Liang, Yan, Li, Xiulian, Tse, Gary, Li, Guangping, Liu, Wenling and Liu, Tong (2021) Diagnostic value of cardiac troponin I and N-terminal pro-B-Type Natriuretic Peptide in cardiac syncope. Current Research in Physiology, 4 . pp. 24-28. ISSN 2665-9441.

Downloaded from
https://kar.kent.ac.uk/98729/ The University of Kent's Academic Repository KAR

The version of record is available from
https://doi.org/10.1016/j.crphys.2021.01.003

This document version
Publisher pdf

DOI for this version

Licence for this version
CC BY-NC-ND (Attribution-NonCommercial-NoDerivatives)

Additional information

Versions of research works

Versions of Record
If this version is the version of record, it is the same as the published version available on the publisher's web site. Cite as the published version.

Author Accepted Manuscripts
If this document is identified as the Author Accepted Manuscript it is the version after peer review but before type setting, copy editing or publisher branding. Cite as Surname, Initial. (Year) 'Title of article'. To be published in Title of Journal, Volume and issue numbers [peer-reviewed accepted version]. Available at: DOI or URL (Accessed: date).

Enquiries
If you have questions about this document contact ResearchSupport@kent.ac.uk. Please include the URL of the record in KAR. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from https://www.kent.ac.uk/guides/kar-the-kent-academic-repository#policies).
Diagnostic value of cardiac troponin I and N-terminal pro-B-Type Natriuretic Peptide in cardiac syncope

Yan Liang a, Xiulian Li a, Gary Tse a,**, Guangping Li a, Wenling Liu b, Tong Liu a,*

a Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin, 300211, People’s Republic of China
b Heart Center, Peking University People’s Hospital, Beijing, People’s Republic of China

ARTICLE INFO

Keywords:
Syncope
cTnI
NT-proBNP
EGSYS
Diagnostic value

ABSTRACT

Objective: The study aims to evaluate the diagnostic accuracy of Cardiac Troponin I (cTnI) and N-terminal pro-B-Type Natriuretic Peptide (NT-proBNP) for identifying patients with cardiac syncope.

Methods: This is a prospective, single-center cohort study of patients presenting with syncope hospitalized from June 21, 2018 to May 30, 2019. The Evaluation of Guidelines in Syncope Study (EGSYS), a syncope-specific diagnostic score, was used for diagnostic comparator.

Results: A total of 118 patients were enrolled (mean age: 69.1 ± 12.3 years, 40% female). Compared to patients with reflex, orthostatic, or unexplained syncope, patients adjudicated to have cardiac syncope showed significantly higher cTnI and NT-proBNP plasma concentrations (p < 0.001 for each comparison). The area under the curve (AUC) of cTnI and NT-proBNP were moderate-to-good [0.77 – 0.78; 95% confidence interval (CI) 0.66 – 0.86], and was similar to that of EGSYS (0.71, 95% CI 0.60 – 0.80). Incorporation of cTnI and/or NT-proBNP into the existing EGSYS score significantly improved the diagnostic accuracy (EGSYS + cTnI: AUC 0.83; 95% CI 0.74 – 0.90; EGSYS + NT-proBNP: AUC 0.81; 95% CI 0.71 – 0.89; EGSYS + cTnI + NT-proBNP: AUC 0.83; 95% CI 0.73 – 0.90).

Conclusions: The cTnI and NT-proBNP levels were significantly higher in patients adjudicated to have cardiac syncope and the addition of both biomarkers to the EGSYS score significantly improved the diagnostic value for cardiac syncope.

1. Introduction

Syncope is a common clinical presentation defined as a transient loss of consciousness due to cerebral hypoperfusion (Brignole et al., 2018). The term cardiac syncope refers to syncope caused by bradyarrhythmia, tachycardia, or hypotension due to low cardiac index, blood flow obstruction, vasodilatation, or acute vascular dissection (Shen et al., 2017). The 2017 ACC/AHA/HRS Guideline have reported cardiac syncope as the second commonest cause of syncope with an estimated prevalence of 9% (Shen et al., 2017). In contrast to reflex syncope, syncope with cardiac causes is associated with a higher risk of hospitalization and death.

Cardiac troponin I (cTnI) and N-Terminal Pro-B-Type natriuretic peptide (NT-proBNP) are commonly used in the diagnosis and the prognosis evaluation of cardiac disease. Both biomarkers have recently been proposed for identifying patients with syncope at risk for adverse events. Probst et al. (2020) reported high-sensitivity cardiac troponin T and NT-proBNP showed a high sensitivity for excluding death and serious cardiac outcomes in older adults with syncope of cardiac cause.

The Evaluation of Guidelines in Syncope Study (EGSYS) was a diagnostic score for cardiac syncope and validated in several studies (Probst et al., 2020; Ungar et al., 2010; Kariman et al., 2015; Kayayurt et al., 2012; Gomes et al., 2016), which was selected as a diagnostic comparator (Del Rosso et al., 2008).

We performed a prospective cohort study to examine the diagnostic accuracy of cTnI and NT-proBNP to identify patients with cardiac syncope and tested the hypothesis that their incorporation into EGSYS can further improve risk stratification.

* Corresponding author. Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, No. 23, Pingjiang Road, Hexi District, Tianjin, 300211, People’s Republic of China.
** Corresponding author.
E-mail addresses: gatyse@tmu.edu.cn (G. Tse), liutongdoc@126.com (T. Liu).

https://doi.org/10.1016/j.crphys.2021.01.003
Received 7 November 2020; Received in revised form 20 December 2020; Accepted 27 January 2021
2665-9441/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
2. Methods

2.1. Study setting and population

This is a prospective, single-center cohort study including patients presenting with syncope hospitalized from June 21, 2018 to May 30, 2019. The study site was at the Second Hospital of Tianjin Medical University, which is a large community hospital and syncope center.

The inclusion criteria were patients aged 18 years or older with a hospitalization due to syncope. Syncope was defined as transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery. The exclusion criteria were: 1) syncope due to intoxication, seizure, stroke, transient ischemic attack, head trauma, or hypoglycemia, 2) new or worsening confusion, or 3) inability to obtain informed consent from the patient or a legally authorized representative. The primary study endpoint was the diagnostic accuracy of cTnl and NT-proBNP. The definitive diagnosis of cardiac syncope referred to the 2017 ESC ST segment Elevation Myocardial Infarction guideline (Jbaz et al., 2017). Secondary study endpoint defined as a composite of death.

Our study was a part of Chinese prospective multicenter registry of syncope patients (Trial Registration No. ChiCTR1900024190), which was carried out according to the principles of the Declaration of Helsinki and approved by the respective Ethics Committees. All patients provided informed consent before participation.

2.2. Data collection

All patients were evaluated including a detail history, physical examination, cardiac biomarker testing, and 12-lead ECG testing. Screening for eligible patients was performed using standard definitions and directly questioned patients about symptoms associated with the syncope episode. Additional diagnostic tests such as transthoracic echocardiography and coronary arteriography were performed at the discretion of the physicians (Probst et al., 2020). Troponin was determined by double antibody sandwich immunology. The stabi by Beckman Access chemiluminescence analysis has a reference 99th percentile cutoff limit of 30 ng/L for cTnl. The NT-proBNP assay used was chemiluminescence analysis, with recommended use of a 125 ng/L lower limit of normal for patients under 75 years and 450 ng/L for patients over 75 years. The EGYSYS included 5 predictors: Abnormal ECG and/or heart disease (3 points), palpitations before syncope (4 points), syncope during effort (3 points) or in supine position (2 points), autonomic prodrromes (–1 points) and predisposing and/or precipitating factors (–1). A score ≥3 identified cardiac syncope (Del Rosso et al., 2008).

2.3. Statistical analysis

The categorical variables were compared using the Pearson Chi-square test or Fisher's exact test and reported as the frequency with proportion. Nonparametric techniques were used to compare continuous variables, reported as the medians (with the interquartile range [IQR]), as appropriate. Wilcoxon 2-sample test was used to assess the differences in the plasmatic concentration variation of cTnl and NT-proBNP between the cardiac and control group. The area under the ROC(AUC) curve with the cut-off value was corresponding to the maximum of the Yoden index. Comparisons of AUCs were performed according to DeLong (DeLong et al., 1998). Statistical analyses were performed with the use of SPSS, version 24.0 (IBM, Munich, Germany).

3. Results

A total of 141 patients presenting with syncope to the study hospital between June 2018 and May 2019 were screened. Of these, 23 (16.3%) were excluded because of no availability of biomarker data or the EGYSYS score could not be calculated. Subsequently, 118 patients with complete data were used for analysis.

3.1. Characteristics of the patients

The baseline characteristics of the study cohort are detailed in Table 1. The mean age of the study sample was 69.1 ± 12.3 years, and 40% were female. There were no significant differences in age, gender, blood pressure or heart rate between cardiac syncope when compared to non-cardiac or unexplained syncope groups. Patients with a diagnosis of cardiac syncope were more likely to have syncope during supine posture. Cardiac syncope patients were more likely to have undiagnosed cardiovascular disease. In addition, the levels of creatinine kinase -MB, glucose, aspartate Aminotransferase were significantly higher in patients with cardiac syncope.

3.2. Concentrations of cTnl, NT-proBNP and syncope etiology

Compared to patients with reflex, orthostatic, or unexplained syncope, cTnl and NT-proBNP plasma concentrations were significantly higher in patients adjudicated to have cardiac syncope (Fig. 1A and Fig. 1B, p < 0.001 for each comparison).

3.3. Diagnostic value for cardiac syncope

The diagnostic values of the clinical scores and biomarkers alone and in combination for cardiac syncope are presented in Table 2. The ROC curves are shown in the Fig. 2 with AUCs values shown in Table 3 and Table 4. The AUCs of cTnl and NT-proBNP were moderate-to-good (all AUCs 0.77–0.78; 95% confidence interval (CI) 0.66–0.86), similar to that of EGYSYS (AUC 0.71, 95%CI 0.60–0.80). Incorporation of cTnl and/or NT-proBNP significantly improved the diagnostic accuracy of the EGYSYS score (EGYSYS + cTnl: AUC 0.83; 95%CI 0.74–0.90; EGYSYS + NT-proBNP: AUC 0.81; 95%CI 0.71–0.89; EGYSYS + cTnl + NT-proBNP: AUC 0.83; 95%CI 0.73–0.90).

3.4. The optimal cTnl and NT-proBNP cut-offs

When the cut-off value was 5 ng/L, the cTnl had a sensitivity of 77.5% (95% CI 61.5–89.2) and specificity of 68.9% (95% CI 53.4–81.8). When the cut-off value was 133 ng/L, the NT-proBNP had a sensitivity of 89.2% (95% CI 74.6–97.0) and specificity of 59.5% (95% CI 43.3–74.4). We were verified the EGYSYS as well, which had a sensitivity of 80.0% (95% CI 64.4–90.9) and specificity of 62.2% (95% CI 46.5–76.2).

4. Discussion

The main findings of this study are that: 1) cTnl and NT-proBNP levels were significantly higher in patients adjudicated to have cardiac syncope than in those with other etiologies. 2) both biomarkers provided moderate-to-high diagnostic accuracy for cardiac syncope, which was similar to that of EGYSYS scores, and 3) incorporation of both biomarkers to the EGYSYS score significantly improved its predictive performance.

Compared with adults who presented with syncope to the emergency department and discharged on the same day, inpatients tended to show more severe symptoms relevant to syncope, with higher incidence of serious adverse outcomes. Therefore, there is a need to devise clinical tools that can accurately identify inpatients with cardiac syncope. The biomarkers, cTnl and NT-proBNP, are previously performed for the presence and severity of cardiac disease and for the risk stratification after syncope (Probst et al., 2020; Gibson et al., 2018; Reed et al., 2007, 2011). In recent years, the usefulness of cTnl and NT-proBNP has been established in the context of syncope diagnosis, but the results were inconsistent (Christ et al., 2015; Costantino et al., 2014; du Fay de Lavallaz et al., 2019). Our study showed that cTnl and NT-proBNP levels...
### Table 1
Characteristics of the patients with syncope.

| Characteristic                        | Cardiac (N = 40) | Non Cardiac (N = 45) | Unexplained (N = 33) | P value |
|---------------------------------------|------------------|----------------------|----------------------|---------|
| Age (years)                           | 69.1 ± 12.3      | 68.8 ± 12.5          | 67.2 ± 12.5          | 0.844   |
| Female sex                            | 16(40.0)         | 22(48.9)             | 17(51.5)             | 0.573   |
| Systolic BP, mm Hg                    | 128.2 ± 27.0     | 136.0 ± 21.9         | 128.7 ± 24.7         | 0.270   |
| Heart rate, beats/min                 | 73.3 ± 33.1      | 74.8 ± 19.3          | 70.9 ± 15.3          | 0.689   |

#### Characteristics of the syncope

| Syncope frequency, n (%)              |                  |                      |                      |        |
|---------------------------------------|------------------|----------------------|----------------------|---------|
| 1                                     | 22(55.0)         | 18(40.0)             | 22(66.7)             | 0.054   |
| 2 or 3                                | 11(27.5)         | 15(33.3)             | 4(12.1)              | 0.098   |
| ≥4                                    | 7(17.5)          | 12(26.7)             | 7(21.2)              | 0.422   |

#### Position of the syncope, n (%)

| Position                      |                  |                      |                      |        |
|-------------------------------|------------------|----------------------|----------------------|---------|
| While standing                | 16(40.0)         | 20(44.4)             | 16(48.5)             | 0.766   |
| While sitting                 | 17(42.5)         | 24(53.3)             | 13(39.4)             | 0.417   |
| While lying                   | 8(20.0)          | 0                    | 4(12.1)              | 0.003   |
| Orthostatic                   | 0                | 10(22.2)             | 0                    | <0.001  |
| Exertion                      | 1(2.5)           | 3(6.7)               | 7(21.2)              | 0.004   |

#### Comorbidities, n (%)

| Comorbidity                       |                  |                      |                      |        |
|-----------------------------------|------------------|----------------------|----------------------|---------|
| Hypotension                       | 22(55.0)         | 25(55.6)             | 16(48.5)             | 0.800   |
| Diabetes                          | 8(20.0)          | 8(17.8)              | 6(18.2)              | 0.963   |
| Coronary artery disease           | 6(15.0)          | 13(28.9)             | 17(51.5)             | 0.003   |
| Arrhythmia                        | 12(30.0)         | 10(22.2)             | 11(33.3)             | 0.524   |
| Congestive heart failure          | 2(5.0)           | 1(2.2)               | 2(6.1)               | 0.628   |
| Cerebrovascular disease           | 6(15.0)          | 6(13.3)              | 6(18.2)              | 0.840   |

#### Laboratory parameters, median (IQR)

| Parameter                       | Cardiac (N = 40) | Non Cardiac (N = 45) | Unexplained (N = 33) | P value |
|---------------------------------|------------------|----------------------|----------------------|---------|
| cTnI, ng/L                      | 38.5(6.3–261.0)  | 2.0(1.0–11.0)        | 4.0(2.0–14.0)        | <0.001  |
| NT-proBNP, ng/L                 | 575.0(249.5–2033.0) | 99.2(49.3–440.8) | 494.0(84.3–1527.8) | <0.001  |
| D-dimer, ng/mL                  | 643.4(291.8–1162.3) | 456(231.5–1035.41) | 723.1(309.5–1566.3) | 0.395   |
| CK, U/L                         | 63.5(31.3–213.5) | 68.4(49.1–97.5)      | 68.0(35.0–131.0)     | 0.806   |
| CK-MB, U/L                      | 14.0(9.0–30.0)   | 10.8(5.0–15.4)       | 12.0(8.0–17.0)       | 0.039   |
| Creatinine, ummol/L             | 73.8(61.5–92.8)  | 74.3(57.5–85.6)      | 71.7(58.6–89.8)      | 0.721   |
| Glucose, mmol/L                 | 7.4(5.8–9.6)     | 5.9(5.0–7.1)         | 6.7(5.0–8.3)         | 0.009   |
| ALT, U/L                        | 21.1(14.0–34.2)  | 17.7(11.0–26.7)      | 15.3(9.4–23.7)       | 0.053   |
| AST, U/L                        | 24.5(14.8–67.7)  | 17.1(14.8–21.3)      | 17.1(13.3–22.9)      | 0.032   |
| Hemoglobin, g/L                 | 132.0(115.5–137.0) | 132.5(118.3–144.8) | 128.0(113.0–143.5)   | 0.754   |
| Hematocrit value, %             | 38.6(35.3–46.0)  | 39.8(35.1–42.6)      | 38.6(34.5–42.4)      | 0.677   |

IQR = interquartile range, cTnI = Cardiac Troponin I, NT-proBNP = N-Terminal Pro-B-Type Natriuretic Peptide, CK = Creatine kinase, CK-MB = Creatine kinase-MB, ALT = Alanine aminotransferase, AST = Aspartate Aminotransferase.

---

**Fig. 1.** (A and B). Scatterplots with median values of cTnI (A) and NT-proBNP (B) plasma levels in different types of syncope (cardiac syncope n = 40, reflex or orthostatic syncope n = 45, unexplained syncope n = 33). C. forest plot representing the AUC of the EG SYS scores, cTnI, NT-proBNP alone and biomarkers and combined. Points represent the AUC, Whiskers represent 95% confidence interval. BM = Biomarker.

26
Diagnostic values of clinical scores and biomarkers alone and in combination.

|                  | Sensitivity (95%CI) | Specificity (95%CI) | LR+(95%CI) | LR-(95%CI) | PPV (95%CI) | NPV (95%CI) |
|------------------|---------------------|---------------------|------------|------------|-------------|-------------|
| EGSYS Score      | 80.00(64.4–90.9)    | 62.22(46.5–76.2)    | 2.12(1.4–3.2) | 0.32(0.2–0.6) | 65.3(55.6–73.9) | 77.8(64.4–87.1) |
| cTnl>5 ng/L      | 77.50(61.5–89.2)    | 68.89(53.4–81.8)    | 2.49(1.6–4.0) | 0.33(0.2–0.6) | 68.9(58.2–77.9) | 77.5(65.2–86.3) |
| NT-proBNP>133 ng/L | 89.19(74.6–97.0) | 59.52(43.3–74.4) | 2.21(1.5–3.2) | 0.18(0.07–0.5) | 66.0(56.9–74.0) | 86.2(70.6–94.2) |
| EGSYS + cTnl     | 70.00(53.5–83.4)    | 84.44(70.5–93.5)    | 4.50(2.2–9.2) | 0.36(0.2–0.6) | 80.0(66.3–89.1) | 76.0(66.0–83.8) |
| EGSYS + NT-proBNP| 75.68(58.8–88.2)    | 83.33(68.6–93.0)    | 4.54(2.3–9.1) | 0.29(0.2–0.5) | 80.0(66.5–89.0) | 79.0(58.4–87.5) |
| cTnl + NT-proBNP | 72.97(55.9–86.2)    | 72.81(58.0–86.1)    | 2.79(1.6–4.8) | 0.37(0.2–0.6) | 71.1(58.8–80.9) | 75.6(63.9–84.4) |
| EGSYS + cTnl + NT-proBNP | 83.78(68.0–93.8) | 76.19(60.5–87.9) | 3.52(2.0–6.2) | 0.21(0.1–0.5) | 75.6(63.9–84.4) | 84.2(71.6–91.9) |

Unexplained syncope is defined as syncope for which a cause is undetermined after an initial evaluation that is deemed appropriate by the experienced healthcare provider (Shen et al., 2017). A systematic review evaluated implantable loop recorders (ILRs) in unexplained syncope. The results suggested that around 50% of patients finally diagnosed with arrhythmic syncope (Solbiati et al., 2017). Therefore, patients with syncope of undetermined etiology were excluded in AUC analysis. EGSYS was the only syncope-specific diagnostic score for ED patients reported by A Del Rosso et al., in 2008 (Del Rosso et al., 2008). The diagnostic accuracy of EGSYS was validated in several studies and it was first used to assess hospitalized patients. In our study, comparisons of the AUCs revealed that the EGSYS and biomarkers provided similar diagnosis accuracy. However, the diagnosis accuracy increased when the EGSYS was combined with biomarkers, especially with cTnl.

5. Limitations

There are several limitations of this study that need to be considered. Firstly, this is a single-center, observational study and the sample size was small, and multivariate adjustment was not performed. Secondly, there may be a bias in selecting patients because they mostly hospitalized to the cardiology department, with only few patients admitted to the neurology or other departments. Thirdly, the time from syncope to biomarkers measurement was not available. Thus, the reliability of the results may be limited.

Fig. 2. The ROC curve for the identification of patients with cardiac syncope. (A) The ROC curve for cTnl, NT-proBNP or EGSYS score. (B) The ROC curve for cTnl, NT-proBNP levels and the EGSYS score combined.
conclusions drawn from this analysis may be limited, and future evaluations should include precise timing of biomarker measurements (Christ et al., 2015).

6. Conclusions

The cTnI and NT-proBNP levels were significantly higher in patients adjudicated to have cardiac syncope and the incorporation of both biomarkers to the EGSYS score significantly increased its diagnostic value for cardiac syncope.

CRediT authorship contribution statement

Yan Liang: Conceptualization, Data analysis, Writing- Original draft preparation. Xiulian Li: Data analysis, Investigation. Gary Tse: Supervision, Writing- Reviewing and Editing. Wenling Liu: Investigation, Validation. Tong Liu: Project administration, Writing- Reviewing and Editing.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

Brignole, M., Moya, A., de Lange, F.J., et al., 2018. Esc guidelines for the diagnosis and management of syncope. Eur. Heart J. 39, 1883-1948, 2018.

Christ, M., Geier, F., Popp, S., et al., 2015. Diagnostic and prognostic value of high-sensitivity cardiac troponin t in patients with syncope. Am. J. Med. 128, 161–170 e161.

Costantino, G., Solbiati, M., Casazza, G., et al., 2014. Usefulness of n-terminal pro-b-type natriuretic peptide increase as a marker for cardiac arrhythmia in patients with syncope. Am. J. Cardiol. 113, 98–102.

De Rosso, A., Ungar, A., Maggi, R., et al., 2008. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital: the egsys score. Heart 94, 1620-1626.

DeLong, E.R., DeLong David, M., Clarke-Pearson, D.L., 1998. Comparing the areas under two or more correlated receiver operating characteristic curves: A Nonparametric Approach. Biometrics 44, 837-845.

du Fay de Lavallaz, J., Badertscher, P., Nestelberger, T., et al., 2019. B-type natriuretic peptides and cardiac troponins for diagnosis and risk-stratification of syncope. Circulation 139, 2403-2418.

Gibson, T.A., Weiss, R.E., Sun, R.C., 2018. Predictors of short-term outcomes after syncope: a systematic review and meta-analysis. West. J. Emerg. Med. 19, 517-523.

Gomes, D.G., Kus, T., Sant'anna, R.T., et al., 2016. Simple risk stratification score for prognosis of syncope. J. Intervent. Card Electrophysiol. 47, 153-161.

Ibanez, B., James, S., Agewall, S., et al., 2017. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur. Heart J. 39, 119-177, 2018.

Kariman, H., Harati, S., Safari, S., et al., 2015. Validation of egsys score in prediction of cardiogenic syncope. Emerg. Med. Int. 2015, 515370.

Kayayurt, K., Akoglu, H., Limon, O., et al., 2012. Comparison of existing syncope rules and newly proposed anatolian syncope rule to predict shortterm serious outcomes after syncope in the Turkish population. Emerg. Med. Int. 5, 178–181.

Probst, M.A., Gibson, T., Weiss, R.E., et al., 2020. Risk stratification of older adults who present to the emergency department with syncope: the faint score. Ann. Emerg. Med. 75, 147-158.

Reed, M.J., Newby, D.E., Coull, A.J., et al., 2007. The risk stratification of syncope in the emergency department (rose) pilot study: a comparison of existing syncope guidelines. Emerg. Med. J. 24, 270-275.

Reed, M.J., Henderson, S.S., Newby, D.E., et al., 2011. One-year prognosis after syncope and the failure of the rose decision instrument to predict one-year adverse events. Ann. Emerg. Med. 58, 250-256. https://doi.org/10.1016/j.annemergmed.2010.12.021. Epub 2011 Feb 10.

Shen, W.K., Sheldon, R.S., Benditt, D.G., et al., 2017. acc/aha/hrs guideline for the evaluation and management of patients with syncope: a report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. J. Am. Coll. Cardiol. 70, e39-e110, 2017.

Solbiati, M., Casazza, G., Dipaola, F., et al., 2017. The diagnostic yield of implantable loop recorders in unexplained syncope: a systematic review and meta-analysis. Int. J. Cardiol. 231, 170-176.

Ungar, A., Del Rosso, A., Giada, F., et al., 2010. Early and late outcome of treated patients referred for syncope to emergency department: the egsys 2 follow-up study. Eur. Heart J. 31, 2021–2026.