Predicting Short-term Risk of Arrhythmia among Patients With Syncope: The Canadian Syncope Arrhythmia Risk Score

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ABSTRACT

Background: Syncope can be caused by serious occult arrhythmias not evident during initial emergency department (ED) evaluation. We sought to develop a risk tool for predicting 30-day arrhythmia or death after ED disposition.

Methods: We conducted a multicenter prospective cohort study at six tertiary care EDs and included adults (≥16 years) with syncope. We collected standardized variables from clinical evaluation and investigations including electrocardiogram and troponin at index presentation. Adjudicated outcomes included death or arrhythmias including procedural interventions for arrhythmia within 30 days. We used multivariable logistic regression to derive the prediction model and bootstrapping for interval validation to estimate shrinkage and optimism.

Results: A total of 5,010 patients (mean ± SD age = 53.4 ± 23.0 years, 54.8% females, and 9.5% hospitalized) were enrolled with 106 (2.1%) patients suffering 30-day arrhythmia/death after ED disposition. We examined 39 variables and eight were included in the final model: lack of vasovagal predisposition, heart disease, any ED systolic blood pressure < 90 or > 180 mm Hg, troponin (>99th percentile), QRS duration > 130 msec, QTc interval > 480 msec, and ED diagnosis of cardiac/vasovagal syncope (optimism corrected C-statistic 0.90 [95% CI = 0.87–0.93]; Hosmer-Lemeshow p = 0.08). The Canadian Syncope Arrhythmia Risk Score had a risk ranging from 0.2% to 74.5% for scores of –2 to 8. At a threshold score of ≥0, the sensitivity was 97.1% (95% CI = 91.6%–99.4%) and specificity was 53.4% (95% CI = 52.0%–54.9%).

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Conclusions: The Canadian Syncope Arrhythmia Risk Score can improve patient safety by identification of those at risk for arrhythmias and aid in acute management decisions. Once validated, the score can identify low-risk patients who will require no further investigations.

Syncope is defined as a sudden transient loss of consciousness followed by spontaneous complete recovery.[1] Syncope constitutes 1% to 3% of emergency department (ED) visits and up to 3% of hospitalizations from the ED.[2,3] Syncope can be benign (e.g., vasovagal syncope) or can be caused by serious underlying conditions: arrhythmias (e.g., ventricular tachycardia) or nonarrhythmic serious conditions (e.g., myocardial infarction or significant hemorrhage).[4,5] During the initial evaluation immediately after syncope, patients with nonarrhythmic serious conditions need to be detected by thorough evaluation. Concern for these serious underlying conditions particularly arrhythmia and the associated mortality leads to prolonged monitoring of patients in the ED, in observation units or in inpatient settings.[6–8] Hence, wide variations in hospitalization and in-hospital and outpatient investigations exist among physicians, institutions, and countries.[2,9–11] Several risk tools have been developed to identify patients at risk for any serious outcome (both arrhythmic and nonarrhythmic serious conditions) related to syncope and one tool to predict long-term risk of arrhythmia.[5,12–14] We recently developed a tool to predict all serious conditions within 30 days after ED disposition.[15] However, there are no risk tools that predict the short-term risk of arrhythmia after ED evaluation to facilitate identification of patients who will benefit from electrocardiographic monitoring. The use of newly available prolonged cardiac monitoring technology has had limited impact on patient care due to lack of tools to identify patients who will benefit the most from these monitoring devices.[16,17] The goal of this study was to prospectively develop and internally validate a risk stratification tool for adult patients with syncope to identify those at risk for arrhythmia or death within 30 days after ED disposition.

METHODS

Study Setting and Population

We conducted a prospective cohort study at six large EDs to include adults (≥16 years) with syncope who presented within 24 hours of the event. Patients who did not suffer true syncope as defined in previously published guidelines were excluded: prolonged loss of consciousness (>5 minutes), change in their mental status from baseline after the syncope, obvious witnessed seizure, or head trauma causing loss of consciousness.[1,18] We excluded patients with major trauma requiring admission as it would be difficult to attribute outcomes to syncope. We also excluded patients who were unable to provide proper history due to alcohol intoxication, illicit drug use, or language barrier. The study was observational with no patient interventions. Hence, the research ethics committees at all study sites approved the protocol with the requirement of only verbal consent.

On-duty ED staff (physicians, nurses, emergency medicine residents, and on-site research personnel) screened consecutive patients with presenting complaints of syncope, presyncope, fainting, black out, loss of consciousness, fall, collapse, seizure, dizziness, or light-headedness. ED physicians applied the above-mentioned inclusion and exclusion criteria and obtained consent before inclusion in the study.

Data Collection

All ED physicians and emergency medicine residents were trained on the study protocol through a 1-hour didactic session. The training included assessment of standardized variables from history and physical examination and the diagnostic criteria for the type of syncope as per the European Society of Cardiology (ESC) guidelines for arriving at the final ED diagnosis.[1] We collected the following variables prospectively during the patient's index ED visit: time and date of index syncope, event characteristics, history of cardiovascular disease, family history of sudden death or congenital heart disease, and final ED diagnosis. The following variables were collected by chart review: age, sex, all vital signs, all laboratory results, and all electrocardiogram (ECG) variables. The ECG variables were abstracted as per methodologic standards for chart abstraction.[19]

Emergency medicine residents under the treating physician supervision completed the data collection forms. The emergency physician treating the patient was ultimately responsible for the integrity of the data collected. A cardiologist reviewed all ECGs performed during the index ED visit and all ECGs with any abnormalities were reviewed by a second (study)

cardiologist for extraction of ECG variables.[20] A comprehensive list of variables was generated based on literature review, previous studies, and consensus of an expert panel (ED physicians, cardiologists, and syncope researchers).[18,21–23] A subset of the variables was identified as candidate predictors for the risk tool development for this study. For estimation of interobserver agreement of the eligibility criteria and predictor variables, when feasible, a second physician assessed a subset of the study patients. Patients with presenting complaints suggestive of syncope but who were not eligible and those who were missed were identified by trained research assistants by reviewing all ED visits at the study hospitals during the study period.

Outcomes

We defined the outcome of interest as a composite of death (due to arrhythmia or unknown cause), arrhythmia, or procedural interventions to treat arrhythmias within 30-days of ED disposition (Data Supplement S1, Appendix 1, available as supporting information in the online version of this paper, which is available at https://doi.org/onlinelibrary.wiley.com/doi/10.1111/acem.13275/full). The outcome measures were selected and defined based on previous studies and consensus guidelines; we also collected the location of outcome occurrence, inside or outside the hospital.[5,18] Some investigators have previously questioned the inclusion of procedural interventions in the composite outcome. However, as patients will potentially benefit from such lifesaving interventions, an international panel of experts that included cardiologists and electrophysiologists recommended it be included as an outcome.[18]

The following approach was used to confirm the occurrence of outcomes. First, we undertook a structured review of all documents in medical records related to index and subsequent ED visits, hospitalizations, results of all investigations, and hospital death records. Second, we conducted a scripted telephone follow-up immediately after 30 days. Third, we reviewed health records at all local adult hospitals for Ontario patients and administrative health database (NetCare) for Alberta patients for all documents related to return visits, outpatient investigations, or hospitalizations. Finally, for Ontario patients with no follow-up data by the above steps, the provincial coroner's office was searched for matching records. An adjudication committee composed of three physicians blinded to the predictor variables confirmed all positive study outcomes.

Data Analysis

Patients with arrhythmia or nonarrhythmic serious conditions identified during ED evaluation were excluded as these patients do not need risk stratification. We recently reported the wide variations in disposition of patients with syncope at the study sites.[11] Hence, both patients who were hospitalized and discharged from the ED were included in the analysis.

Continuous data were reported as mean, range, and standard deviation (SD); categorical variables were reported as frequency with proportion for descriptive analysis. The interobserver agreement was reported as proportion of agreement beyond chance, using kappa (κ) coefficient.

From the entire list of variables collected, we identified a list of candidate predictors for analysis of unadjusted tests of association with the outcome, followed by multivariable analysis. The following predictors were excluded: those with fewer than five expected events as they will likely cause model instability; predictors that exceeded the threshold of 2.5 for variance inflation factors due to multicollinearity; those with >25% missing values; and those with lower interobserver agreement with $\kappa < 0.4$.[24] There were more candidate predictors than the degrees of freedom available for multivariable analysis. Hence, we selected predictors for logistic regression by testing the association of each predictor with the outcome at the 5% significance level using chi-square or Fishers' exact test for categorical variables and two-sample t-tests for continuous variables. To create a complete data set for multivariable analysis, we performed multiple imputation for missing predictors. We generated 10 multiple imputation data sets using the Markov Chain Monte Carlo procedure with the inclusion of the outcome, all candidate predictors, as well as additional variables that were anticipated to be correlated with the missing predictors.[25] After the missing variables were imputed, we dichotomized continuous predictors using a combination of clinical rationale as well as analysis of receiver operating characteristic (ROC) curves which identified the optimal cut point based on measures of sensitivity and specificity and the Youden index.[2122,26] Using the dichotomized continuous and categorical predictors selected during initial analysis, we derived a reduced model by performing multivariable logistic regression using stepwise backward elimination with a 5% significance level to stay in the model. We report the combined regression estimates for the reduced model from the 10 multiple imputation data sets.[25]

Internal validation was performed using 500 bootstrap samples. For bootstrapping, the variable selection procedure was repeated in each bootstrap sample and the stability of the stepwise variable selection procedure was determined by the percentage of times each variable was selected. Optimism in model performance measures was estimated and optimism-corrected performance indicators for the model with 95% bootstrap confidence intervals (CIs) were obtained. Using the calibration slopes across the bootstrap samples, model shrinkage was calculated and the shrinkage factor was applied to the regression coefficients to correct for overfitting.[27]

We translated the shrinkage-corrected model into a point scoring system by dividing all regression coefficients by the smallest coefficient and rounding to the nearest integer. We assessed the calibration of the model by comparing the observed versus expected risk at each score level, as well as Hosmer-Lemeshow chi-square goodness-of-fit statistic by risk deciles.

To assess the diagnostic yield of the previously published Canadian Syncope Risk Score for all serious conditions and the newly developed Canadian Syncope Arrhythmia Risk Score, we compare the prediction of 30-day arrhythmia or death between the two scores at various thresholds.

We considered physician gestalt as all serious outcomes that were identified in hospital or through follow-up investigations organized by the ED physician and the remainder of the patients who suffered serious outcomes outside the hospital were designated as missed. We compared the areas under the ROC curves for physician gestalt and the Canadian Syncope Arrhythmia Risk Score.

Sample Size

The sample size required for the study was calculated based on the estimation of precision of the sensitivity of the tool to be developed in the study population.[28] We determined that 100 patients with positive study outcome within 30 days after ED disposition was required to achieve a target of 100% sensitivity with a 95% exact binomial CI of 96.4% to 100%. Assuming a prevalence of 2% for positive outcomes after ED disposition, we calculated a total required sample size of 5,000 patients.

RESULTS

We enrolled 5,358 patients with syncope at the study hospitals from September 2010 to March 2015; 348 (6.5%) patients had incomplete outcome assessments leaving 5,010 patients for analysis (Figure 1). A second physician performed inter-rater reliability assessments on 207 patients (4.1%), and the agreement for syncope confirmation and inclusion in the study was excellent (κ = 0.89; 95% CI = 0.79–0.98).

The characteristics of the 5,010 study patients, their ED management and outcomes are detailed in Table 1. At 30-day follow-up, 106 patients (2.1%, 95% CI = 1.7%–2.5%) suffered study outcomes after ED disposition, with 45 patients (0.9%) suffering them outside the hospital (Table 2). Twenty-nine patients in our study had pacemaker insertion performed for presumed profound bradycardia or high-degree atrioventricular block without documented evidence of the arrhythmias listed as an outcome.

We selected an initial list of 39 candidate predictors for developing the model (Data Supplement S1, Appendix 2). Three were excluded for sparse distribution, and one was excluded for large proportion of missing values; however, none were excluded due to low kappa values. The troponin assays performed at the study sites were different and the values were not comparable. Additionally, 54.2% of study patients did not have troponin levels measured during initial

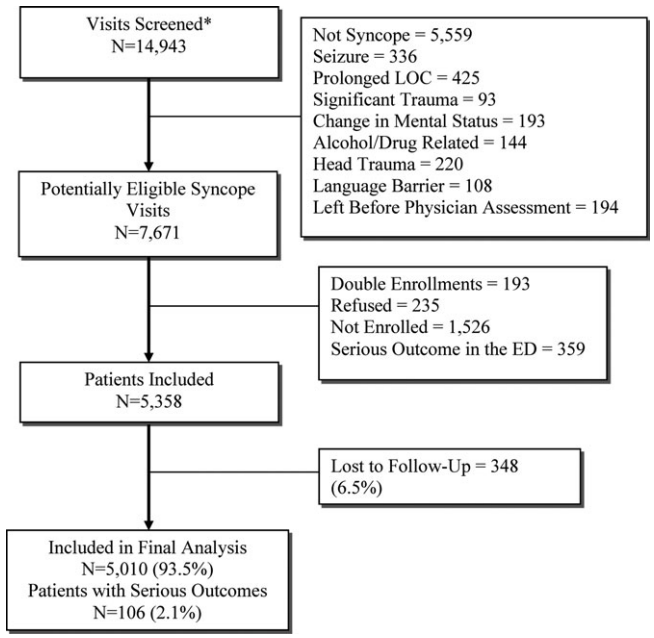

Figure 1. Patient flow. *On-duty ED staff including physicians as well as on-site research personnel screened consecutive patients presenting with syncope, presyncope, fainting, blackout, loss of consciousness, fall, collapse, seizure, dizziness, or light-headedness. ED physicians applied the above-mentioned inclusion and exclusion criteria to confirm eligibility and obtained consent before inclusion in the study. LOC = loss of consciousness.

Table 1
Patient Characteristics, ED Management, and Outcomes Among 5,010 Syncope Patients

Characteristics	
Age (y)	53.4 (±23.0)
Mean (±SD)	
Range	16–102
Female	2,746 (54.8)
Arrival by Ambulance	3,224 (64.4)
Medical history	
Hypertension (n = 5,006)	1,581 (31.6)
Diabetes (n = 5,004)	502 (10.0)
Coronary artery disease (n = 5,004)	579 (11.6)
Atrial fibrillation/flutter	353 (7.1)
Valvular heart disease (n = 5,001)	163 (3.3)
Congestive heart failure	181 (3.6)
Management	
Electrocardiogram performed	4,780 (95.4)
Blood tests performed	4,252 (84.9)
Admitted to hospital	475 (9.5)
Study outcomes*	
Serious outcomes while hospitalized	61 (1.2)
Serious outcomes outside the hospital	45 (0.9)

*Study outcomes include death due to arrhythmia or unknown cause, arrhythmia, or procedural interventions to treat arrhythmias within 30 days of ED disposition

Table 2
Outcomes Among 5,010 Syncope Patients After ED Disposition

Outcomes	Outcomes In Hospital (n = 61)	Outcomes Outside the Hospital (n = 45)
Total deaths*	9	13
Deaths due to unknown cause	4	11
Arrhythmia	57	34
Sinus node dysfunction	12	11
New/uncontrolled atrial fibrillation	1	9
High-grade atrioventricular block	7	5
Ventricular arrhythmia	12	3
Supraventricular tachycardia	1	1
Pacemaker insertion	24	5

*Patients with a known cause for their death suffered one of the serious arrhythmias and hence are not counted toward the total.

evaluation. We compared the characteristics of patients with and without troponin measurements and found that those with no levels measured were younger with low prevalence of comorbidities and with a very low proportion suffering serious outcomes (Data Supplement S1, Appendix 3). Hence, we dichotomized troponin at the 99th percentile cutoff value for the normal population and assumed that all missing values were within the normal range. We performed bivariable tests of association for the remaining 35 predictors and excluded 12 that failed to reach significance on testing. Variance inflation factors (VIFs) for the remaining 23 variables (Data Supplement S1, Appendix 4) revealed that two candidate predictors, triage systolic blood pressure (sBP) and highest ED sBP, were involved in near linear dependencies (VIF = 2.5 and 3.1, respectively); for that reason, we defined a composite variable "any ED systolic blood pressure," prior to multivariable modeling (Table 3).

Excluding the predictor troponin, the proportion of missing values among the remaining candidate predictors ranged from 0% to 18.5%. The following two predictors were missing with the highest frequency: creatinine 18.5% and triage respiratory rate 18.0%. Two additional predictors were missing among < 5% of patients: ECG predictors 4.6% and history of heart disease among 4.6% of patients. The remaining predictors were missing in ≤ 3% of patients. After multiple imputation, we included all 5,010 patients in further analysis. We dichotomized the 10 continuous predictors and, after stepwise backward elimination, we combined the results across the multiple imputation data sets to account for imputation uncertainty using Rubin's rules.[25] We developed the final model with eight predictors (Table 4): three predictors from clinical evaluation (lack of predisposition to vasovagal syncope [warm-crowded place, prolonged standing, fear, emotion, or pain], history of heart disease, any ED sBP < 90 or > 180 mm Hg); three predictors from investigations (elevated troponin levels [>99th percentile of normal population]); two ECG predictors (QRS duration > 130 msec and QTc interval > 480 msec); and two final ED diagnosis predictors (vasovagal or cardiac syncope). The apparent C-statistic for the model was 0.91 (95% CI = 0.89–0.93); after accounting for optimism of 0.007, the optimism-corrected C-statistic was 0.90 (95% CI = 0.87–0.93). We calculated a model shrinkage factor of 0.93 using the bootstrap internal validation, indicating that approximately 9% of the apparent model performance can be attributed to statistical overfitting.

We multiplied the regression coefficients by the shrinkage factor to create the Canadian Syncope Arrhythmia Risk Score (Figure 2).[29] The total score for the tool ranged from −2 to +8, with a shrinkage-adjusted expected risk ranging from 0.2% to 74.5%, respectively. For the threshold score of ≥0 the sensitivity is 97.1% (exact 95% CI = 91.6% to 99.4%) and

Table 3
Bivariable Tests of Association and Categorization of Continuous Predictors

Predictors*	Serious Outcomes (n = 106) Mean or %	No Serious Outcome (n = 4,904) Mean or %	p-value	κ†
Demographics				
Age (y)‡	74.6	52.9	<0.0001	—
Female sex	37.7	55.2	0.0004	—
Medical/family history				
History of vascular disease§ (n = 106; 4,897)	14.2	6.0	0.0006	0.95
History of heart disease‖ (n = 100; 4,675)	70.0	21.7	<0.0001	0.81
Event details				
Predisposition to vasovagal symptoms¶ (n = 106; 4,840)	12.3	43.0	<0.0001	0.47
Presence of prodrome** (n = 103; 4,838)	54.4	76.0	<0.0001	0.54
Vital signs in the ED‡				
Triage sBP (n = 102; 4,756)	136.7	125.2	0.0008	—
Highest ED sBP (n = 105; 4,860)	152.0	137.0	<0.0001	—
Lowest ED dBP (n = 104; 4,858)	59.6	65.4	<0.0001	—
Highest ED dBP (n = 105; 4,857)	84.9	80.6	0.0191	—
Triage respiratory rate (n = 84; 4,022)	17.8	17.2	0.0444	—
Triage oxygen saturation (n = 104; 4,803)	94.1	96.5	<0.0001	—
Lowest heart rate (n = 106; 4,872)	63.6	70.0	<0.0001	—
Laboratory values				
Troponin elevated (>99th percentile normal population)	20.75	3.18	<0.0001	—
Creatinine‡ (n = 106; 3,978)	108.7	88.1	0.0005	—
Electrocardiogram variables (n = 106; 4,674)				
Left bundle branch block	15.4	2.4	<0.0001	0.88
Left axis deviation	17.9	5.5	<0.0001	0.85
Right axis deviation	9.4	2.1	<0.0001	—
QRS duration‡	120.2	93.0	<0.0001	—
QRS axis‡	12.4	36.9	0.0005	—
Corrected QT interval‡	467.4	432.4	<0.0001	—
ED diagnosis (n = 105; 4,899)				
Vasovagal syncope	13.3	54.2	<0.0001	0.65
Cardiac syncope	39.1	4.6	<0.0001	0.65
Categorization of continuous predictors				
Age > 75 y	52.8	22.1	<0.0001	—
Any sBP < 90 or > 180 mm Hg†† (n = 105; 4,886)	32.4	11.8	<0.0001	—
Highest ED dBP > 110 mm Hg	10.5	2.5	<0.0001	—
Triage respiratory rate > 20/min	8.3	3.5	0.0169	—
Triage oxygen saturation < 89%	8.65	1.92	<0.0001	—
Lowest heart rate < 50/min	14.2	5.1	<0.0001	—
Creatinine > 150 μmol/L	14.2	5.5	0.0001	—
QRS duration > 130 msec	42.3	5.0	<0.0001	—
Abnormal QRS axis (<–30 or >110)	37.5	8.4	<0.0001	—
Corrected QT interval > 480 msec	44.2	6.6	<0.0001	—

*The numbers within parentheses indicate patients with data available for the variable in the two groups. Where numbers are not reported, all patients had data available.
†Interobserver assessments conducted on 207 patients (4.1%).
‡Mean values compared between groups for continuous predictors and categorization of continuous predictors shown in the bottom of the table.
§Medical history of transient ischemic attack, cerebrovascular accident, or peripheral vascular disease.
‖Includes history of coronary or valvular heart disease, cardiomyopathy, congestive heart failure, or nonsinus rhythm (ECG evidence during the index visit or documented history of ventricular or atrial arrhythmias or device implantation).
¶Warm crowded place, prolonged standing, fear, emotion. or pain.
**Dizziness, light-headedness, vision changes, nausea, or vomiting.
††Includes blood pressure values from triage until ED disposition.

Table 4
Independent Predictors of 30-Day Arrhythmias or Deaths After ED Disposition as Determined by Logistic Regression to Derive the Canadian Syncope Arrhythmia Risk Score

Variable	β Coefficient	p-value	OR	95% CI	
				Lower	Upper
Vasovagal predisposition*	–0.66	0.0484	0.52	0.27	1.00
History of heart disease†	0.91	0.0001	2.49	1.57	3.94
Any ED sBP < 90 or > 180 mm Hg‡	0.83	0.0004	2.31	1.45	3.67
ED diagnosis of vasovagal syncope	–0.76	0.0211	0.47	0.24	0.89
ED Diagnosis of cardiac syncope	1.46	<0.0001	4.29	2.65	6.94
Troponin elevated (>99th percentile normal population)	0.75	0.0105	2.11	1.19	3.73
QRS duration > 130 msec	1.30	<0.0001	3.65	2.20	6.05
Corrected QT interval > 480 msec	1.07	<0.0001	2.91	1.77	4.78
Intercept	–4.77	<0.0001	—	—	—

Hosmer-Lemeshow goodness-of-fit p-value = 0.078.
Area under ROC curve (optimism-corrected C-statistic) = 0.90 (0.87, 0.93).
ECG = electrocardiogram; ROC = receiver operating characteristic.
*Warm crowded place, prolonged standing, fear, emotion, or pain.
†Includes history of coronary or valvular heart disease, cardiomyopathy, congestive heart failure, or nonsinus rhythm (ECG evidence during the index visit or documented history of ventricular or atrial arrhythmias or device implantation).
‡Includes blood pressure values from triage until ED disposition.

Canadian Syncope Arrhythmia Risk Score

Items	Points
1. Clinical Evaluation	
a) Vasovagal predisposition*	**-1**
b) History of heart disease†	**+1**
c) Any ED systolic blood pressure < 90 or >180 mmHg‡	**+1**
2. Investigations	
a) Troponin elevated (> 99%ile normal population)	**+1**
b) QRS duration >130 milliseconds	**+2**
c) Corrected QT interval >480 milliseconds	**+1**
3. Final ED Diagnosis	
a) ED diagnosis of vasovagal syncope	**-1**
b) ED diagnosis of cardiac syncope	**+2**
Total Score (-2 to 8):	____

Risk Categories for Arrhythmias/Death

Total Score	Risk§	Category
-2	0.2%	Very Low
-1	0.5%	Very Low
0	0.9%	Very Low
1	1.9%	Low
2	3.8%	Medium
3	7.5%	Medium
4	14.3%	High
5	25.4%	High
6	41.1%	Very High
7	58.8%	Very High
8	74.5%	Very High

Figure 2. Canadian Syncope Arrhythmia Risk Score to identify patients at risk for serious arrhythmias within 30 days of ED disposition. *Warm-crowded place, prolonged standing, fear, emotion, or pain. †Includes history of coronary or valvular heart disease, cardiomyopathy, congestive heart failure, or nonsinus rhythm (ECG evidence during the index visit or documented history of ventricular or atrial arrhythmias, or device implantation). ‡Includes blood pressure values from triage until ED disposition. §Shrinkage-adjusted expected risk. ECG = electrocardiogram.

specificity was 53.4% (exact 95% CI = 52.0% to 54.9%). The diagnostic characteristics (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) for each of the threshold scores are given in Table 5. The PPV for a score of ≥6 (we collapsed scores ≥ 6 due to very small number of patients with higher scores) is 0.35 (95% CI = 0.19–0.54). The model showed acceptable agreement between observed and expected probabilities of serious outcomes at various score levels (Figure 3; Hosmer-Lemeshow goodness-of-fit statistic $\chi 2 = 9.9$, df = 5, p = 0.08). Table 5 shows the distribution of patients with each score and the diagnostic characteristics at the score thresholds.. We examined the frequency of each predictor selection in the backward elimination across the bootstrap samples and found the eight predictors that are part of the score were the most common selected during 500 replications (Data Supplement S1, Appendix 5).

Appendix 6 in Data Supplement S1 shows the comparison of the prediction probabilities for 30-day arrhythmia or death between the Canadian Syncope and the Canadian Syncope Arrhythmia Risk Score. We conduced sensitivity analysis by removing the two final ED diagnosis predictors and found that the remaining predictors in the model became more significant with odds ratio (OR) estimates moving farther away from one (Data Supplement S1, Appendix 7). The area under the ROC curve for physician gestalt was 0.79 and the difference in the areas under the ROC curves when compared to the Canadian Syncope Arrhythmia Risk Score was significant at –0.125 (95% CI = –0.172 to –0.078; p < 0.001).

Table 5
Classification Performance for the Canadian Syncope Arrhythmia Risk Score

Canadian Syncope Arrhythmia Risk Score	Number of Patients*	Expected Probability of Serious Outcome	Sensitivity†	Specificity†	Positive Predictive Value†	Negative Predictive Value†
−2	1,181	0.002	1.000	0.000	0.022	1.000
−1	1,264	0.005	1.000	0.258	0.029	1.000
0	1,146	0.009	0.971	0.534	0.044	0.999
+1	468	0.019	0.912	0.784	0.086	0.998
+2	260	0.038	0.745	0.882	0.124	0.994
+3	173	0.075	0.598	0.936	0.172	0.991
+4	106	0.143	0.441	0.970	0.249	0.987
+5	46	0.254	0.226	0.987	0.307	0.983
≥+6	29	0.459	0.098	0.996	0.345	0.980

*A total of 4,673 patients had information for the all the component predictors in the score.
†The diagnostic characteristics reported are for that value of the risk score or higher.

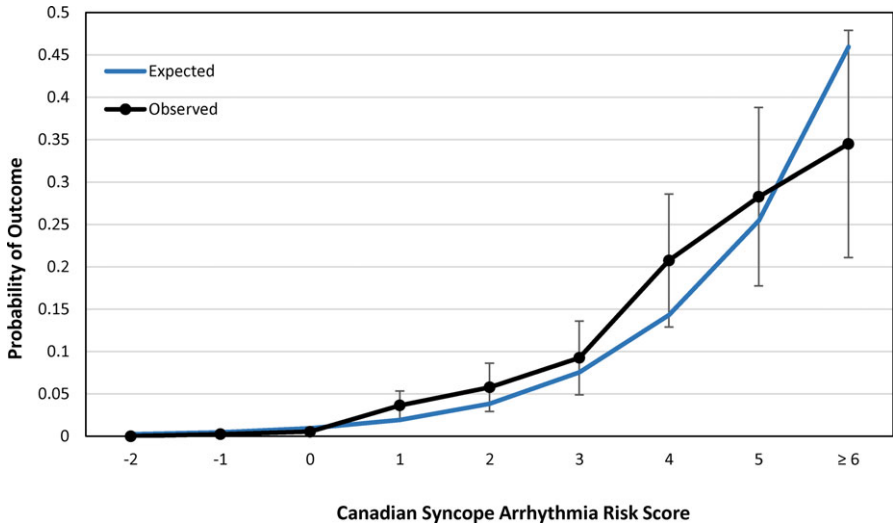

Figure 3. Observed versus expected probability for outcomes within 30 days for Canadian Syncope Arrhythmia Risk Scores after ED disposition. [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

A small but important number of patients suffer arrhythmia or death after ED disposition, with a significant proportion suffering them outside the hospital. In this multicenter study, we developed the Canadian Syncope Arrhythmia Risk Score, a risk tool that is sensible and applicable in clinical settings to predict the 30-day risk of arrhythmia or death after ED disposition among patients presenting with syncope. A score of ≤0 is associated with < 1% risk, scores of 1–3 associated with 1.9%–7.5% risk, and scores of 4–8 is associated with 14.3%–22.2% risk of arrhythmia or death within 30 days of ED disposition. This scoring system will allow physicians to risk stratify patients with syncope and aid in management and disposition.

There are no previous studies that have identified predictors for short-term (30-day) arrhythmia or death after initial evaluation of acute syncope. There are four studies that report risk factors for arrhythmias, deaths, or cardiac syncope on long-term follow-up. Two prospective studies derived and validated predictors for 1-year arrhythmias or deaths. Martin et al.[30] identified abnormal ECG, previous history of ventricular arrhythmia or congestive heart failure (CHF), and age > 45 years as risk factors for 1-year arrhythmia or death. Colivicchi et al.[31] identified age > 65 years, cardiovascular disease, syncope without prodrome, and abnormal ECG as risk factors for all-cause 1-year mortality. Sarasin et al.[32] developed a risk score (abnormal ECG, history of CHF, and age > 65 years) to predict

arrhythmias among ED patients with unexplained syncope after initial evaluation. In this study, outcomes were assessed only for hospitalized patients and those discharged from the ED were not followed up. The Evaluation of Guidelines in Syncope Study (EGSYS) score was prospectively derived and validated to predict mortality at 2 years and to identify cardiac syncope.[14] The study found that abnormal ECG and/or heart disease, palpitations before syncope, syncope while effort or supine, absence of prodrome, and absence of precipitating factors were predictors of cardiac syncope. In this study, arrhythmic syncope was diagnosed by presence of specific abnormalities in ECG or electrophysiologic testing. However, the study did not report the time lag between the arrhythmic syncope diagnosis and the index syncope as arrhythmia occurring 2 years later is less likely related to the index syncope.

The results of our study are consistent with the above studies, despite the fact that we only examined risk factors associated with short-term outcomes. Similar to the above studies, we found that abnormal ECG, heart disease, and absence of precipitating factors were associated with arrhythmia or death. In our study, we found that advanced age and absence of prodrome were significantly associated with arrhythmia or death; however, when adjusted for other variables, these predictors were not part of the final model. Additionally, we found that palpitations prior to syncope and syncope supine or exertion were not significantly associated with outcomes.

Two previous studies evaluated the role of troponin in identification of syncope patients at risk for serious outcomes. Christ et al.[33] reported the limited utility of troponin in the diagnosis of cardiac syncope. This study evaluated troponin in isolation without examining other clinical and ECG predictors. Sun et al. reported that abnormal troponin (>99th percentile of normal population) was an independent risk factor for all serious outcomes, both arrhythmic and nonarrhythmic among older (≥60 years) patients with syncope.[34] Our recently published study found that abnormal troponin levels in conjunction with other predictors can identify syncope patients at short-term risk of all serious outcomes. Our current study results show that abnormal troponin levels independently predict short-term arrhythmia and death among ED syncope patients.

Our risk score includes two predictors based on final ED diagnosis: vasovagal and cardiac syncope, which are arguably subjective. However, these predictors showed good interobserver agreement. Their large ORs and 100% selection in bootstrap internal validation suggests that these variables are robust. If the cause of syncope is unknown, our sensitivity analysis shows that the remaining predictors can prognosticate the probability of short-term arrhythmia or death. Physicians must undertake a robust clinical evaluation and attempt to assign a cause for the syncope and the cause should be designated as unknown only after appropriate clinical evaluation. The importance of physician diagnostic impression in evaluation of syncope has been previously reported and physician diagnostic impressions have been a part of well-validated models for venous thromboembolism detection and chest pain risk stratification.[35–38]

While the score needs to be validated before it can be applied to clinical practice, from the results of our study it is clearly evident that patients with higher scores are at higher risk for arrhythmias within 30 days. If these patients are discharged home, they would likely benefit from outpatient cardiac monitoring. Additionally, at the end of ED evaluation if the concern for the treating physician is only arrhythmia, a validated Canadian Syncope Arrhythmia Risk Score would likely lead to efficient use of outpatient electrocardiographic monitoring.

STRENGTHS

No previous studies have identified risk factors for short-term arrhythmia or death among ED patients presenting with syncope. Our study with 5,010 patients is the largest prospective syncope study to date with sufficient numbers of patients with arrhythmia or death to develop a robust model. Previous studies that assessed risk factors for long-term outcomes enrolled fewer than 650 patients. We conducted our study as per the methodologic standards for clinical decision tool studies, and our reporting meets all the listed Transparent Reporting of prediction model for Individual Prognosis or Diagnosis (TRIPOD) criteria.[39,40] Previously published studies predicting long-term arrhythmia, death, or cardiac syncope define "abnormal ECG" a priori and also differently. In our study, we assessed and identified specific ECG predictors that are independently associated with study outcomes. We used robust model developing techniques that included safeguards for overfitting and model performance overestimation. The components of the risk

score can be readily assessed among syncope patients and, hence, the score can be easily incorporated into practice.

LIMITATIONS

Our study does have several limitations. As the ED is a very busy environment, approximately one-fifth of eligible patients were not enrolled because the emergency physicians did not complete the study forms. We believe that this is an overestimation as we chose to assign doubtful cases as eligible nonenrolled. The characteristics of the missed eligible patients were similar to those of the study cohort (mean ± SD age = 55.4 ± 22.9 years; 53.1% females). There were no systematic reasons for nonrecruitment, and hence, we do not believe that our study sample was biased. In our study, we did not mandate prolonged electrocardiographic monitoring for arrhythmias for all patients. As there is no robust evidence for prolonged electrocardiographic monitoring of ED syncope patients after an acute assessment, we designed our study pragmatically. Additional cardiac testing and monitoring were ordered as per the discretion of the treating physician and the patients sought care based on their own perceived needs or symptoms. Our study did have a substantial proportion of patients who did not have troponin levels measured; however, we found that patients with missing troponin values were younger with less comorbidity and, therefore, imputation within the normal range was plausible. Among the remaining predictor variables, the majority were missing in less than 3% of patients. We performed multiple imputation for these missing predictors. Despite our comprehensive efforts to achieve follow-up, a small proportion (6.5%) of patients were lost to follow-up. However, we did check for any matching records for these patients using NetCare and the Ontario coroner's office records for return health care visits and deaths. Given the large study sample, we believe these patients who were lost to follow-up are unlikely to bias the results.

CONCLUSIONS

After the initial ED evaluation, a small but important number of patients suffer arrhythmia or death within 30 days. We have developed the Canadian Syncope Arrhythmia Risk Score to identify these patients. Once validated, the score can be applied for making discharge decision for lower-risk patients. By accurately risk stratifying patients with syncope, this score has the potential to aid in physician management decisions including disposition and follow-up investigations. ED patients who are classified as higher risk will likely benefit from outpatient cardiac monitoring if discharged home.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13275/full

Data Supplement S1. Supplementary material.