Del Rosso et al. [15] diagnosed PE in 5/516 patients; 4 were diagnosed with a CT scan and 1 diagnosed with an echocardiogram. Neither the reason for ordering CT scan or echocardiogram nor the clinical presentations of patients was reported. Quinn et al. [16] diagnosed PE in 5/684 patients. PE was confirmed by ventilation perfusion (V/Q) scanning, CT of the chest, pulmonary angiography or on autopsy. It is not reported how many patients were suspected to have PE and underwent confirmatory tests nor their clinical presentations prompting further testing.

Among the hospitalized cohort, Grossman et al. [17] reported on 3 groups of patients; full admissions, 1-day admission and ED observation unit. We combined these and analyzed them as part of hospitalized cohort. No study systematically screened for PE. The use of CT scans was based on clinical decision-making.

3.4. Prevalence of PE in the ED syncope cohort (Fig. 2)

The pooled estimate of PE prevalence in ED syncope cohort was 0.8% (95% CI 0.5–1.3%, $I^2 = 0$, SEM = 0.3). The prevalence of PE in ED patients in the Prandoni et al. [7] study was 3.8%, which is significantly higher than the pooled estimate of the other studies ($p < 0.0001$). The pooled estimate of PE prevalence in ED studies which reported on methods of diagnosing PE (i.e. CT scans, V/Q scan, echocardiogram etc.) was 1.1% (95%CI 0.7–1.8%, $I^2 = 5.3$, SEM = 0.2).

3.5. Prevalence of PE in the hospitalized syncope cohort (Fig. 2)

The pooled estimate of PE prevalence in hospitalized syncope cohort was 1.0% (95% CI 0.5–1.9%, $I^2 = 0$, SEM = 0.2). The prevalence of PE in hospitalized patients with syncope in the Prandoni et al. [7] study was 17.3%, which is significantly higher than other studies ($p < 0.0001$).

3.6. Prevalence of PE in ED and hospitalized cohorts combined (Fig. 2)

The overall pooled estimate of PE prevalence in syncope patients was 0.9% (95%CI 0.6–1.3%, $I^2 = 46.7\%$, SEM = 0.2).

4. Discussion

We conducted a systematic review that found the prevalence of pulmonary embolism to be <1% in patients presenting with syncope, confirming it to be an uncommon finding in current practice patterns.

Table 1
Study characteristics

Author/year	Study design	n	Setting	Age	Men(%)	Admission(%)	PE Prev alence
Blanc, 2001 [27]	Prospective Observational	454	ED	57 ± 23	43	63	4/454 (0.9%)
Del Rosso, 2008 [15]	Prospective Cohort	516	ED	63 ± 21	54	–	5/516 (1%)
Quinn, 2004 [16]	Prospective Cohort	684	ED	62 ± 23	41	55	5/684 (0.7%)
Sarasin, 2001 [14]	Prospective Cohort	650	ED	60 ± 23	48	–	8/650 (1.2%)
Saravi, 2015 [28]	Prospective Cohort	124	ED	60 ± 20	46	–	2/124 (1.6%)
Sun, 2009 [29]	Retrospective Chart Review	2871	ED	75 ± 11	46	43	7/2871 (0.2%)
Sun, 2007 [30]	Prospective Cohort	477	ED	–	44	51	1/477 (0.2%)
Suzuki, 2004 [31]	Retrospective Chart Review	715	ED	58 ± 20	55	–	4/715 (0.6%)
Vandrabant, 2011 [13]	Retrospective Chart Review	117	ED	57 ± 22	45	28	3/117 (2.5%)
Grossman, 2016 [17]	Prospective Cohort	351	Hosp	71 ± 18	45	–	3/351 (0.9%)
Cook, 2016 [32]	Prospective Cohort	299	Hosp	70 ± 18	59	7	4/299 (1.3%)
Sule, 2011 [33]	Retrospective Chart Review	325	Hosp	66 ± 17	59	–	2/325 (0.6%)

Abbreviations: ED-emergency department, PE-pulmonary embolism, Hosp-hospitalized, (−) not reported.

In contrast, Prandoni et al. [7] reported much higher prevalences: 3.8% and 17.3% for patients in the ED and in hospitalized, respectively.

4.1. Current diagnostic approaches to syncope

There is significant variability in the workup of syncope which is in party due to a lack of consensus on a gold standard approach. The challenge to the ED physician, in addition to establishing an etiology, is deciding whether patient's presentation warrants an admission, a specialist referral or discharge home [1]. Most guidelines agree that history, physical examination and ECG are the best initial diagnostic tests in establishing a diagnosis [1,18,19]. However, if a diagnosis is still not made, considerable variability exists on subsequent testing recommendations. Furthermore, while risk stratification is important, no clinical decision rule has been shown to be better than the judgment of the bedside physician. One of the major limitations of the risk schemes is the inclusion of all patients regardless of whether or not the underlying comorbid conditions are associated with syncope [19]. Moreover, the methods used to establish these scores and risk markers from history, physical exam, study end-points, adverse event rates and time interval between events are very variable between studies [19].

4.2. Systematic approach to diagnosing pulmonary emboli in syncope patients

In our studies, CT scans were obtained according to clinical judgment. The patient characteristics, presenting symptoms and reason for ordering the CT scan were not reported. Only Prandoni et al. [7] conducted a protocol-driven systematic search for PE. They screened hospitalized patients with first episode of syncope for the likelihood of PE using the Simplified Wells Score and D-dimer measurement. Patients who had a Wells Score >4 and/or a positive D-dimer underwent V/Q scan or CT chest. Prandoni et al. [7] obtained a D-dimer in all hospitalized patients and the cut off value for a positive test was between 250 and 500 ng/ml, which is contrary to PE guidelines which recommend using age adjusted D-dimer thresholds or at the minimum a cut of >500 ng/ml for imaging [20]. Furthermore, 59% of patients underwent an imaging test based on a positive D-dimer alone and a low Simplified Wells Score. The specificity of D-dimer test in hospitalized patients is lower than in outpatients or ED patients due to co-morbidities, length of hospitalization and older age affecting the levels in the inpatient population [21,22]. Therefore, it is possible that in the Prandoni et al. study a substantially higher number of patients underwent CT scans or V/Q scans because of a lower threshold for ordering confirmatory tests, which led to higher diagnoses of segmental and sub-segmental PEs. Their clinical significance is unclear.

The methods of diagnosing PE are not always reliable. In our review, only 4/12 (Vandrabant [13], Sarasin [14], Del Rosso [15], Quinn [16]) reported on the method of diagnosis of PE. Prandoni et al. [7] used CT pulmonary angiography (CTPA) for diagnosis in 74% (72/97) of their PE patients who had high pre-test probability based on their cut offs. CTPA has a high sensitivity and specificity for diagnosing PE but in patients with low pre-test probability the false positive rate can be as high as 42% [23]. Furthermore, the inter-reader reliability is poor particularly when reading smaller vessels. For example [24] in one study, the rate of discordance among radiologists was 26% in all positive CTPA examinations and increased to 67% where a solitary PE was located in the segmental or sub-segmental arteries. These constituted 33% of PE patients in Prandoni et al. [7].

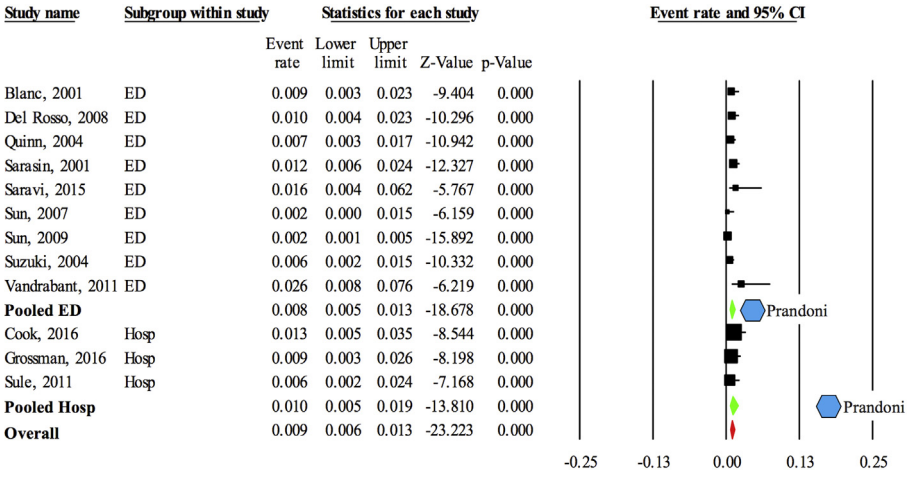

Fig. 2. Pooled analysis of prevalence of pulmonary embolism in syncope patients compared to data of Prandoni et al. Abbreviations: Hosp-Hospitalized, ED-emergency department.

4.3. Pulmonary emboli and outcomes in syncope

It is postulated that the main mechanisms of PE causing syncope include acute right ventricular failure, Bezold-Jarisch type reflex and dysrhythmias associated with PE [25]. Not all PEs present with syncope, and the location of the PE is relevant to clinical outcomes (including syncope) and has prognostic value. In a prior study, only main pulmonary artery and lobar artery PEs were associated with syncope [25,26]. However, this association is seen only in small number of patients with PE, in other instances patients with large pulmonary artery PE do not present with syncope [25,26]. The studies in our review did not explicitly report the characteristics of the PE. In the Prandoni et al. [7] study, about 1 in 3 of diagnosed PE was segmental or sub-segmental which are clinically unlikely to cause syncope. Furthermore, the location of the PE and not the clot burden is associated with increased risk for all-cause mortality and morbidity, proximal clots being more significant [26]. Therefore, it is unclear whether the presence of the PE in the Prandoni et al. [7] study was a direct cause of syncope, or simply an innocent bystander. It is also not clear whether they had prognostic significance.

4.4. Limitations

Our study has several limitations. The clinical presentations and patient characteristics triggering the investigations for PE were not explicitly listed in the studies. Therefore, a direct comparison between Prandoni et al. [7] and clinical decision making approach cannot be made. Given the wide range of causes of syncope, inferring a specific etiologic cause from test findings is difficult and uncertain. The study is subject to bias due to clinical heterogeneity among the included studies, including differences in medical decision making leading to the evaluation of possible PE as well as baseline characteristics of the population enrolled. Furthermore, it is unclear what follow up was done for patients discharged from the ED to ensure they did not have a PE. Our results are subject to the limitation of meta-analyses which include the aggregation of data from different studies with variable methods, patient population and baseline characteristics.

5. Conclusion

At this point the clinical implications of the Prandoni study are unclear. We do not know if the higher prevalence of PE was due to systematic screening, or whether the PE caused syncope, or simply resulted from co-morbidities and hospitalization, or indeed whether they had prognostic significance. This is important not only due to treatment of patients with oral anticoagulants and exposure to bleeding risks, but also due to potential for missing a serious underlying cause. However, the magnitude of the Prandoni et al. findings cannot be ignored and requires further assessment.

Funding

None.

Conflicts of interest

None of the authors have any conflict, financial or otherwise.

Appendix A. Medline search strategy

1. exp. Syncope/
2. (syncope or faint* or unconscious* or drop attack*).kw,tw.
3. 1 or 2
4. exp. Pulmonary Embolism/.
5. (pulmonary emboli* or PE or thromboemboli* or pulmonary infarct*).kw,tw.
6. 4 or 5
7. 3 and 6
8. remove duplicates from 7

Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ajem.2017.09.015.

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