

## REVIEW ARTICLE

# Review article: Utility of troponin after syncope: A systematic review and meta-analysis

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## Abstract

The role of serum troponin testing in patients presenting to the ED after syncope is unclear. The aim of this systematic review was to examine the practice and utility of troponin testing among patients presenting to the ED after syncope. We conducted a search of MEDLINE, Embase, Cochrane Library, Web of Science and Scopus databases from 1990 to February 2017 using keyword and subject headings for syncope and troponin testing. Design and results of the included studies are extracted. Studies were assessed for heterogeneity and the pooled proportion of measured troponin and positive troponin result described. There were nine studies included for analysis. Significant statistical heterogeneity among studies was observed ( $P < 0.001$ ). Using the random effects model, the pooled proportion of patients presenting to the ED after syncope who had troponin measured was 0.64 (95% CI 0.46–0.82). Among patients who had been troponin tested, the pooled proportion who had a positive result was 0.19 (95% CI 0.13–0.26). Variability among reported outcomes prevented further meta-analysis. Troponin testing was commonly performed for the assessment of patients with syncope with a substantial proportion returning positive results. The

correlation between raised troponin and patient outcomes was not adequately reported. It is possible that an elevated troponin may indicate serious illness, rather than myocardial damage alone.

**Key words:** *syncope, troponin.*

## Introduction

Syncope represents a common problem accounting for 1–3% of all ED presentations.<sup>1–6</sup> Syncope is defined as the ‘transient loss of consciousness due to transient global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery’.<sup>7</sup> It can be caused by a range of serious and life-threatening conditions, such as dysrhythmias, myocardial infarction, pulmonary embolism or haemorrhage.<sup>2,4,5,8–11</sup> Conversely, syncope can be, and more often is reflex mediated. This is also known as neutrally mediated or vasovagal.

Assessment of patients presenting to the ED after syncope have been reported to have wide practice variation, high expenses and unclear benefit with current approaches.<sup>9,12–15</sup> Associated hospital admission rates vary from 7.4 to 83%.<sup>1,8,10,11,16–22</sup> Standard practice includes a detailed history, performing a physical

## Key findings

- Troponin testing is commonly performed in patients presenting to the ED after syncope.
- A substantial proportion of those who had troponin testing had a positive result.
- A raised troponin result was not adequately correlated with outcomes.

examination, standard 12-lead electrocardiography (ECG) and orthostatic blood pressure measurement. The utility of other investigations, including cardiac biomarkers, is controversial, and evidence for routine laboratory investigations is currently lacking.

Among patients presenting to the ED after syncope, one-third leave the hospital without getting a diagnosis.<sup>13,23</sup> In this group of patients, risk stratification is key as a substantial proportion of short- and medium-term serious adverse events (AEs) may not be apparent during initial evaluation in the ED.<sup>20</sup> Several risk stratification tools have been developed to aid this process; however, none has been widely adopted into clinical practice.<sup>12</sup>

The objective of the present study is to conduct a systematic review to assess the practice and utility of troponin testing among patients presenting to the ED after syncope. The primary aim of this systematic review was to identify the frequency of troponin testing among patients presenting with syncope. Secondary outcomes were to assess the utility of troponin testing after syncope in predicting death and disability at discharge, 3 months and 6 months. We

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Accepted 8 January 2018

also aimed to assess the outcome of acute myocardial infarction (AMI) at discharge, 3 months and 6 months.

## Methods

### *Information sources and search strategy*

The study protocol ([https://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42017058181](https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017058181)) was registered with PROSPERO, an international prospective register of systematic reviews. The search strategies, in Appendix S1, were developed using subject headings and text words relating to syncope and troponin. We searched for English language articles in MEDLINE (1990–February 2017), Embase, the Cochrane Library, Scopus and Web of Science. We also manually searched reference lists of included studies, and grey literature using Google Scholar.

### *Eligibility criteria*

We included studies of adult patients presenting after syncope that reported on troponin testing. Included studies had to report on adult populations with acute syncope that was not induced as part of investigations (i.e. tilt-table testing) and report quantitative measurement of troponin levels. We excluded studies involving children (age <16 years), case reports, narrative reviews, including editorials and letters to the editor. Duplicates with exact matching titles were removed.

### *Study selection and data collection*

Two independent reviewers (CBS and BM) assessed the titles and abstracts of retrieved articles for eligibility. Full text articles were reviewed for final inclusion or if there was insufficient information provided in the abstract on eligibility criteria. Disagreements were resolved by discussion with a third reviewer (DS). We extracted the following data: author, year of publication, study type, study setting, definition of syncope used, total number of

participants included in the study, number of patients who had troponins measured, troponin biomarker used, troponin reference ranges applied and outcome measures including length of follow up.

Studies were first grouped according to whether they reported proportion of troponin testing in a population of patients presenting with syncope and then on utility of syncope. As data were considered sufficiently clinically homogenous (in terms of population, setting and outcomes) meta-analysis was performed using a random effects model to calculate the pooled proportion of patients currently undergoing troponin testing and the proportion of patients who had a positive troponin with 95% confidence intervals (CIs). Heterogeneity between studies was assessed using the  $\chi^2$  statistic and quantified using the  $I^2$  statistic. Statistical analyses were conducted using Stata (version 11.0; StataCorp, College Station, TX, USA).

### *Risk of bias assessment*

Two review authors independently assessed the risk of bias. Results were compared and any disagreement resolved by discussion or consultation with a senior member of the review team. To assess risk of bias in observational studies, we used the Newcastle-Ottawa Quality Assessment Scale<sup>24</sup> (Appendix S2). This assessment tool uses a 'star system' to judge risk of bias over eight individual items across three main areas: the selection of study groups; the comparability of groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

## Results

### *Study identification and exclusions*

The initial search yielded 636 citations. After removal of duplications, and screening by title and abstract 57 manuscripts were eligible for full text assessment. Of these, 48 were

excluded for the following reasons: only abstract available, ineligible patient population, outcome of interest not report, article retracted and narrative review. The search and selection process is illustrated using a PRISMA template presented in Figure 1. Details of the nine studies have been included in the final analysis are provided in Table 1.

### *Definitions of syncope*

The definitions of syncope varied between studies. Only two studies strictly used the definition according to the European Society of Cardiology Diagnosis and Management of Syncope guidelines,<sup>25,32</sup> outlining global cerebral hypoperfusion as the cause for the transient loss of consciousness (T-LOC). There was variation between all the other definitions. All but one manuscript referred to the loss of consciousness as transient, with the other terming it as a 'brief' loss of consciousness. Only one manuscript defined transient as a period of <5 min.<sup>29</sup> Definitions of syncope along with demographics of patients and troponin assays used are described in Table 2.

### *Proportion of troponins measured*

Among studies that investigated a population of patients with syncope, the proportion of patients whom had troponin measured is described in Table 3 and a Forest plot of incidence illustrated in Figure 2. Using a random effects model, the pooled proportion of patients with troponins measured after syncope was 0.64 (95% CI 0.46–0.82). Significant statistical heterogeneity among studies was observed ( $\chi^2 = 2250.74$ ;  $P < 0.001$ ), with 99.7% of variation in estimated size attributable to differences in study characteristics ( $I^2 = 99.7$ ). Reed *et al.*<sup>31</sup> noted the mean age was higher in those who had troponin measured ( $74 \pm 14$  vs  $68 \pm 18$  years,  $P = 0.018$ ).

### *Proportion of positive troponins*

Among studies that investigated troponin measured in patients with

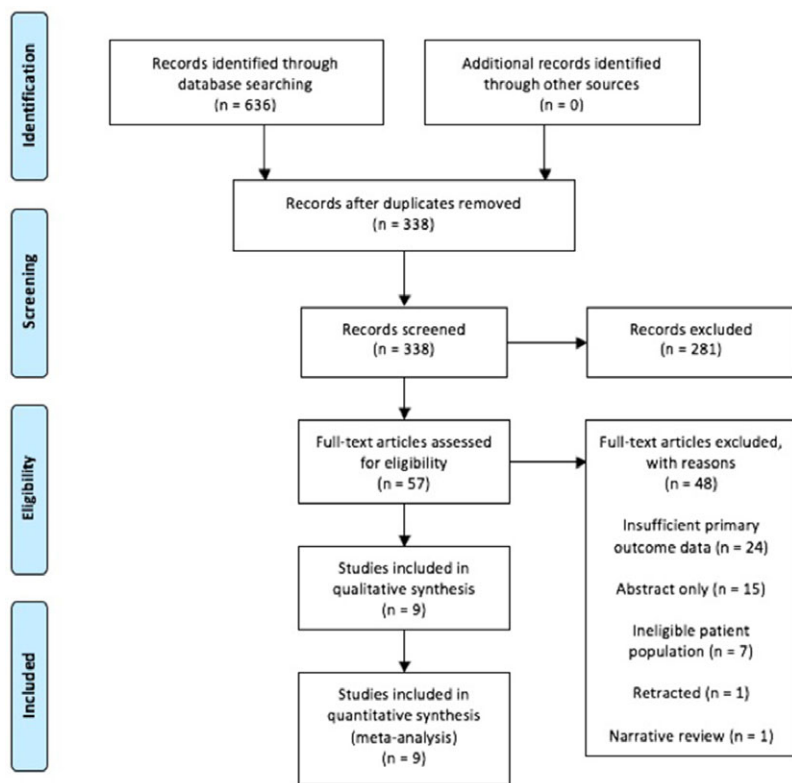


Figure 1. PRISMA flow diagram illustrating search and selection process.

syncope, the proportion that were positive is described in Table 3 and Forest plot of incidence is illustrated in Figure 3. Of patients with troponin tested, the pooled proportion of patients who had a positive result was 0.19 (95% CI 0.13–0.26). Significant statistical heterogeneity among studies was observed ( $\chi^2 = 394.63$ ;  $P < 0.001$ ), with 98% of variation in estimated size attributable to differences in study characteristics ( $I^2 = 98$ ).

### Death

Variability among reported outcomes precluded meta-analysis. Chiu *et al.* assessed mortality at 30 days and found a positive association with elevated troponin on initial assessment.<sup>29</sup> There were two of 19 (10.5%) patients with a raised troponin level had died at 30 days as compared to five of 298 (1.7%). Christ *et al.* found that at 180 days, 19 of 148 with a raised troponin died (5.3% vs 1.9% in patients without elevated troponin;  $P < 0.001$ ).<sup>28</sup> Reed *et al.* found any rise in

troponin was associated with increased risk of death at 1 month and 1 year ( $P < 0.001$ ).<sup>30</sup> Lindner *et al.* found that one of 55 patients with raised troponin died in hospital as compared to zero from 66 with a normal troponin level.<sup>32</sup> They concluded there was no benefit from determination of high-sensitive troponin. Hing *et al.*<sup>33</sup> found two of four patients with a raised troponin had died at 30 days as compared to zero of 96 with normal troponin levels. The single troponin was not shown to be a sensitive predictor of outcome.

### AMI

The outcome measure of AMI was defined by Reed *et al.* according to the universal definition<sup>34</sup> and by Christ *et al.* according to the World Health Organization (WHO) troponin cut-off point for AMI at  $\geq 100$  ng/L.<sup>35,36</sup> Reed *et al.* concluded that AMI was infrequent (1.4%) and estimation of troponin I provided little additional benefit to the presenting ED ECG in identifying patients with

syncope because of AMI.<sup>31</sup> Christ *et al.* found that at 180 days, of the 148 who had an elevated troponin, nine had an AMI. There were zero of 212 patients with normal troponin levels had an AMI within 180 days.<sup>28</sup>

### Major adverse cardiac event (MACE)

Sun *et al.* concluded that abnormal troponin I level was independently associated with MACE at 30 days after ED evaluation.<sup>26</sup> Supporting this conclusion, Hing *et al.* found single troponin levels at 4 h was highly predictive of adverse cardiac outcome at 3–6 months after presentation ( $P = 0.04$ ) but had a low sensitivity (0.13; 95% CI 0–0.3). Of the 23 patients with adverse cardiac outcome, 20 patients had negative troponins.<sup>33</sup> In contrast, Christ *et al.* found that high sensitivity troponin T level is not an independent predictor of MACE.<sup>28</sup>

### Hospitalisation

The study by Lindner *et al.* was the only study to report hospitalisation rates and was the only study to consider baseline elevated troponin as well as a dynamic change of  $\pm 30\%$  change from baseline.<sup>32</sup> Of the 45% with abnormal troponin, three received coronary angiography, none of whom then received intervention for coronary revascularisation.<sup>32</sup>

### Other serious AEs

There were four manuscripts that concluded increased rates of serious AEs in patients with syncope and elevated troponin levels. Thiruganasambandamoorthy *et al.* found that of those with elevated troponin, 25.2% (37 of 147) had a serious AE (defined in Table 2) by death, myocardial infarction, arrhythmia, serious structural heart disease, aortic dissection, pulmonary embolism, severe haemorrhage, severe pulmonary hypertension, subarachnoid haemorrhage and any other serious condition causing syncope and procedural interventions for the treatment of syncope) within 30 days, as compared to 3.4% with normal troponin levels (132 of 3883)  $P < 0.001$ . Troponin was

TABLE 1. Study characteristics

Author (year)	Study type	Patient population	No. patients enrolled	No. troponins measured	Troponin biomarker	Cut-off value
Thiruganasambandamoorthy <i>et al.</i> (2016) <sup>25</sup>	Prospective	Adult ( $\geq 16$ years) presenting within 24 h of syncope to the ED	4030	1930	Assays varied according to study site	>99th percentile of normal population
Sun <i>et al.</i> (2009) <sup>26</sup>	Retrospective	Older ( $\geq 60$ years) ED syncope and near syncope patients	2581	1995	Troponin I	$\geq 40$ ng/L
O'Neill <i>et al.</i> (2016) <sup>27</sup>	Retrospective	All ED syncope patients	253	43	HS troponin I	HS troponin • Men $\geq 34$ ng/L • Women $\geq 16$ ng/L • $\geq 14$ ng/L
Christ <i>et al.</i> (2015) <sup>28</sup>	Prospective	Adult ( $\geq 18$ years) ED syncope and near syncope patients	360	360	HS troponin T	>100 ng/L
Chiu <i>et al.</i> (2014) <sup>29</sup>	Prospective	Adults ( $\geq 18$ years) ED syncope patients	570	317	Troponin T	>0.05 ng/mL
Reed <i>et al.</i> (2012) <sup>30</sup>	Prospective	Adult ( $\geq 16$ years) ED syncope patients with HS troponin measurements 12 h after the syncope	528	338	HS troponin I	$\geq 200$ ng/L
Reed <i>et al.</i> (2010) <sup>31</sup>	Prospective	Adults ( $\geq 16$ years) ED syncope patients	289	281	Troponin I	$\geq 14$ ng/L
Lindner <i>et al.</i> (2013) <sup>32</sup>	Retrospective	All patients presenting to the ED with syncope	121	121	HS troponin T	>0.30 ng/L
Hing <i>et al.</i> (2005) <sup>33</sup>	Prospective	Adults ( $\geq 18$ years) ED syncope patients	113	100	Troponin T	>0.30 ng/L

HS, high sensitivity; ng/L, nanogram/litre; ng/mL, nanogram/millilitre.

TABLE 2. Study characteristics

Author (year)	Country of origin	Age (mean)	Sex	Type of ED	Troponin assay	Definition of syncope
Thiruganasambandamoorthy <i>et al.</i> (2016) <sup>25</sup>	USA	53.6 years	55.5% F 44.5% M	Five large EDs in teaching hospitals in California	Assays varied according to study site	Transient loss of consciousness because of transient global cerebral hypoperfusion followed by spontaneous and complete recovery
Sun <i>et al.</i> (2009) <sup>26</sup>	California	75 years	46% M	Three EDs within a regional managed care system	Troponin I	Syncope: sudden transient loss of consciousness Near syncope: sensation of imminent loss of consciousness without actual syncope
O'Neill <i>et al.</i> (2016) <sup>27</sup>	Scotland	59 years	NR	ED of the Royal Infirmary of Edinburgh, a UK tertiary centre	HS troponin I	Transient loss of consciousness with an inability to maintain postural tone, followed by spontaneous recovery without any intervention
Christ <i>et al.</i> (2015) <sup>28</sup>	Germany	70.5 years	44.2% F 55.8% M	Large community hospital and level III trauma centre	HS troponin T	Sudden, transient loss of consciousness because of temporary global cerebral hypoperfusion with spontaneous recovery and is usually accompanied by loss of postural tone
Chiu <i>et al.</i> (2014) <sup>29</sup>	USA	57.2 years	60.4% F	Large urban teaching hospital (2007–2008)	Troponin T	Sudden and transient (<5 min) loss of consciousness producing a brief period of unresponsiveness and a loss of postural tone, ultimately resulting in spontaneous recovery requiring no resuscitation measures
Reed <i>et al.</i> (2012) <sup>30</sup>	Scotland	63.1 years	45% M	Royal Infirmary of Edinburgh	HS troponin I	Transient loss of consciousness with an inability to maintain postural tone, followed by spontaneous recovery without any intervention
Reed <i>et al.</i> (2010) <sup>31</sup>	Scotland	NR	49.8% M 50.2% F	Royal Infirmary of Edinburgh	Troponin I	Transient loss of consciousness with an inability to maintain postural tone followed by spontaneous recovery without any intervention
Lindner <i>et al.</i> (2013) <sup>32</sup>	Switzerland	67 years	65% M 35% F	Large university hospital	HS troponin T	Transient loss of consciousness caused by a self-limiting global cerebral hypoperfusion characterised by rapid onset, short duration and spontaneous complete recovery
Hing <i>et al.</i> (2005) <sup>33</sup>	Australia	NR	53% F 47% M	Tertiary referral hospital	Troponin T	Brief loss of consciousness induced by a temporarily insufficient flow of blood to the brain ( <i>concise medical dictionary</i> )

F, female; M, male; NR, not recorded.

TABLE 3. Outcomes

Study	Outcome measures	No. participants	No. troponins tested	No. troponin positive
Hing <i>et al.</i> (2005) <sup>33</sup>	3–6 month adverse cardiac outcome: diagnosis or intervention for ischemic heart disease, arrhythmia requiring medical management or pacemaker, cardiac death	113	100	4
Sun <i>et al.</i> (2009) <sup>26</sup>	30 day serious event: death, arrhythmias, AMI, new structural heart disease, cardiac procedural interventions, pulmonary embolism, aortic dissection, stroke/TIA, subarachnoid or non-traumatic cerebral haemorrhage, or haemorrhage/anaemia requiring transfusion	2581	1995	347
Reed <i>et al.</i> (2010) <sup>31</sup>	1 month serious outcome: MI, life-threatening arrhythmia, pacemaker/ICD insertion, pulmonary embolism, stroke, haemorrhage requiring transfusion, acute procedural or endoscopic intervention, all-cause death	289	281	14
Reed <i>et al.</i> (2012) <sup>30</sup>	1 month and 1 year serious outcome: all-cause death, MI, life-threatening arrhythmia, pacemaker/ICD insertion, pulmonary embolism, stroke, subarachnoid haemorrhage, haemorrhage requiring C 2 units red blood cells, acute surgical or endoscopic interventions	528	338	120
Chiu <i>et al.</i> (2014) <sup>29</sup>	30 day outcomes: cardiac/syncope-related death, arrhythmias, structural heart disease, MI, pulmonary embolism, aortic dissection, haemorrhage/anaemia requiring transfusion, recurrent syncope with injury, pacemaker/ICD insertion, CPR	570	317	19
O'Neill <i>et al.</i> (2016) <sup>27</sup>	1 month and 1 year serious outcome: all-cause death, AMI, life-threatening arrhythmia, insertion of a pacemaker or internal cardiac defibrillator device, pulmonary embolus, cerebrovascular accident or subarachnoid haemorrhage, haemorrhage requiring a blood transfusion of 2 U of more or an acute surgical procedure or endoscopic intervention	253	43	7
Thiruganasambandamoorthy <i>et al.</i> (2016) <sup>25</sup>	Serious AE within 30 days: death, MI, arrhythmia, serious structural heart disease, aortic dissection, pulmonary embolism, severe haemorrhage, severe pulmonary hypertension, subarachnoid haemorrhage and any other serious condition causing syncope and procedural interventions for the treatment of syncope	4030	1929	169

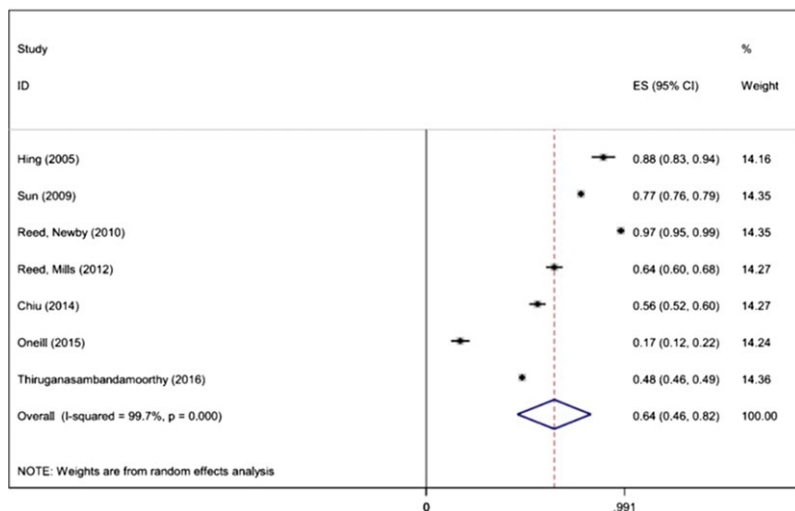


Figure 2. Forest plot illustration of proportion of troponins measured.

subsequently included in a developed ‘Canadian Risk Syncope Score’, which they found showed good calibration and discrimination for 30 day risk of serious AEs after ED disposition.<sup>25</sup>

Reed *et al.* concluded that in patients with syncope, any increase in troponin concentration was associated with increasing rates of serious outcome at both 1 month and 1 year, even at very low levels of troponin.<sup>30</sup> The number of patients with serious outcome increased across five groups categorised according to increasing troponin ranges at both 1 month (0, 9, 13, 26, 70%) and 1 year (10, 22, 26, 52, 85%). Sun *et al.* concluded that

in patients 60 years or older presenting after syncope to the ED, elevated conventional troponin I was associated with adverse 30 day outcome.<sup>26</sup> Of the 173 patients with who had a 30 day serious event 25 had raised troponin levels (14.5%), as compared to 10 patients with raised troponins of the 2411 patients who did not have a serious AE (0.4%).

Reed *et al.* concluded seven of 14 (50%) patients with raised troponin levels had outcome of interest compared to 16 of 267 (6%) patients with normal troponin levels.<sup>31</sup>

Similar findings were not reported in the two remaining studies that looked at the outcome measure of other serious AEs. Christ *et al.* and

O’Neill *et al.* both found that serum troponin levels had a limited predictive accuracy for identifying those at increased risk of serious AEs.<sup>27,28</sup>

## Discussion

Troponin testing among patients presenting with syncope was commonly reported during initial assessment (pooled proportion 0.64 [95% CI 0.46–0.82]). Among patients with syncope who had troponin testing, a substantial proportion had positive results, suggesting evidence of possible benefit in risk stratification of patients. However, clinical outcomes were variably reported and conclusions towards association of raised troponin and adverse outcomes of death or MACE could not be conclusively concluded. Heterogeneity among studies and low quality of included studies, all of which were observational, further limited confidence in the conclusions.

Heterogeneity was observed between studies encompassing in all modalities of study design, population, troponin assays performed, troponin assay cut-off values and outcomes assessed. There were five studies that used high sensitivity assays, four used contemporary assays and one study did not specify assay used as it varied according to study site. Given the variation in not only assay used but the cut-off at which a troponin rise was deemed significant the data is difficult to compare. Only one study specified the use of a sex-specific troponin cut-off value. Considering many institutions will use sex-specific cut-off values this decreases the generalisability of the study findings. Study size varied with the largest study measuring troponins in 1930 of 4030 patients as compared to the smallest study with only 43 of 253 patients. Most studies did not report which diagnoses were associated with AEs. Christ *et al.* found that patients with syncope classified as cardiac were 5.74 times more likely to have an AE within 180 days of follow up (95% CI 2.235–13.109;  $P \leq 0.001$ ) on multivariable regression analysis. Similarly, Sun *et al.* found 34.9% of those with adverse outcomes had been diagnosed with cardiac syncope in the

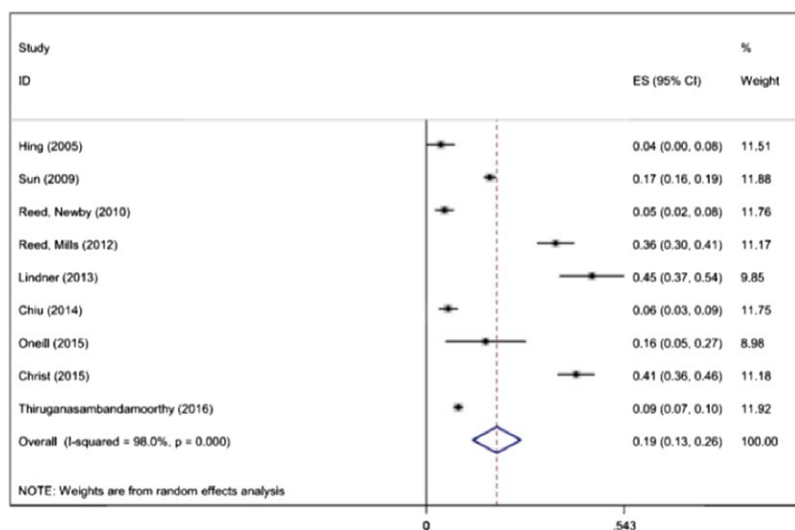


Figure 3. Forest plot illustration of positive troponins.

ED. The heterogeneity was both observed clinically and statistically and should be considered when interpreting the findings of this review. Ideally future research should report outcomes according to standardised ED syncope research guidelines.<sup>37</sup>

Traditionally, troponin has been used as a diagnostic tool for AMI. Multiple studies have demonstrated correlation of elevated troponin with acute coronary syndrome.<sup>38,39</sup> However, elevated troponins may be a marker of disease processes independent of coronary artery disease.<sup>40</sup> Such diagnoses may not be obvious on initial assessment in the ED. An elevated troponin may therefore be an indication of inpatient observation and monitoring for patients at risk of serious diagnoses as listed in Table 3. However, such diagnoses have not been considered in assessment of high troponin results in included studies.

The recent development of high-sensitivity assays compared to the previous contemporary assay has changed the role of troponins in clinical practice. The increased sensitivity of the newer assays has come at the cost of the specificity, decreasing the diagnostic role of a raised troponin. Our analysis did not group contemporary and high sensitivity troponin assays separately so the independent role of both troponins cannot be commented on. However, this systematic review and previous literature have concluded the diagnostic yield of troponin testing in patients presenting after syncope to the ED is minimal. The focus must then be shifted to the prognostic role of troponin in predicting all-cause mortality and serious AEs.

The association of troponin testing and clinical outcomes was uncommonly reported, with only two included manuscripts concluding an association between raised troponin and poor outcome, evidenced by inclusion in a risk stratification tool.<sup>25,26</sup> Five of the studies did not definitively conclude if troponin testing is prognostically useful or not and instead used phrases such as 'may have prognostic significance', 'limited prognostic significance' or called for further research.<sup>27-31</sup> One study concluded that the use of

troponin should be reserved for patients presenting after syncope with symptoms suggestive for an acute cardiac aetiology.<sup>32</sup> Finally, one study concluded that risk stratification, in the present study the OESIL score, is better than the use of cardiac biomarkers.<sup>33</sup> Given the lack of consensus surrounding the utility of troponin testing in patients presenting to the ED after syncope, further research in this area is indicated.

A strength of this review is the comprehensive and systematic approach to searching the literature, assessment of study eligibility and extraction of data. When interpreting the quantitative outcomes found in this review caution should be exercised as there is substantial observed and statistical heterogeneity. Variation in the definition of syncope to select the patient population, population size, troponin assay used, troponin cut-off value applied and outcomes limit confidence in conclusions. Patient outcomes were variably reported and could not be pooled for a meta-analysis.

Another notable limitation in the analysis of the studies is that troponins were not measured in all patients presenting with syncope. This limits the ability to draw conclusions about the proportion of patients presenting with syncope that would have elevated troponin levels. In all the retrospective studies, troponin was taken at the discretion of the treating clinician. None noted the routine use of any risk stratification tools that involved troponin testing.

Regardless, this review contributes to the existing evidence surrounding the utility of troponin testing in patients presenting to the ED after syncope and supports the need for further research to outline the utility of troponin testing in these patients.

## Conclusion

Troponin testing was commonly performed for the assessment of patients with syncope with a substantial proportion returning positive results. However, correlation of such results with patient outcomes were poorly reported, and it is possible that elevated troponins may be a marker of serious illness distinct from acute

coronary syndromes. A focus towards the variety of possible adverse outcomes, not just cardiac AEs, and followed up over a longer time-period may help elucidate the benefit of troponin testing in assessing patients with syncope to the ED.

## Competing interests

None declared.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

**Appendix S1.** Literature and search strategies.

**Appendix S2.** Newcastle Ottawa Scale.