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Predictors of Clinically Significant Echocardiography Findings in Older Adults with Syncope: A Secondary Analysis.

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Abstract

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Background: Syncope is a common reason for visit to the emergency department (ED) and is associated with significant healthcare resource utilization.

Objective: To develop a risk-stratification tool for clinically significant findings on echocardiography among older adults presenting to the ED with syncope or near-syncope.

Design: Prospective, observational cohort study from April 2013 to September 2016

Setting: 11 EDs in the United States.

Patients: We enrolled adults (≥60 years) who presented to the ED with syncope or near-syncope who underwent transthoracic echocardiography (TTE).

Measurements: Primary outcome was a clinically significant finding on TTE. Clinical, electrocardiogram, and laboratory variables were also collected. Multivariable logistic regression analysis was used to identify predictors of significant findings on echocardiography.

Results: A total of 3,686 patients were enrolled. Of those, 995 (27%) received echocardiography. Of these, 215 (22%) had a significant finding on echocardiography. Regression analysis identified five predictors of significant findings: 1) history of congestive heart failure, 2) history of coronary artery disease, 3) abnormal electrocardiogram, 4) high-sensitivity troponin-T >14 pg/ml, and 5) N-terminal pro B-type natriuretic peptide >125 pg/ml. These five variables make up the ROMEO (Risk Of Major Echocardiography findings in Older adults with syncope) criteria. The sensitivity of a ROMEO score of zero for excluding significant findings on echocardiography was 99.5% (95%CI: 97.4–99.9%,) with a specificity of 15.4% (95%CI: 13.0–18.1%).

Conclusions: If validated, this risk-stratification tool could help clinicians determine which syncope patients are at very low risk of having clinically significant findings on echocardiography.

Registration: ClinicalTrials.gov Identifier NCT01802398.

Keywords

Syncope; Diagnostic imaging; Observational Study Designs; echocardiography; risk-stratification

INTRODUCTION.

Syncope, defined as a transient loss of consciousness and postural tone followed by complete, spontaneous return to neurological baseline, accounts for over 1 million (or approximately 1%) of all emergency department (ED) visits per year in the United States (US).[1,2] Given the breadth of etiologies for syncope, including certain life-threatening conditions, extensive diagnostic evaluation and hospitalization for this complaint is common.[3–7] The estimated costs of syncope-related hospitalizations are over $2.4 billion annually in the US.[8]

The 2011 American College of Cardiology Foundation appropriate use criteria for echocardiography state that syncope is an appropriate indication for transthoracic echocardiography (TTE) even when there are no other symptoms or signs of cardiovascular disease.[9] This broad recommendation may be appropriate since a finding of severe valvular disease would generally merit a consultation with a cardiothoracic surgeon to assess the

potential for surgical intervention.[10] However, routine use of echocardiogram in all syncope patients could result in increased healthcare costs, patient discomfort, and incidental findings of unclear significance, while rarely changing diagnosis or management.[11,12]

In an attempt to reduce potentially unnecessary TTE testing, several studies have attempted to identify patients at very low risk of structural heart disease.[13–17] These investigations suggest that TTE is not indicated in syncope patients with a normal ECG and a normal cardiac exam. However, this literature is limited by retrospective study design and/or small sample sizes. The 2017 American Heart Association/ American College of Cardiology/ Heart Rhythm Society syncope guidelines recommend TTE for patient in whom structural heart disease is suspected but are not explicit about how to make this determination.[18] Thus, it is still unclear which syncope patients require TTE since a standardized approach to assessing risk of clinically significant findings on TTE has not yet been rigorously developed.

The objective of this study was to develop a risk-stratification tool to identify older adults at very low risk of having a major, clinically significant finding on rest TTE after presenting to the ED with syncope or near-syncope. Using clinical, ECG, and cardiac biomarker data, we created the ROMEO (Risk Of Major Echocardiography findings in Older adults with syncope) score to help optimize resource utilization for syncope.

METHODS

Study design and setting

We conducted a large, multicenter, prospective, observational cohort study of older adults who presented to an ED with syncope or near-syncope (ClinicalTrials.gov identifier: NCT01802398). The study was approved by the institutional review boards at all sites and written, informed consent was obtained from all participating subjects. The study was conducted at 11 academic EDs across the US (See Appendix Table 1).

Study Population

Patient inclusion criteria for eligibility were age ≥ 60 years with a complaint of syncope or near syncope. Syncope was defined as transient loss of consciousness, associated with postural loss of tone, with immediate, spontaneous, and complete recovery. Near syncope was defined as the sensation of imminent loss of consciousness. Patients were excluded if their symptoms were thought to be due to intoxication, seizure, stroke, head trauma, or hypoglycemia. Additional exclusion criteria were the need for medical intervention to restore consciousness (e.g. defibrillation), new or worsening confusion, and inability to obtain informed consent from the patient or a legally authorized representative.

This analysis included only patients who received a TTE during the index visit (either in the ED, observation unit, or while admitted to the hospital). This dataset was also used for other analyses addressing questions relevant to the ED management of syncope.

Measurements

All patients underwent standardized history, physical examination, laboratory, and 12-lead ECG testing. Trained research assistants (RA) directly queried patients about symptoms associated with the syncopal episode. Data on the patient's past medical history, medications, and physical examination findings were collected prospectively from treating providers.

Research staff obtained blood samples for testing at a core laboratory (University of Rochester, Rochester, NY). Two assays were performed using the Roche Elecsys platform: N-terminal pro B-type natriuretic peptide (NT-proBNP) and the 5th generation high-sensitivity cardiac troponin T (hs-TnT). NT-proBNP was classified as abnormal above a cutoff of 125 pg/ml. Hs-TnT was classified as abnormal above the 99th percentile for a reference population (14 pg/ml). Although hs-TnT was not approved by the U.S. Food and Drug Administration (FDA) at the time of the study, we anticipated that this assay would receive approval and be integrated into future standard of care (FDA approval was granted in January 2017). Rest TTEs were ordered at the discretion of the treating providers.

Outcome Measures

The primary outcome for this secondary analysis was a major, clinically significant finding on TTE.[13,14,16,19] These included severe aortic stenosis (<1cm2), severe mitral stenosis, severe aortic/mitral regurgitation, a reduced ejection fraction (defined either quantitatively as less than 45% or qualitatively as "severe left ventricular dysfunction"), hypertrophic cardiomyopathy with outflow tract obstruction, severe pulmonary hypertension, right ventricular dysfunction/strain, large pericardial effusion, atrial myxoma, or regional wall motion abnormalities.

All echocardiogram reports were independently reviewed by two research physicians. Discrepant reviews were resolved by the research physicians and two of the study investigators (BS, CB). Of note, all the TTEs obtained were formal echocardiographic studies, not bedside ultrasonography performed by the emergency physician.

Candidate Predictors

Potential candidate predictors were identified through a prior expert panel process.[20,21] Candidate predictors included age, gender, abnormal heart sounds, exertional syncope, shortness of breath, chest pain, near syncope, family history of sudden cardiac death, high (>180 mmHg) or low (<90 mmHg) systolic blood pressure, abnormal ECG, elevated hs-TnT, elevated NT-proBNP, and history of the following: hypertension, cardiac dysrhythmia, renal failure, diabetes, congestive heart failure (CHF), and coronary artery disease (CAD).

The first obtained ECG was abstracted by one of five research study physicians blinded to all clinical data. Research study physicians demonstrated high interrater reliability (kappa > 0.80) in distinguishing normal from abnormal ECGs in a training set of 50 ECGs. Abnormal ECG interpretations included non-sinus rhythms (including paced rhythms), multiple premature ventricular complexes, sinus bradycardias (≤ 40 bpm), ventricular hypertrophies, short PR segment intervals (<100 milliseconds [ms]), axis deviations, first degree blocks

(>200 ms), complete bundle branch blocks, Brugada patterns, Wolff-Parkinson-White patterns, abnormal QRS duration (>120 ms) or abnormal QTc prolongations (>450 ms), and Q/ST/T segment abnormalities suggestive of acute or chronic ischemia.

Statistical Analysis

We calculated descriptive statistics for each predictor variable, stratified by presence or absence of TTE findings. Chi-square and *t*-tests were used to test associations between categorical or continuous variables and TTE findings using a significance level of 0.05 and 2-sided hypothesis testing. To identify a robust set of predictors of the primary outcome, we used multivariate logistic regression with the LASSO (Least Absolute Shrinkage and Selection Operator) to fit a parsimonious model.[22] The LASSO selects variables and shrinks the associated coefficients to avoid overfitting.[23–25] We then used a bootstrap to generate confidence intervals for coefficient estimates. Cases with missing echocardiography reports were excluded from the analysis. Bootstrap results were summarized as the percentage of bootstrap iterations in which each variable's coefficient was 1) chosen and negative, 2) shrunk to zero, or 3) chosen and positive.

We assessed different weighting schemes to generate a risk score from significant variables identified by regression modeling. These included weighting by regression coefficients rounded to the nearest integer and simple summation of the presence or absence of each variable.

Based on these results, a predictive score was developed to risk stratify patients on their probability of major, clinically significant findings on TTE. The sensitivity and specificity of a score of zero to predict findings on TTE was calculated. For confidence intervals, we used Wilson's method for binomial confidence intervals.[26] The receiver operating characteristic (ROC) curve and its associated area under the curve (AUC) were calculated, and a confidence interval for the AUC was obtained through bootstrap resampling with 2000 iterations. As part of our sensitivity analyses, we also calculated the ROC curve and AUC after excluding the patients with a known history of CHF and significant finding on TTE. Data analyses were performed in R.[27] Two sensitivity analyses were performed: 1) we used multiple imputation to impute 1000 complete data sets and then used the same LASSO methodology as with the complete data to assess whether incorporating missing data changed the results; and 2) we simulated a conventional troponin assay by raising the positive threshold for hs-TnT to >30 pg/mL (corresponding to limit of detection for conventional troponin).[28]

Role of the Funding source

This project was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01 HL111033. Roche Diagnostics supplied the high-sensitivity troponin-T assays. The sponsoring organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, or review of the manuscript.

RESULTS

Characteristics of Study Subjects

Patient screening occurred from April 2013 to September 2016. There were 6,930 patients that met eligibility criteria, of which 3,686 (53%) were consented and enrolled into the study (See Figure 1). Of those, 995 (27%) received TTE. The mean age of patients receiving TTE was 74 years; 55% were male. Characteristics of patients obtaining and not obtaining TTE are presented in Appendix Table 2. Patients who received TTE were more likely to be older, have abnormal heart sounds, abnormal EKGs, elevated hs-TnT, elevated NT-proBNP, and have a history of congestive heart failure. Of the 995 subjects receiving TTE, 215 (21.6%) had a major, clinically significant finding.

Main Results

Univariate analysis identified 14 variables significantly associated with major findings on TTE. These included male gender, shortness of breath, abnormal heart sounds, history of renal failure, diabetes, congestive heart failure, coronary artery disease, abnormal ECG, and elevated cardiac biomarkers, among others (See Table 1). The most common major finding on TTE was regional wall motion abnormality, followed by reduced left ventricular ejection fraction (See Table 2). Of the 995 patients who received TTE, 20 (2%) were discharge directly from the ED, 444 (45%) were observed and 531 (53%) were admitted. On average, patients who received TTE had a longer length of stay than those that did not (3.4 days vs 1.9 days).

LASSO multivariable logistic regression produced five predictors associated with major findings on TTE: 1) history of congestive heart failure, 2) history of coronary artery disease, 3) abnormal ECG, 4) hs-TnT above 14 pg/ml, and 5) NT-proBNP above 125 pg/ml (See Table 3).

The five high-risk clinical variables which retained their importance after multivariate analysis form the ROMEO (Risk Of Major Echocardiography findings in Older adults with syncope) score.

The sensitivity and specificity of a ROMEO score of zero for excluding major findings on TTE was 99.5% (95% CI: 97.4% to 99.9%) and 15.4% (95% CI: 13.0% to 18.1%), respectively. Patients with a ROMEO score of 0 were at very low risk of having a major finding on TTE: 0.8% (95% CI: 0.02% to 4.5%) (Appendix Table 3). Only one out of 121 patients with none of the ROMEO criteria was found to have a major finding on TTE (regional wall motion abnormality). Patients with a score of 1 or more were at moderate-to-high risk of having a major finding (7.3% to 55.6%).

There was a linear relationship between the ROMEO score and probability of major findings on TTE (See Appendix Figure 1). The AUC was 0.77 (95% CI = 0.72 to 0.79) indicating good accuracy of the combination of the five high-risk clinical variables to predict major findings on TTE (See Appendix Figure 2). After excluding the 72 patients with known CHF and significant findings on TTE, the AUC was similar: 0.73 (95%CI: 0.69 to 0.77). There were 139 patients with at least one missing variable (14%) (See Appendix Table 4). A

multiple imputation sensitivity analysis identified the same five high-risk clinical variables in 85% of imputations.

There were 253 patients with high sensitivity troponin level between 15–30 pg/ml (inclusive). Using a higher hs-TnT threshold (>30 pg/ml) to simulate a conventional troponin assay again identified the same five high-risk variables along with shortness of breath as a potential sixth variable though with an odds ratio approaching unity (See Appendix Table 5). The ROMEO score would have missed 2 additional patients with major findings if the troponin cutoff were raised to 30 pg/ml from 14 pg/ml, i.e. it would have identified 212/215 (98.6%) of the major findings rather than 214/215 (99.5%).

DISCUSSION

Older adults with syncope often present to the ED and undergo a variety of diagnostic tests, including TTE, and a significant proportion get admitted to the hospital.[2] There is currently no standardized, evidence-based approach to guide TTE-ordering for these patients. Using a large, prospective dataset of syncope patients, we sought to develop a risk-stratification tool to help clinicians identify which syncope patients would be at very low risk for clinically significant findings on TTE. We found that in the absence of these five high-risk clinical variables, the rate of significant findings on TTE in our sample was less than 1%. All five high-risk variables included in the tool remained predictive in our sensitivity analyses, speaking to the robustness of our model.

Other retrospective, and smaller prospective, studies have identified a combination of low-risk criteria including: a normal ECG alone[15], a normal physical exam and normal ECG[14,17], a negative cardiac history and normal ECG[16]. Han et al. performed a chart review of 241 patents presenting to the ED with syncope and identified three risk factors for abnormal TTE findings using multiple logistic regression: Age, abnormal ECG, and BNP greater than 100 pg/ml.[13] While these studies' results are generally consistent with ours, the retrospective nature and small sample size of these studies limit the generalizability of these results. Thus, using a large, multicenter prospective dataset, we derived a clinical decision instrument (the ROMEO score) to determine which older adults with syncope are at very low risk for major, clinically significant findings on TTE.

Our results add to the recent American College of Cardiology/American Heart Association/ Heart Rhythm Society guidelines on the management of syncope which recommend TTE in "selected patients presenting with syncope if structural heart disease is suspected".[18] Our risk-stratification tool offers a simple, standardized approach to determining specifically when to defer TTE testing.

Our findings can guide clinicians deciding when to obtain TTE for ED syncope patients in the following way: Older adults presenting with syncope or near-syncope to the ED who have none of the ROMEO criteria are at extremely low risk for clinically significant findings on TTE and thus need not undergo such testing solely because of the syncopal event. Patients who have only one or more high-risk clinical variable are at higher risk (7.3–56%) of significant TTE findings. In this subset, other factors, (e.g., physician gestalt, recent

previous echocardiography, patient preference, availability of echocardiography) can help guide TTE ordering. Patients with a greater number of high-risk variables may benefit from a more urgent echocardiographic evaluation.

Although, on average, patients undergoing TTE had a longer length of stay than those that did not, this finding does not necessarily imply that ordering a TTE was the cause of the increased length of stay. It is possible that this positive association was due to greater underlying medical complexity or acuity of illness that resulted in a greater likelihood of admission/observation, and in turn, greater length of stay.

Prior to implementation, our results should be externally validated in other clinical settings. In the interim, this risk-stratification tool may be used by clinicians, in conjunction with clinical judgement, to help guide the appropriate use of TTE in older adults presenting with syncope.

Our study has certain limitations. As we only enrolled patients 60 years and above, our findings may not necessarily be valid in younger populations of syncope patients. However, structural heart disease is less common in younger patients and is generally more of a concern for clinicians when evaluating syncope patients in the older age range.[29] In our study, 47% of eligible patients declined to participate and thus sampling bias may have occurred. TTEs were ordered at the discretion of treating providers, which was likely subject to physician, institutional, and regional variation; the prevalence of major TTE findings may be lower in the overall cohort than in patients who received TTE. Prior TTE reports were not available; therefore, we were not able to determine if these major findings were previously known. Importantly, we did not perform an internal or external validation of the ROMEO score due to time and resource constraints. Thus, this study represents solely a derivation of the score and would require external validation prior to clinical implementation. As well, to calculate the ROMEO score, both a hs-TnT and NT-proBNP level must be obtained. Thus, the cost savings of any potential reduction in TTE ordering may be partially offset by the costs of increased laboratory testing. Lastly, hs-TnT assays are not currently widely available in hospitals in the United States; earlier generation cardiac troponin assays may not be a perfect substitute for hs-TnT assays. Our sensitivity analysis using an elevated threshold for hs-TnT attempted to mitigate this limitation and resulted in similar findings.

In summary, this risk-stratification tool, using five simple criteria, could help clinicians determine which older adult syncope patients can safely forgo TTE. If validated, this tool could help optimize resource utilization, and increase the value of healthcare, for patients presenting with syncope.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Univariate Analysis: Clinical Variables associated with Major Findings on Echocardiography after Syncope

Clinical Variable	No. (%)	Normal/minor findings on TTE (N=780)	Major Findings on TTE (N=215)	Odds Ratio	95% CI
Age, mean (SD)	74.1 (9.1)	73.9 (8.9)	74.8 (9.9)	1.01	(0.99, 1.03)
Male gender	547 (55)	409 (52)	138 (64)	1.63	(1.19, 2.22)
Race					
-White	813 (82)	639 (82)	174 (81)	ref	ref
-Black	146 (15)	110 (14)	36 (17)	1.20	(0.84, 1.81)
-Other	33 (3)	28 (4)	5 (2)	0.66	(0.25, 1.72)
Shortness of breath	213 (21)	147 (19)	66 (31)	1.90	(1.35, 2.68)
Exertional syncope	194 (19)	145 (19)	49 (23)	1.29	(0.89, 1.86)
Abnormal heart sounds	133 (13)	87 (11)	46 (21)	2.15	(1.45, 3.19)
Chest discomfort	86 (9)	63 (8)	23 (11)	1.41	(0.85, 2.34)
Near syncope	296 (30)	216 (28)	80 (37)	1.55	(1.13, 2.13)
SBP > 180 mmHg	10 (1)	7 (1)	3 (1)	1.56	(0.40, 6.08)
SBP < 90 mmHg	42 (4)	35 (4)	7 (3)	0.72	(0.31, 1.64)
History of SCD in 1st degree relative	95 (10)	64 (8)	31 (14)	1.89	(1.19, 2.99)
History of hypertension	683 (69)	520 (67)	163 (76)	1.56	(1.10, 2.20)
History of dysrhythmia	250 (25)	173 (22)	77 (36)	1.95	(1.41, 2.70)
History of renal failure	119 (12)	78 (10)	41 (19)	2.11	(1.40, 3.20)
History of diabetes	266 (27)	191 (24)	75 (35)	1.65	(1.19, 2.28)
History of CHF	153 (15)	81 (10)	72 (33)	4.33	(3.01, 6.24)
History of CAD	304 (31)	193 (25)	111 (52)	3.24	(2.37, 4.42)
Abnormal ECG	611 (61)	437 (56)	174 (81)	4.08	(2.74, 6.07)
History of reduced EF	35 (4)	13 (2)	22 (10)	6.71	(3.32, 13.56)
History of structural heart disease	159 (16)	101 (13)	58 (27)	2.48	(1.72, 3.57)
Hs-TnT (>14 pg/ml)	479 (48)	330 (42)	149 (69)	3.6	(2.53, 5.14)
NT-proBNP (>125 pg/ml)	698 (70)	509 (65)	189 (88)	5.82	(3.36, 10.06)

TTE: Transthoracic Echocardiography. CI: Confidence Interval. SD: Standard Deviation. SBP: Systolic Blood Pressure. mmHg: millimeters of mercury. SCD: Sudden Cardiac Death. CHF: Congestive Heart Failure. CAD: Coronary Artery Disease. ECG: Electrocardiogram. EF: Ejection Fraction. Hs-TnT: high-sensitivity cardiac troponin T. NT-proBNP: N-terminal pro B-type natriuretic peptide.

Those with a race of “White” were used as the reference standard to which “Black” or “Other” were compared to.

Table 2.

List of Major, Clinically Significant Echocardiogram Findings, n=215

Major Finding	Frequency, No. (%)
Regional wall motion abnormalities	118 (11.9)
Reduced Ejection Fraction (either <45% or qualitative “severe LV dysfunction”)	71 (7.1)
Right ventricular dysfunction/strain	23 (2.3)
Severe aortic stenosis (<1cm2)	20 (2.0)
Severe pulmonary hypertension (e.g. severely elevated PA systolic pressure)	15 (1.5)
Severe aortic regurgitation or severe mitral stenosis/regurgitation (qualitative)	14 (1.4)
Hypertrophic cardiomyopathy with outflow tract obstruction	4 (0.4)
Obstructive physiology (large pericardial effusion, atrial myxoma)	1 (0.1)

cm: centimeter, LV: Left Ventricular, PA: Pulmonary Artery.

(Sum of individual findings greater than 215 due to some subjects having more than one finding.)

Table 3.

Clinical Variables associated with Major Findings on Echocardiography using Multivariate LASSO regression

Clinical Variable	Odds Ratio	95% CI
History of CHF	**1.60**	**(1.02, 2.57)**
Abnormal ECG	**1.53**	**(1.18, 2.48)**
NT-proBNP>125 pg/ml	**1.34**	**(1.00, 2.61)**
HS-TnT>14 pg/ml	**1.29**	**(1.00, 2.03)**
History of CAD	**1.24**	**(1.00, 1.96)**
Age	1.00	(1.00, 1.00)
Male gender	1.00	(1.00, 1.43)
Abnormal heart sounds	1.00	(1.00, 1.55)
Exertional syncope	1.00	(1.00, 1.26)
Shortness of breath	1.00	(1.00, 1.67)
Chest pain	1.00	(1.00, 1.18)
Near syncope	1.00	(1.00, 1.43)
Family history of SCD	1.00	(1.00, 2.06)
SBP > 180 mmHg	1.00	(0.82, 1.00)
SBP < 90 mmHg	1.00	(1.00, 1.55)
History of hypertension	1.00	(1.00, 1.00)
History of dysrhythmia	1.00	(1.00, 1.20)
History of renal failure	1.00	(1.00, 1.04)
History of diabetes	1.00	(1.00, 1.12)

CI: Confidence Interval. CHF: Congestive Heart Failure. ECG: Electrocardiogram. NT-proBNP: N-terminal pro B-type natriuretic peptide. Hs-TnT: high-sensitivity cardiac troponin T. CAD: Coronary Artery Disease. SCD: Sudden Cardiac Death. SBP: Systolic Blood Pressure. mmHg: millimeters of mercury.