

Predicting short-term adverse outcomes in the geriatric population presenting with syncope: a comparison of existing syncope rules and beyond

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ABSTRACT

OBJECTIVES Syncope at age 65+ is associated with increased mortality, irrespective of cause. Syncope rules were designed to aid in risk-stratification but were only validated in the general adult population. Our objective was to determine if they can be applied to a geriatric population in predicting short-term adverse outcomes.

METHODS In this single-center retrospective study, we evaluated 350 patients aged 65+ presenting with syncope. Exclusion criteria included confirmed non-syncope, active medical condition, drug or alcohol-related syncope. Patients were stratified into high or low risk based on Canadian Syncope Risk Score (CSRS), Evaluation of Guidelines in Syncope Study (EGSYS), San Francisco Syncope Rule (SFSR), and Risk Stratification of Syncope in the Emergency Department (ROSE). Composite adverse outcomes at 48-hour and 30-day included all-cause mortality, major adverse cardiac and cerebrovascular events (MACCE), return emergency department visit, hospitalization, or medical intervention. We assessed each score's ability to predict the outcomes using logistic-regression and compared performances using receiver-operator curves. Multivariate analyses were performed to study the associations between recorded parameters and outcomes.

RESULTS CSRS outperformed with AUC of 0.732 (95% CI: 0.653-0.812) and 0.749 (95% CI: 0.688-0.809) for 48-h and 30-day outcomes, respectively. Sensitivities for CSRS, EGSYS, SFSR, and ROSE for 48-hour outcomes were 48%, 65%, 42% and 19%; and for 30-day outcomes were 72%, 65%, 30% and 55%, respectively. Atrial fibrillation/flutter on EKG, congestive heart failure, antiarrhythmics, systolic blood-pressure < 90 at triage, and associated chest pain highly correlated with 48-h outcomes. An EKG abnormality, heart disease history, severe pulmonary hypertension, BNP > 300, vasovagal predisposition, and antidepressants highly correlated with 30-day outcomes.

CONCLUSIONS Performance and accuracy of four prominent syncope rules were suboptimal in identifying high-risk geriatric patients with short-term adverse outcomes. We identified some significant clinical and laboratory information that may play a role in predicting short-term adverse events in a geriatric cohort.

The total annual cost of syncope-related hospital evaluation is over 2 billion dollars.^[1] Patients with syncope often present a challenging diagnosis with extreme variability in mortality and morbidity depending on the underlying diagnosis. In contrast to young patients, where syncope presents as an isolated occurrence, syncope

in the elderly is often multifactorial, prevalent, and associated with many predisposing factors.^[1,2] For example, a study by Wong, *et al.*^[3] demonstrated that the incidence of syncope sharply increases from 5.4 events per 1000 person-years in those ages 60-69 years to around 11.1 events per 1000 person-years in those ages 70-79 years, reaching 19.5 events per

1000 person-years in those ages 80 and above. For those over 65, syncope is associated with increased mortality, irrespective of the cause.^[2] Age-related cardiovascular structure and function changes include attenuated baroreceptor and autonomic reflexes, diastolic dysfunction, impaired adrenergic responsiveness, and impaired maintenance of intravascular volume related to decreased salt/water handling and reduced renin-aldosterone levels.^[4] To improve patient outcomes and reduce syncope-related hospital costs, elderly patients with syncope must be risk-stratified in a unique way to identify individuals at high risk for short-term adverse events that require hospitalization.

Because of the significant difference in the morbidity and mortality associated with the underlying etiology of syncope, the percentage of patients admitted to the hospital from the Emergency Department (ED) with a principal diagnosis of syncope varied widely from 13%-83%.^[5-8] As a result, multiple syncope prediction tools have been developed to aid clinicians in decision-making, with a recent emphasis focusing on risk-stratification and disposition decisions. These prediction tools usually incorporate significant predictors of outcomes from history, physical examination, and basic diagnostic tests.^[9] Namely, the San Francisco Syncope Rule (SFSR), Evaluation of Guidelines in Syncope Study Univariate (EGSYS), the Canadian Syncope risk score (CSRS), and Risk Stratification of Syncope in the Emergency Department (ROSE) are prominent among them.^[10-14] These instruments were validated mostly in the setting of the adult population rather than the geriatric population. They have demonstrated high sensitivity with variable specificity in predicting adverse outcomes in the general population.^[10-14] Comparative evaluations, external validations, and meta-analysis of studies of risk scoring models suggested significant heterogeneity among the instruments' performance characteristics and clinical utility.^[5-8,15-22]

However, it is important to note that none of these measures were created explicitly to risk stratify the elderly population, who may comprise the majority of patients admitted through the ED for additional workup.^[23-25] The identification of low-risk syncope in the elderly has the potential to reduce hospital admissions, enable specific deployment of resources,

and prevent excessive workup of those with benign causes. The primary objective of this study was to compare and assess the efficacy of the SFSR, EGSYS, CSRS, and ROSE in risk stratifying patients over the age of 65 who present to the ED with syncope for short-term adverse events within 48 hours and 30 days. A secondary objective was to identify the individual clinical and laboratory characteristics most significantly associated with short-term adverse events in our geriatric population.

METHODS

Study Design and Setting

This was a single-center health records review of 350 patients who presented to Wake Forest Baptist Medical Center Adult Tertiary Care Emergency Department between 01/01/2018 to 12/31/2019, with a chief complaint of syncope. The Institutional Research Ethics Review Board approved the protocol and exempted it from informed consent.

Subject Selection Criteria

Patients were selected from Wake Forest Clinical and Translational Science Institute (CTSI) research database based on the inclusion and exclusion criteria search. We identified patients using an inbuilt search function of the CTSI i2b2 Data warehouse system using search terms "syncope", "presyncope", "fall", "near syncope", or "loss of consciousness". Secondary manual screening of the records to identify patients 65 years or older with a primary diagnosis of syncope was performed. Exclusion criteria were age < 65, those presented > 24 h after the episode, the presence of polytrauma requiring hospital admission, confirmed non-syncopal syndromes such as stroke, vertigo, coma, shock, witnessed seizure, sustained unconsciousness > 5 min, head injury preceding loss of consciousness, pregnancy, alcohol, drug-related loss of consciousness, change in mental status from baseline after syncope, hypoglycemia, severe metabolic acidosis, or sepsis. Initial evaluation and inclusion were done by one trainee physician with subsequent review by one of the faculty investigators without knowledge of the patient's outcome status. Weekly data integrity meetings were held to review cases that were diffi-



cult to include or exclude based on the evaluation of a trainee physician and supervising faculty. If consensus was not reached about the appropriate inclusion criteria, then those cases were excluded from the study (Figure 1).

Outcome Measures

The outcomes of interest were the occurrence of any adverse event (1) within 48 h; and (2) within 30 days of syncope. Adverse events included death, major adverse cardiovascular and cerebrovascular events (MACCE), need for procedural intervention (left heart catheterization, right heart catheterization, ablation, pacemaker placement, ICD placement, synchronized cardioversion, and defibrillation) and any condition resulting in a return ED visit or hospitalization. Secondarily, we assessed the ability of each syncope risk score to predict these outcomes and compared the performance of 4 syncope risk scores. Finally, we examined other selected clinical and laboratory characteristics for relationships with outcomes in our cohort.

Analytical Plan

Data on demographics, medications, and clinical characteristics were collected. Descriptive statistics were computed, including means $\pm$ SD for continuous variables or frequencies and percentages for categorical variables. Scores were calculated for the above-mentioned syncope scoring rules, and each patient's risk status for syncope (high or low) was determined for each score. High-risk scores for CSRS, SFSR and ROSE are 1 and above, while for EGSYS is a score of 3 or above. Univariable associations between individual factors and clinical outcomes (either 48-h or 30-day adverse events) were assessed using *t*-tests for continuous variables and chi-square tests (or Fisher's exact test when warranted by small expected cell counts) for categorical variables. Each score's ability to predict the two outcomes in the Wake Forest (WF) sample was assessed using a univariate logistic regression model. Receiver-operating characteristic (ROC) curves were examined, and a comparison of predictive abilities between scores was evaluated by testing for differences in the area under the ROC curves.

Multivariable models to predict WF patients at

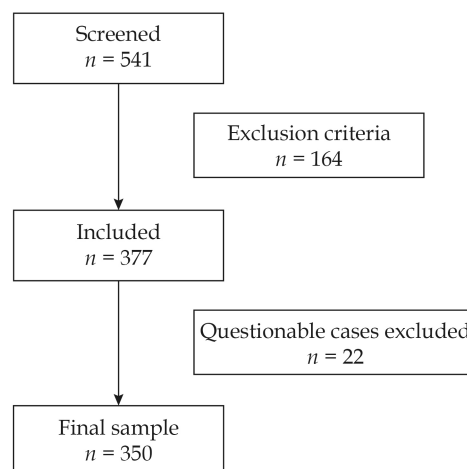


Figure 1 541 patients were initially screened after searching at the Clinical and Translational Science Institute (CTSI) i2b2 research database. 164 patients were excluded using the exclusion criteria. Consensus was not reached about the appropriate inclusion criteria for 22 patients.

high risk of 48-h and 30-day adverse outcomes were constructed using forward stepwise variable selection. Candidate variables included demographic, medication and clinical characteristics that were observed in at least 95% of patients. For each model, selection started by including the most significant predictor with *P*-value less than 0.10 and continued to include predictors with entry-level *P*-value less than 0.10 after evaluating joint significance at each step. Model selection was stopped when only those factors remaining significant at *P*-value less than 0.05 remained. Model classification was assessed using ROC curves.

RESULTS

After applying the exclusion criteria and eliminating questionable syncope presentations, a total of 350 eligible patients' charts over the age of 65 were reviewed. Table 1 shows the baseline characteristics of our study population. Mean age was 77 ± 8 years, 44% were male, 77% were white, mean BMI was 28 ± 13 kg/m², and 49% were active or former smokers, with more than two-thirds having three or more medications and co-morbidities. Table 2 shows the frequency of 48-h and 30-day outcomes in our cohort. The percentage of vasovagal syncope was 8.3%, cardiac syncope was 22.3%, orthostatic syncope was 20.9%, and other/unknown were 48.6%. The incidence of composite adverse events was 8.9%

Table 1 Baseline characteristics.

Characteristics	Sample (N)	Overall	Characteristics	Sample (N)	Overall
Age, yrs	350	77.2 ± 8.1	History, %	350	
Male gender, %	350	44.3%	Vasovagal predisposition [#]		11.4%
			Shortness of breath		11.4%
Race, %	350		Chest pain		6.9%
White		76.9%	Palpitations		3.7%
Non-white		23.1%	Medications, %	350	
Active/Former smoker, %	348		Beta-blockers		50.6%
		48.6%	ACE/ARBs		47.4%
Comorbidities, %	350		Diuretics		44.6%
Hypertension		85.7%	Anti-depressants		38.6%
Hyperlipidemia		62.6%	Antiepileptics		19.4%
Diabetes mellitus		36.3%	Alpha-blockers		13.4%
Coronary artery disease		34.9%	Anti-arithmetic		10.0%
History of syncope		34.0%	Polypharmacy [†]	247	70.6%
Chronic kidney disease III+		30.0%	Vitals triage	350	
Congestive heart failure		25.7%	Saturation ≤ 94%		15.4%
Atrial fibrillation/flutter		25.1%	Systolic pressure < 90 mmHg		4.3%
Obesity		22.0%	Heart rate		74.3 ± 15.1
Stroke/Transient ischemic attack		22.6%	Orthostatic		32.0%
Dementia		18.0%	Body mass index		27.9 ± 13.2
Multi-morbidity*	294	84.0%	Laboratory parameters		
EKG findings (%)	350		Hemoglobin	350	12.6 ± 1.8
Sinus rhythm		82.9%	Hematocrit < 30%	350	7.1%
Normal QRS axis		79.1%	Potassium	350	4.1 ± 0.7
Abnormal EKG**		62.3%	Creatinine	350	1.4 ± 1.1
AV conduction abnormality		25.5%	Magnesium	190	1.9 ± 0.3
Corrected QTc > 480 ms		16.9%	Brain natriuretic peptide	72	283.6 ± 406.7
QRS > 130 ms		14.9%	Brain natriuretic peptide > 300	350	4.6%
Q waves present (except III)		12.5%	Troponin	307	0.043 ± 0.114
Atrial fibrillation/flutter		8.9%	Troponin elevated > 99% Pop.	350	14.9%

*Multi-morbidity = 3 or more co-morbidities. **Abnormal EKG = bradycardia (< 50 beat/minute), ST changes (>1 mm elevation or depression), QT prolongation (QTc > 480 ms), ventricular tachycardia, atrioventricular block (second or third degree), sick sinus syndrome, ventricular and rapid paroxysmal supraventricular arrhythmias, sinus pauses, and pace malfunction. [#] Vasovagal predisposition = syncope predisposed by prolonged standing, emotion, pain, fear or being in a crowd. [†]Polypharmacy = 3 or more medications. ACE/ARB: angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker.

at 48 hours and 19.7% at 30 days. Mean CSRS score 2.2 ± 2.5 (< 1 [low risk] vs ≥ 1 [high risk]), mean EGSYS score 1.8 ± 1.9 (< 3 vs. ≥ 3), mean SFSR score 0.6 ± 0.8 (< 1 vs. ≥ 1), and mean ROSE score 0.5 ± 0 . (< 1 vs. ≥ 1). Prevalence of high-risk Canadian, EGSYS, SFSR, and ROSE scores were 71.7%, 50.9%, 46.0% and 37.7%, respectively.

Figure 2 shows the comparison of ROC analysis

of the four syncope rules when predicting 48-hour and 30-day composite outcomes. The CSRS performed the best in both outcomes with AUC of 0.732 (95% CI: 0.653 to 0.812) and 0.749 (95% CI: 0.688 to 0.809), respectively, indicating moderate discriminating ability, when the point score of 1 was selected as the cut-off value between low-risk and high-risk syncope patients. In comparison, the AUC of EGSYS,



Table 2 Frequency of 48-h and 30-day adverse outcomes.

Adverse outcome	48-h frequency	30-day frequency
High grade atrioventricular block	1 (0.3%)	2 (0.6%)
Any cardiac rhythm anomaly requiring intervention*	23 (6.6%)	50 (14.3%)
Cardiac arrest	0	3 (0.9%)
Myocardial infarction/Coronary intervention	3 (0.9%)	11 (3.1%)
Pulmonary embolism	0	0
Aortic dissection	0	0
Severe pulmonary hypertension	0	8 (2.3%)
Hemodynamically significant bleed	0	0
Acute stroke (ischemic or hemorrhagic)	2 (0.6%)	4 (1.1%)
Critical artery stenosis or vertebral artery stenosis	0	8 (2.3%)
Death due to any cause	2 (0.6%)	9 (2.6%)
Composite	31 (8.9%)	69 (19.7%)

Data are presented as *n* (%). *Left heart catheterization, right heart catheterization, ablation, pacemaker placement, Implantable-cardioverter-defibrillator placement, synchronized cardioversion, and defibrillation.

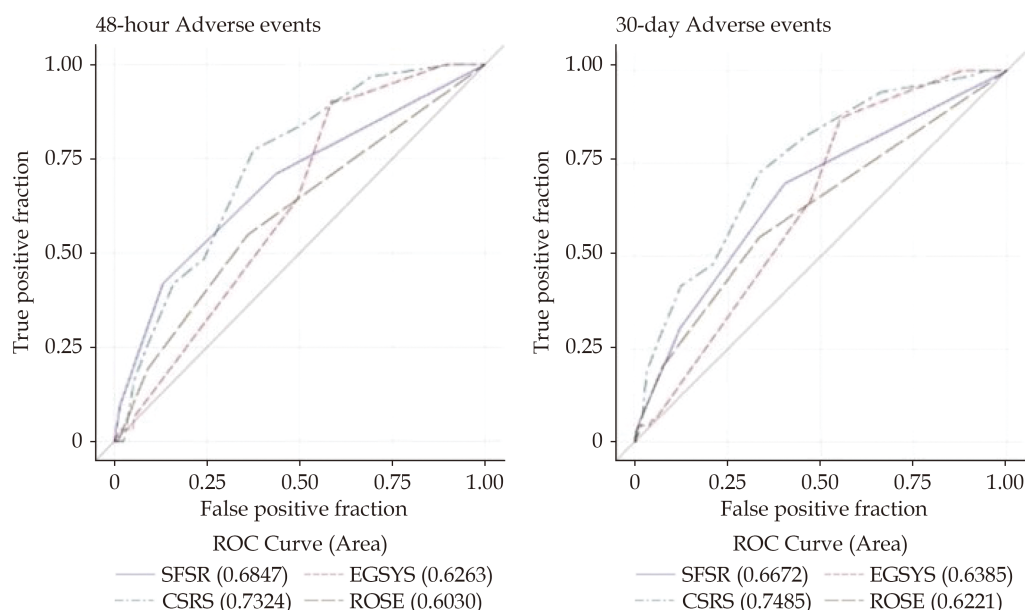


Figure 2 CSRS outperformed the remaining syncope rules with AUC of 0.732 (95% CI: 0.653-0.812) and 0.749 (95% CI: 0.688-0.809) for 48 h and 30-day outcomes, respectively. The AUCs of Evaluation of Guidelines in Syncope Study (EGSYS), San Francisco Syncope Rule (SFSR), and Risk Stratification of Syncope in the Emergency Department (ROSE) were 0.626, 0.685, 0.603 for 48-hours and 0.639, 0.667, 0.622 for 30-day composite outcomes. AUC: area under the curve; CSRS: Canadian Syncope Risk Score.

SFSR, and ROSE were 0.626 (95% CI: 0.551 to 0.701), 0.685 (95% CI: 0.584 to 0.786), 0.603 (95% CI: 0.505 to 0.701) for 48-h and 0.639 (95% CI: 0.581 to 0.696), 0.667 (95% CI: 0.560 to 0.735), 0.622 (95% CI: 0.553 to 0.691) for 30-day composite outcomes. The sensitivity, specificity, positive and negative predictive values for each score are shown in Table 3.

In secondary analyses to identify individual variables that were related to adverse outcomes, uni-

variate analysis identified several factors as seen in Tables 4 and 5. When examined in multivariable models, fewer variables remained significant. Forward stepwise regression analysis found EKG indications of atrial fibrillation/atrial flutter, congestive heart failure, antiarrhythmic medication, systolic blood-pressure of < 90 at triage, and complaint of chest pain associated with syncope as significant predictors of 48-h outcome events. For 30-days ad-

Table 3 Sensitivities, specificities, positive and negative predictive values of existing syncope rules in predicting composite outcomes.

Statistics	CSRS (95% CI)	EGSYS (95% CI)	SFSR (95% CI)	ROSE (95% CI)
48-h composite outcomes sensitivity	0.48 (0.31–0.66)	0.65 (0.48–0.81)	0.42 (0.25–0.59)	0.19 (0.05–0.33)
Specificity	0.76 (0.71–0.81)	0.50 (0.45–0.56)	0.89 (0.83–0.91)	0.91 (0.88–0.94)
Positive predictive value	0.16 (0.88–0.24)	0.11 (0.06–0.16)	0.24 (0.12–0.35)	0.17 (0.05–0.30)
Negative predictive value	0.94 (0.91–0.97)	0.94 (0.90–0.97)	0.94 (0.91–0.97)	0.92 (0.89–0.95)
30-day composite outcomes				
Sensitivity	0.72 (0.62–0.83)	0.65 (0.54–0.76)	0.30 (0.20–0.41)	0.55(0.43–0.67)
Specificity	0.67 (0.61–0.72)	0.53 (0.47–0.59)	0.88 (0.84–0.92)	0.67 (0.61–0.72)
Positive predictive value	0.35 (0.27–0.43)	0.25 (0.19–0.32)	0.38 (0.25–0.51)	0.29 (0.21–0.37)
Negative predictive value	0.91 (0.87–0.95)	0.86 (0.81–0.91)	0.84 (0.80–0.88)	0.86 (0.81–0.90)

verse outcomes, seven parameters were identified as significant predictors: any abnormality on EKG, heart disease history (composite), severe pulmonary hypertension by echo, Brain natriuretic peptide (BNP) > 300, predisposition to vasovagal syncope, and being on anti-depressants (Table 6).

When we explored qualitative concordance and discordance of parameters involved in clinical decision rule (CDR) models, we found 26 variables in total with high heterogeneity between the models, with fewer variables appearing more frequently across the models. When WF model was also considered, a history of congestive heart failure appeared in 4 out of 5 syncope model scores. Similarly, a systolic blood-pressure < 90 mmHg at triage, abnormal EKG on presentation, heart disease history

(composite), and vasovagal predisposition appeared in 3 out of 5 models (Table 7).

DISCUSSION

Syncope in the geriatric population is highly prevalent, but this “common problem” is not always associated with a benign outcome. To the best of our knowledge, this is the first reported study to compare four different validated syncope CDRs in a geriatric population. The findings of the present study revealed the superiority of the Canadian Syncope Risk Score (CSRS) over EGSYS, SFSR, and ROSE in predicting both 48-h and 30-day adverse outcomes in our geriatric population presenting with syncope based on the Area Under the Cu-

Table 4 Univariate analysis of continuous variables for 48-hour and 30-day composite outcomes.

Variable	Had Outcome			Did not have outcome			P-value
	N	Mean	Standard deviation	N	Mean	Standard deviation	
48-h outcomes							
Height (inches)	31	64.6	3.3	319	66.3	4.2	0.038
PR Interval	31	168	87	319	132	59	0.032
QRS duration	31	92	23	319	102	34	0.030
Ferritin	13	103	94	92	203	324	0.022
30-day outcomes							
Body mass index	69	26.3	5.2	281	28.4	14.4	0.053
PR interval	69	149	76	281	132	58	0.075
QTC duration	69	465	60	281	451	40	0.061
Albumin	58	3.6	0.6	209	4.0	2.6	0.084
Brain natriuretic peptide	24	585	566	48	133	154	0.001
Ferritin	27	318	441	78	146	232	0.062
Troponin	64	0.071	0.147	243	0.035	0.103	0.075



Table 5 Univariate analysis of dichotomous variables for 48-hour and 30-day composite outcomes.

Variables	Odds ratio	P-value	Variables	Odds ratio	P-value
48-h outcomes					
Antiarrhythmic	3.03	0.024	EKG: Sinus rhythm	0.33	0.005
Antiepileptic	2.53	0.018	EKG: AV conduction abnormality	1.98	0.075
Venous thromboembolism	2.73	0.067	EKG: Atrial fibrillation/flutter	5.52	0.001
Heart failure, preserved ejection	3.12	0.016	EKG: Non-sinus rhythm/EKG change	3.53	0.003
Heart failure, reduced ejection	3.05	0.003	EKG: Abnormal**	4.52	0.002
Implantable cardioverter-defibrillator	2.16	0.096	Systolic pressure < 90 mmHg triage	4.15	0.035
Atrial fibrillation/flutter comorbidity	2.73	0.007	Brain natriuretic peptide > 300	3.79	0.043
Heart disease history*	5.08	0.001	Elevated troponin	2.63	0.031
EKG: QTC > 480 ms	2.20	0.058	Chest pain	3.04	0.049
30-day outcomes					
Male sex	1.72	0.044	Echo: mod/severe pulmonary hypertension	6.36	0.001
Beta blocker	1.68	0.056	Echo: wall motion abnormality	1.85	0.076
Antiarrhythmic	2.38	0.022	Echo: Ejection fraction < 45%	3.09	0.001
Benzodiazepines	0.41	0.062	EKG: AV conduction abnormality	1.63	0.092
Antidepressants	0.45	0.008	EKG: Sinus Rhythm	0.45	0.011
Vasodilators	0.17	0.059	EKG: Atrial fibrillation/flutter	3.39	0.011
Coronary artery disease	2.13	0.005	EKG: Ventricular Ectopy	3.14	0.004
Heart failure, preserved ejection	2.46	0.006	EKG: Non-sinus rhythm/EKG change	3.29	0.001
Heart failure, reduced ejection	2.18	0.031	EKG: ST-T changes inferior	4.48	0.005
Implantable cardioverter-defibrillator	2.05	0.040	EKG: Abnormal QRS axis	1.93	0.046
Obesity	0.47	0.045	EKG: QTC > 480 ms	3.09	0.002
Atrial fibrillation/flutter comorbidity	2.52	0.001	EKG: Abnormal**	5.19	0.001
Hyperlipidemia	0.63	0.087	Brain natriuretic peptide >300	7.77	0.001
Congestive heart failure	2.83	0.001	Significant chest X-ray findings	3.88	0.001
Multi-morbidity (3+ comorbidity)	2.27	0.065	Non-significant chest x-ray findings [†]	0.24	0.001
Heart disease history*	5.91	0.001	Vasovagal predisposition [#]	0.30	0.039
Echo: mod/severe LV hypertrophy	2.10	0.067	Elevated troponin	2.56	0.003

*Heart disease history: CAD, Heart failure with preserved or reduced ejection fraction, valvular pathology, congenital heart disease, pericardial pathology or any history of arrhythmia. **Abnormal EKG = bradycardia (< 50 beat/minute), ST changes (>1 mm elevation or depression), QT prolongation (QTC > 480 ms), ventricular tachycardia, atrioventricular block (second or third degree), sick sinus syndrome, ventricular and rapid paroxysmal supraventricular arrhythmias, sinus pauses, and pace malfunction; ^{||}Significant chest X-ray: cardiomegaly, consolidation, pulmonary congestion, lung volume loss, pneumothorax, pleural effusion, pneumonitis; [†]Non-significant Chest X-ray: none of the above; [#]Vasovagal predisposition = syncope predisposed by prolonged standing, emotion, pain, fear or being in a crowd. AV: Atrioventricular; CAD: cardiovascular disease; LV: Left ventricle.

rove (AUC). However, even though our study showed relatively better performance of CSRS over other scores, overall sensitivities were 48% for the 48-h outcome and 72% for the 30-day outcome, while specificities were 76% and 67%, respectively (Table 3). This highlights the poor discriminating ability of EGSYS, SFSR, and ROSE in predicting significant adverse events, and hence risk-stratifying this cohort of patients. Moreover, the sensitivity and specificity of all 4 CDRs were average. These findings are surprising considering that the results of stud-

ies on the general adult population were more robust. For instance, in the original derivation cohort, the ROSE rule had a sensitivity and specificity of 87.27, and 25.72 respectively,^[14] while SFSR and EGSYS had a sensitivity and specificity of 96% and 62%, and 92% and 62%, respectively.^[12,13] Sensitivity for CSR In the CSRS derivation study was almost 99%, but a cut-off score of -2 or less^[11] was used to identify low-risk patients. It is important to note that our cohort of patients had one major difference beyond that of age; we used a higher cut-off value



Table 6 Multivariate analysis of variables for 48-h and 30-day composite outcomes.

Variables	Odds ratio (95% CI)	P-value
48-h outcomes		
Antiarrhythmic	4.02 (1.39-11.61)	0.0103
Congestive heart failure	4.05 (1.73-9.49)	0.0013
Chest pain	4.39 (1.31-14.79)	0.0169
Atrial fibrillation/flutter (EKG)	5.59 (2.03-15.4)	0.0009
Systolic pressure < 90 mmHg	6.08 (1.49-24.78)	0.0119
30-day outcomes		
Vasovagal Predisposition*	0.15 (0.04-0.63)	0.0097
Antidepressants	0.48 (0.25-0.93)	0.0294
ED diagnosis (Vasovagal/Cardiac)	2.31 (1.24-4.30)	0.0084
EKG: Abnormal**	2.44 (1.20-4.96)	0.0138
Heart disease history	3.42 (1.56-7.52)	0.0022
Brain natriuretic peptide > 300	5.51 (1.70-17.88)	0.0044
Echo: Mod/Severe pulmonary hypertension	5.87 (2.09-16.47)	0.0008

*Vasovagal predisposition = syncope predisposed by prolonged standing, emotion, pain, fear or being in a crowd; **Abnormal EKG = bradycardia (< 50 beat/minute), ST changes (> 1 mm elevation or depression), QT prolongation (QTc > 480 ms), ventricular tachycardia, atrioventricular block (second or third degree), sick sinus syndrome, ventricular and rapid paroxysmal supraventricular arrhythmias, sinus pauses, and pace malfunction; ^{||}Heart disease history = CAD, Heart failure with preserved or reduced ejection fraction, valvular pathology, congenital heart disease, pericardial pathology or any history of arrhythmia

of CSRS to differentiate high and low risk patients.

In the context of external validation, these scores had less robust and less consistent performance. For instance, the performance of SFSR, Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL), EGSYS, and clinical judgment were evaluated in a meta-analysis by Constatino, *et al.*^[16] using individual patient data from 6 studies. They showed that SFSR's sensitivity ranged between 69%-86% and specificity ranged between 44%-60%, while EGSYS's sensitivity and specificity were 63% and 61%, respectively. The sensitivity of clinical judgment alone was close to 90%, with a wide range of specificity, highlighting the lack of superiority of these rules to individualize clinical decisions regarding the prediction of short-term outcomes of syncope patients.^[16] A recent external validation of CSRS by original authors using -1 as a score cutoff point demonstrated a sensitivity of 97.8%. In first validation analysis of CSRS outside Canada, Solbiati, *et al.*^[26] showed a sensitivity of 70% in predicting 30-day serious outcomes. The development of CSRS involved the largest prospective syncope study to date, robust methodological standards, and well-defined predictors compared to other rules which may explain its superior discriminating ability com-

pared to other scores. Nevertheless, with AUCs < 0.8, the CSRS can technically be considered a suboptimal discriminating tool in our cohort, though it should be noted that a point score of 1 was selected as the cut-off value between low-risk and high-risk syncope patients for our cohort, which correlates with an estimated 3.1% risk of serious adverse event as per the original study. We chose this point score because ≥ 1 point in the original study is categorized as a medium risk that necessitates further inpatient investigation. Our assumption was that it might be of value to test higher cut-off points for the CSRS rule in the geriatric population to see if that would yield a higher discriminating ability since the elderly, despite their comorbidities, are also predisposed to benign causes of syncopal events including autonomic dysfunction and transient orthostatic hypotension related to medications. Recent external validation studies used a cut-off score of ≤ 0 . A similar cutoff score might have improved the sensitivity of CSRS in our study, but overall, CDRs did not perform better than clinical judgment in most instances.^[6,26]

Risk-stratifying patients for anticipated adverse events within 48 hours versus 30 days may be of immense value to the patient and the healthcare



Table 7 Comparison of variables between existing syncope rules.

Variables	SFSR (points)	EGSYS (points)	CSRS (points)	ROSE (points)	WF 48 hrs. (Z-score)	WF 30 days (Z-score)
Hematocrit < 30% or Hb < 9	1 Point			1 point		
Systolic pressure < 90 at triage	1 Point		2 Points		2.52	
Shortness of breath	1 Point					
EKG: non-sinus rhythm/EKG change	1 Point	3 Points			3.32	2.30
Congestive heart failure	1 Point	3 Points	1 Point		3.22	
EKG: abnormal*		3 Points				2.30
Supine syncope		2 Points				
Autonomic prodrome		-1 Point				
Palpitations		4 Point				
Effort syncope		3 Point				
Heart disease history**		3 Point	1 Point			3.07
Vasovagal predisposition		-1 Point	-1 Point			-2.59
Elevated troponin			2 Point			
QRS duration > 130 ms			1 Point			
Corrected QT > 480 ms			2 Point			
ED diagnosis (cardiac vs. vasovagal)			2/-2 Points			2.64
Brain natriuretic peptide > 300 pg/mL				1 Point		5.48
Saturation < 94% on room air				1 Point		
Bradycardia < 50				1 Point		
Fecal occult blood				1 Point		
Chest pain				1 Point	2.39	
Q waves				1 Point		
Antiarrhythmic medication					2.57	
EKG: atrial fibrillation/flutter					3.32	
Antidepressants						-2.18
Echo: Moderate/Severe pulmonary hypertension						3.36

*Abnormal EKG = bradycardia (< 50 beat/minute), ST changes (> 1 mm elevation or depression), QT prolongation (QTC > 480 ms), ventricular tachycardia, atrioventricular block (second or third degree), sick sinus syndrome, ventricular and rapid paroxysmal supraventricular arrhythmias, sinus pauses, and pace malfunction. Heart disease history = CAD, Heart failure with preserved or reduced ejection fraction, valvular pathology, congenital heart disease, pericardial pathology or any history of arrhythmia. ^{||}Vasovagal predisposition = syncope predisposed by prolonged standing, emotion, pain, fear or being in a crowd.

system. It may aid clinicians in triaging patients for immediate inpatient observation versus an outpatient but an expedited workup, which can further reduce healthcare costs and avoid unwanted hospitalization for the elderly. Unfortunately, CDRs performed relatively poorly in predicting 48-hour outcomes compared to 30-day outcomes in our cohort. Beyond CDR models, we evaluated the impact of individual clinical and demographic variables in 48-hour and 30-day outcomes. Five parameters were found to have significant predictive value for our geriatric population for 48-hour adverse events: the presence of atrial-fibrillation or flutter, systolic

blood-pressure < 90 mmHg at triage, patients on antiarrhythmic medications, chest pain as an associated symptom, and a history of congestive heart failure (Table 7). For serious outcomes within 30 days, seven parameters were identified as having significant predictive value for those over the age of 65 (Table 7). We found that vasovagal syncope was negatively associated with serious adverse events, as seen in CSRS and EGSYS scores. We also found that an elevated BNP is associated with serious outcomes, consistent with ROSE. It should be noted that for the remaining patients who did not have BNP data available ($n = 78$), we relied on the clinic-

al assumption that there was no indication for obtaining a BNP and hence automatically considered that value as clinically insignificant. Other variables of significance were history of heart disease, abnormal EKG, clinical diagnosis of cardiac syncope by the admitting emergency physician, and pulmonary hypertension (PH). Interestingly, being on anti-depressants was negatively associated with adverse outcomes. When comparing these findings with variables in the other 4 CDRs, there is significant heterogeneity among the five models (including our model). Nevertheless, out of the 26 variables of interest, a history of any heart disease, abnormal EKG on presentation, predisposition to vasovagal syncope, and systolic blood-pressure less than 90 mmHg at triage were found to be significant on at least 3 out of 5 models. The history of heart disease/congestive heart failure was part of 4 CDR models except ROSE. We can potentially derive a new CDR incorporating these variables if validated in a prospective study. Two additional variables emerged as significant in our study: pulmonary hypertension and treatments with antidepressants. There are numerous studies that show that PH-related mortality rates are high. For example, a study of the Registry to Evaluate Early and Long-term PAH Disease (REVEAL) trial showed a 5-year survival rate of only 27% among patients with PH in the US, and a more recent study suggested mortality of 6% and 23% in 1 and 3 years, respectively.^[27,28] Syncope in any patient with moderate to severe pulmonary hypertension likely has significant hemodynamic implications, thereby owing to its high mortality. The negative association of antidepressant use to serious outcomes is intriguing, though not strongly correlated as that of a vasovagal syncope presentation. Studies have shown that depressed patients can be more susceptible to experiencing myocardial infarction despite controlling for cardiovascular risk factors.^[29,30] It has also been shown that there is a 2-fold increase in orthostatic hypotension in patients taking antidepressants.^[31,32] Given the above, we are unsure if our finding is driven by a potential “cardiac protective” effect of antidepressants or perhaps influenced by an increased prevalence of a more “benign” orthostatic hypotension. This will need further exploration in future prospective studies.^[33]

Limitations

Our study has many limitations. This was a single-center, retrospective observational study. Data reliability was verified at multiple levels during data entry, but the influence of incomplete and poor documentation was, even though minimal, can be considered substantial. The primary goal of the study was to compare the risk stratification ability of 4 CDRs mentioned above in a cohort of older adults. None of these were specifically derived for the geriatric population. A recently derived CDR (FAINT score) to risk stratify older adults was not compared in this study.^[18] Though relevant to our study, it has yet to be externally validated. We adopted a significantly higher cut-off score of 1 for CSRS compared to the original derivation study and recent external validation studies.^[11,30] We were unable to further explore “protective” effect of antidepressant use due to lack of granular data on class and type of antidepressants patients were taking. Many patients did not have BNP values during the index encounter.

Conclusions

The present study’s findings showed that the overall performance of major CDRs for syncope risk stratification was suboptimal. Canadian Syncope Risk Score (CSRS) performed better over EGSYS, SFSR, and ROSE in predicting both 48-hour and 30-day adverse outcomes in those over the age of 65. We were also able to identify some significant clinical and laboratory variables that can potentially help predict short-term adverse events in the geriatric population. A history of heart disease, abnormal EKG, lack of predisposition to vasovagal syncope, and systolic blood-pressure less than 90 mm of Hg at triage were the most consistent variables in helping predict adverse outcomes across the CDR models.

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