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Incidence, etiology and predictors of adverse outcomes in 43,315 patients presenting to the Emergency Department with syncope: An international meta-analysis

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ABSTRACT

Background: Syncope remains challenging for Emergency Department (ED) physicians due to difficulties in assessing the risk of future adverse outcomes. The aim of this meta-analysis is to establish the incidence and etiology of adverse outcomes as well as the predictors, in patients presenting with syncope to the ED.
Methods: A systematic electronic literature review was performed looking for eligible studies published between 1990 and 2010. Studies reporting multivariate predictors of adverse outcomes in patients presenting with syncope to the ED were included and pooled, when appropriate, using a random-effect method. Adverse events were defined as 'incidence of death, or of hospitalization and interventional procedures because of arrhythmias, ischemic heart disease or valvular heart disease'.
Results: 11 studies were included. Pooled analysis showed 42% (CI 95%; 32–52) of patients were admitted to hospital. Risk of death was 4.4% (CI 95%; 3.1–5.1) and 1.1% (CI 95%; 0.7–1.5) had a cardiovascular etiology. One third of patients were discharged without a diagnosis, while the most frequent diagnosis was 'situational, orthostatic or vasavagal syncope' in 29% (CI 95%; 12–47). 10.4% (CI 95%; 7.8–16) was diagnosed with heart disease, the most frequent type being bradyarrhythmia, 4.8% (CI 95%; 2.2–6.4) and tachyarrhythmia 2.6% (CI 95%; 1.1–3.1). Palpitations preceding syncope, exertional syncope, a history consistent of heart failure or ischemic heart disease, and evidence of bleeding were the most powerful predictors of an adverse outcome.
Conclusion: Syncope carries a high risk of death, mainly related to cardiovascular disease. This large study which has established the most powerful predictors of adverse outcomes, may enable care and resources to be better focused at high risk patients.

1. Introduction

Syncope is a common clinical presentation accounting for up to 3% of all Emergency Department (ED) visits and 6% of hospital admissions [1]. Accurate diagnosis and assessment of prognosis [2]are required by ED physicians, as syncope may be due to a wide range of possible etiologies ranging from benign conditions to life-threatening diseases [3,4]. Focused inpatient investigation concentrating on high risk patients may save some of the 2 billion dollars spent every year in the United States of America on the hospitalization of patients with syncope [5,6].

Several clinical decision rules (CDRs) and risk stratification scores have been derived to help physicians with diagnosis and risk assessment. These have performed less well when validated and applied to everyday clinical practice [7], possibly due to relatively small numbers of patients in each.

To our knowledge, no meta-analyses have been performed looking at either the short or long term diagnosis and prognosis of syncope and its most powerful predictors. The aim of this study is therefore to establish the incidence and etiology of adverse outcomes as well

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as the predictors, in patients presenting with syncope to the ED in order to offer physicians a more robust future assessment of risk.

2. Methods

The present research was conducted following current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, and recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [8–11].

2.1. Search strategy and study selection

Possible articles for inclusion were found using established search methods [12] looking for the terms "syncope", "multivariate predictors" and "adverse outcomes". The corresponding authors of possible studies were then directly contacted via email asking for further data and knowledge of further studies [13].

Two independent reviewers (GB-Z, FDA) initially screened all possible articles for inclusion at the title and/or abstract level, with disagreement resolved by consensus. If thought potentially eligible, the complete article was then reviewed according to the following strict selection criteria. Studies had to be both (i) investigating patients presenting to the ED with syncope AND (ii) reporting predictors of adverse outcomes after syncope using multivariate analysis methodology. Exclusion criteria were any of: (i) non-human study, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients was selected) or (iii) differentiated syncope patients (i.e. studies recruiting patients with an already defined diagnosis of syncope e.g. cardiovascular cause only).

2.2. Data extraction

Two unblinded independent reviewers (GB-Z, FDA) abstracted the following data on pre-specified data collection forms: authors, journal, year of publication, location of the study group, baseline features, admission and death rates, inclusion and exclusion criteria, final identified cause of syncope (if any), multivariate predictors of adverse outcomes (point summary estimate of risk, with 95% confidence interval). Pre-defined end-points were incidence of in-hospital admission, incidence of adverse outcomes (defined as incidence of death, or of hospitalization and interventional procedures because of arrhythmias, ischemic heart disease or valvular heart disease') and final identified cause of syncope (if any).

2.3. Internal validity and quality appraisal

Unblinded independent reviewers (GB-Z, FDA) evaluated the quality of the selected studies on pre-specified data collection forms using modified MOOSE criteria to take into account the specific features of included studies [10]. The independent reviewers separately appraised study design, setting, data source, and statistical methods for multivariable analysis, as well as risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias). Where present, incomplete reporting leading to inability to ascertain the underlying risk of bias was also recorded. All studies then received an overall score based as follows: Zero points were awarded for a retrospective design or single center study; One point for prospective design and/or multicenter setting; Two points were awarded for low risk of bias, one point for moderate risk of bias, and zero points for high risk or unclear risk of bias. If the total of these scores was 10 an overall 'very high' credibility rating was awarded, if the total was between 7 and 9 a 'high' credibility rating was awarded, if the total was between 4 and 6 a 'moderate' credibility rating was awarded, if the total was between 1 and 3, a 'low' credibility rating was awarded and for a total score of 0, a 'very low' credibility rating was awarded (see Appendix Table B).

Table 1
Key features of included studies.

Studies	N = 11
Study design	
Prospective cohort	8 (70%)
Retrospective cohort	3 (30%)
Data source	
Clinical database	11 (100%)
Years of publication	2004–2009
Setting	
Single center	5 (45%)
Multicenter	6 (55%)
Location	
North America	5 (45%)
Europe	5 (45%)
Asia	1 (10%)
Total patients presenting with syncope to the Emergency Department	43,315 670 (487–913)
Median number of patients per study (1st–3rd quartile)	
Follow-up in months (median; 1st–3rd quartile)	1 (1–16)

2.4. Data analysis

Continuous variables are reported as mean (standard deviation) or median (range). Categorical variables are expressed as n/N (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark). Graphical inspection of funnel plots was used to assess for study bias. Standard hypothesis testing was set at the two-tailed 0.05 level.

3. Results

201 citations were initially screened of which 17 reports were fully evaluated for consideration in the study. Three reports were excluded as they were non-ED studies [14–16], two were excluded because they reported differentiated patients with a pre-defined diagnosis of syncope (in both cases syncope patients with a diagnosis of cardiovascular syncope) [17,18], one was excluded because it did not report multivariate predictors [2], and one study was excluded because of duplicate reporting [19]. 11 studies were finally included in the meta-analysis [20–30] (Fig. 1).

The main features of the included studies are reported in Table 1. Most of the studies were prospective, multicenter, with a median of 670 patients and a follow up of 1 month. While syncope was variably defined, all included papers essentially defined syncope according to the European Society of Cardiology 2009 guidelines (Table 2) [32].

Appendix Table B details the methodological validity of the 11 included studies. Logistic regression was the most frequent multivariate approach, with most of the studies reporting an overall high credibility. The main limitations were in adjudication and attrition bias.

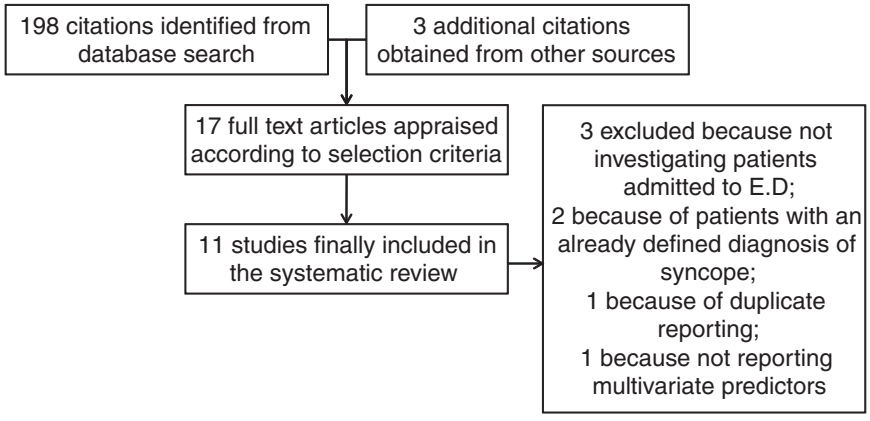

Fig. 1. Study flow diagram.

Table 2
Inclusion and exclusion criteria of included studies.

Author, journal, year	Inclusion criteria	Exclusion criteria
OH, Arch Inter Med, 1999	Sudden transient loss of consciousness (LOC) with an inability to maintain postural tone.	Symptoms compatible with seizure disorder, vertigo, dizziness, coma, shock, or other states of altered consciousness.
Colivicchi, EHJ, 2003	Sudden and transient LOC and of postural tone with spontaneous recovery.	Pre-syncope, dizziness or vertigo, without a clear loss of consciousness or already known seizure disorder and presenting a typical recurrence, with prolonged post-ictal recovery phase.
Sarasin, Acad Emer Med, 2003	Sudden transient LOC with an inability to maintain postural tone, and with spontaneous recovery.	Symptoms clearly compatible with seizure disorder, vertigo, dizziness, coma, shock, or other states of altered consciousness.
Suzuki, Ann Emerg Med, 2003	Sudden transient LOC with an inability to maintain postural tone.	Seizure, vertigo, dizziness, coma, shock, or other altered states of consciousness.
Quinn, Ann Inter Med, 2004	Sudden transient LOC.	Altered mental status, alcohol or illicit drug-related loss of consciousness, a definite seizure, or transient loss of consciousness caused by head trauma.
Sun, J Am Geriatr Soc, 2007	Sudden transient LOC.	Witnessed seizure, loss of consciousness after head trauma, ongoing confusion (including baseline cognitive impairment or dementia), intoxication, age younger than 18, inability to speak English or Spanish, do-not-resuscitate (DNR) or do-not-intubate (DNI) status, and lack of follow-up contact information.
Costantino, JACC, 2008	Sudden transient LOC.	Presence of clinical conditions primarily confirmed in the ED that would have required hospital admission independently of the syncope such as myocardial infarction, acute pulmonary embolism, subarachnoid hemorrhage, stroke, cardiac arrest, sustained bradycardia (35 beats/min), complete atrioventricular block, sustained ventricular tachycardia; a referred head injury preceding the loss of consciousness; a referred non-spontaneous return to consciousness; non-syncopal syndromes such as light-headedness, vertigo, coma, shock, and seizure; associated diseases with a prognosis less than 6 months; recent alcohol or drug abuse; unwillingness to provide consent to participate in the study; and unfeasible follow-up (foreigners, homeless).
Del Rosso, BMJ, 2008	Sudden transient LOC.	Definite non-syncopal cause of loss of consciousness on the initial evaluation (seizures, drop attacks, transient ischemic attacks, etc.), those aged, 18 years and those referred 24 h after their episode.
Sun, Ann Emerg Med, 2009	Sudden, transient loss of consciousness, and near-syncope as a sensation of imminent loss of consciousness.	Generalized seizure, intoxication, no spontaneous return to baseline mental status and patients who experienced loss of consciousness as a result of head trauma.
Gabayan, AJC, 2010	Blackout, fainting (near), syncope, vasovagal attack.	Carotid sinus syncope, heat syncope, neurocirculatory asthenia, orthostatic hypotension, shock.
Reed, JACC, 2010	Sudden transient LOC with an inability to maintain postural tone.	Persisting neurological deficit suggestive of stroke, previous recruitment into the study, collapse related to alcohol consumption (raised alcometer reading and no other cause for syncope), hypoglycemia, trauma, or seizure activity with a less 15-min witness reported postictal phase.

45% of patients in the included studies were male, (41–60), reporting in 38% a history of previous syncope, and in 30% a history of previous heart disease, most frequently arrhythmic (11%) or ischemic heart disease (8%) (Table 3).

Pooled analysis of outcomes and diagnosis of all included patients are reported in Tables 4 and 5. At a median follow-up of 1 month, risk of death was 4.4%, which was due to a cardiovascular etiology in 1.1%. 42% of patients were admitted to hospital: 10.4% of patients were diagnosed with heart disease; the most frequent causes were bradyarrhythmic (4.8%) and tachyarrhythmic disease (2.6%). 29% of patients were discharged without a diagnosis and the most frequent diagnosis was situational, orthostatic or vasavagal syncope (29%). The most powerful predictors of adverse outcome (Table 6 and Fig. 2) were palpitations preceding syncope, syncope during effort, a history consistent of heart failure or ischemic heart disease and clinical and laboratory evidence of bleeding.

4. Discussion

The most important findings of our meta-analysis are (a) patients presenting with syncope to the ED carry a low although significant risk of death, (b) one third of deaths are ascribable to cardiovascular diseases, (c) a large proportion of patients are still discharged without a clear diagnosis and (d) simple predictors could be useful to identify high risk patients.

Table 3
Key patient characteristics.

Studies	N = 11
Age (years)	63 (60–64)
Male gender	45% (41–60)
Diabetes	12% (6–13)
Hypertension	39% (35–43)
History of previous syncope	38% (32–44)
History of heart disease	30% (24–49)
History of arrhythmic heart disease	11% (4–19)
History of ischemic heart disease	8% (6–26)
History of heart failure	8% (2–9)
History of valvular disease	1% (0.2–4)
History of ischemic neurological disease.	15% (8–21)

Reported as n (%) or median (1st–3rd quartile).

Table 4
Pooled analysis of syncope etiology.

Diagnosis of cardiovascular disease	10.4% (8–16)
– Rhythmic disease	7.4% (4.5–10)
– Bradyarrhythmic disease	2.6% (1.1–3.1)
– Tachiarrhythmic disease	4.8% (2.2–6.4)
– Myocardial infarction	1.7% (1–2.4)
– Aortic stenosis	1.3% (0.7–2.1)
Diagnosis of stroke	0.8% (0.5–0.9)
Diagnosis of situational, orthostatic or vasovagal syncope	29% (9–49)
Diagnosis of pulmonary embolus	0.6% (0.2–0.96)
Diagnosis of gastrointestinal bleeding/anemia	2.4% (1.5–3.3)
Diagnosis of unexplained syncope	29.6% (11–47)

Reported as% (95% CI).

Table 5
Pooled analysis of patient's management and of adverse outcomes.

Studies	N = 11
Patients discharged to home	58% (48–68)
Patients admitted to hospital	42% (32–52)
Overall death	4.4%[a] (3.1–5.1)
Cardiovascular related death	1.1% (0.7–1.5)
Non cardiovascular related death	1.5% (0.7–2.4)
Unexplained death	1.7% (0.2–3.3)

Reported as% (95% CI).
[a] Overall death was 4.36% made up of cardiovascular death (1.1%), non-cardiovascular death (1.5%) and unexplained death (1.73%).

Table 6
Most common predictors of adverse outcome[a] after a syncopal episode identified in included studies.

Studies	N = 11 (%)
Previous heart disease[b]	11 (100)
Abnormal Electrocardiogram (ECG)[c]	11 (100)
Age (per 10 year increase)	6 (45)
Abnormal values of blood pressure (<90 mm Hg, or >160 mm Hg)	3 (27)
Male gender	3 (27)
Clinical or laboratory evidence of bleeding[d]	2 (18)

The following predictors were reported only in one study each:

>4 episodes of syncope in the last year;
Absence of symptoms preceding syncope;
Abnormal B natriuretic peptide concentration;
Prior cerebrovascular disease or heart disease;
Cancer;
Palpitations preceding syncope;
Syncope while supine,
Syncope during effort or without prodrome,
Trauma;
Abnormal troponin value.

[a] Incidence of death, or of hospitalization and interventional procedures because of arrhythmias, ischemic heart disease or valvular heart disease.
[b] Previous heart failure or ischemic heart disease.
[c] Widely defined as Rhythm abnormalities, Atrioventricular or intraventricular conduction disorders and ST segment and T wave abnormalities consistent with or possibly related to myocardial ischemia.
[d] Diagnosed via complete/full blood count or rectal examination.

Syncope represents a common problem that practitioners often face in the ED or on a hospital ward. Emergency physicians take care of the initial management of patients, while further assessment of patients involves cardiologists and neurologists [32,33]. The diagnosis is often difficult due to many possible underlying causes [7], and because usually patients are totally asymptomatic during medical evaluation [20]. As seen from our data, all hospitalized patients still carry a significant risk of death, mainly related to cardiovascular causes, which persists, as previously showed, at long term [2].

In this study, syncope was thought to be due to situational, orthostatic or vasavagal causes [17] in up to one third of cases but still in one third of cases the etiology of syncope was not clear. Patients with situational syncope are not at risk of death or of adverse outcome and can be managed generally with lifestyle changes [7]. On the other hand unexplained syncope can have adverse outcome, and usually involves older and sicker patients [31].

Simple predictors of adverse outcomes could be very useful to identify high risk patients. In our meta-analysis, palpitations preceding syncope, syncope during effort, history of heart failure or ischemic heart disease and clinical and laboratory evidence or bleeding are the most powerful predictors of adverse outcome, while the most frequent to appear in the included studies are a history of heart disease and an abnormal electrocardiogram (ECG). Most of these factors are easy to assess, both through basic history and physical examination, and could improve diagnostic and therapeutic decision making (Table 6).

This work has many limitations. Firstly adverse outcomes were infrequent, thus leading to potential pitfalls in an accurate reporting [34]. Secondly, predictors were not pooled, mainly because this would have been fraught with a substantial selective reporting bias [35]. Because the present meta-analysis was based only on published studies, publication bias may be a problem, although small study bias was unapparent at funnel plot inspection (Fig. A, Appendix). Another weakness of our work was not performing an individual patient level meta-analysis. This could have provided more detailed information on incidence and predictors, but most likely would have required exclusion of several datasets thus limiting the study's external validity.

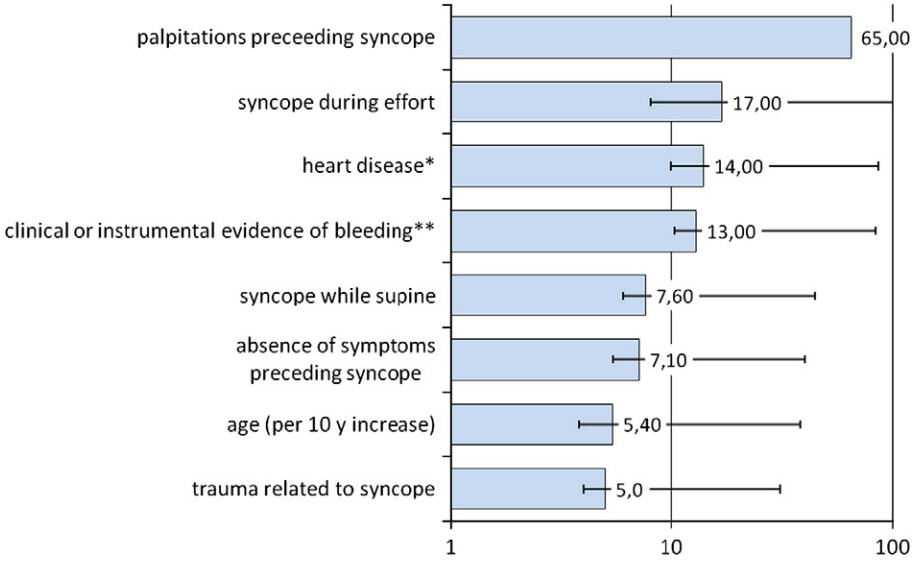

Fig. 2. Most powerful predictors of adverse outcome[+] after syncope (those with an OR>5).[+] Incidence of death, or of hospitalization and interventional procedures because of arrhythmias, ischemic heart disease or valvular heart disease'.* History consistent with heart failure or ischemic heart disease.** Diagnosed via complete/full blood count or rectal examination.

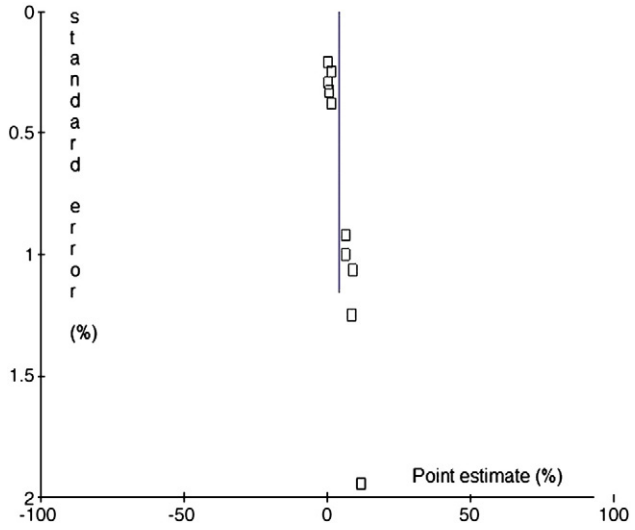

Fig. A. Funnel plot.

Because our study pooled smaller studies, it provides better data on more frequent syncope causes but does not provide any information on rarer causes such as short and long QT syndromes, or Brugada syndrome which may be expected to appear rarely in a study on 43 thousand patients [36,37].

Syncope carries a high risk of death, mainly related to cardiovascular disease. This large study which has established the most powerful predictors of adverse outcome may enable care and resources to be better focused at high risk patients. Future efforts should be focused on standardizing reporting criteria for ED syncope studies to allow better pooling of results from different centers.

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Appendix Table A. Assessment of bias

Bias	Risk of bias
Analytical bias	
– Analysis being performed from different physicians or statistics	Low risk
– Analysis being performed by single physician or statistic	Medium risk
Selection bias	
– Including all consecutive patients with syncope	Low risk
– Excluding patients not because of clinical choices (for ex. those unavailable for follow-up)	Medium risk High risk
– Excluding patients who commonly refer to ED for syncope	
Adjudication bias	
– Independent committee who critically reviewed outcomes	Low risk
– Follow up visits performed in hospital or ambulatories	Medium risk
– Follow up phone calls	High risk
– There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.	Unclear
Attrition bias	
– 100% of patients with a complete follow-up	Low
– Less than 100% of patients completed follow-up—There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.	Medium Unclear

Appendix Table B. Internal validity of included studies

Studies	N = 11
Multivariate analysis approach	
Logistic regression	8 (73%)
Cox proportional hazard models	2 (18%)
Recursive partitioning	1 (9%)
Analytical bias	
Low risk	6 (55%)
Moderate risk	5 (45%)
Selection bias	
Low risk	7 (63%)
Moderate risk	4 (37%)
Adjudication bias	
Low risk	7 (63%)
Moderate risk	4 (37%)
Attrition bias	
Low risk	5 (45%)
Moderate risk	6 (55%)
Overall credibility	
Moderate	3 (27%)
High	8 (73%)

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