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Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 55, No. 8, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.09.049

The ROSE (Risk Stratification of Syncope in the Emergency Department) Study

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Objectives The aim of this study was to develop and validate a clinical decision rule (CDR) to predict 1-month serious outcome and all-cause death in patients presenting with syncope to the emergency department.

Background Syncope is a common, potentially serious condition accounting for many hospital admissions.

Methods This was a single center, prospective, observational study of adults presenting to the emergency department with syncope. A CDR was devised from 550 patients in a derivation cohort and tested in a validation cohort of a further 550 patients.

Results One-month serious outcome or all-cause death occurred in 40 (7.3%) patients in the derivation cohort. Independent predictors were brain natriuretic peptide concentration ≥300 pg/ml (odds ratio [OR]: 7.3), positive fecal occult blood (OR: 13.2), hemoglobin ≤90 g/l (OR: 6.7), oxygen saturation ≤94% (OR: 3.0), and Q-wave on the presenting electrocardiogram (OR: 2.8). One-month serious outcome or all-cause death occurred in 39 (7.1%) patients in the validation cohort. The ROSE (Risk stratification Of Syncope in the Emergency department) rule had a sensitivity and specificity of 87.2% and 65.5%, respectively, and a negative predictive value of 98.5%. An elevated B-type natriuretic peptide (BNP) concentration alone was a major predictor of serious cardiovascular outcomes (8 of 22 events, 36%) and all-cause deaths (8 of 9 deaths, 89%).

Conclusions The ROSE rule has excellent sensitivity and negative predictive value in the identification of high-risk patients with syncope. As a component, BNP seems to be a major predictor of serious cardiovascular outcomes and all-cause death. The ROSE rule and BNP measurement might be valuable risk stratification tools in patients with emergency presentations of syncope and should now be subjected to external validation. (J Am Coll Cardiol 2010;55:713–21) © 2010 by the American College of Cardiology Foundation

There have been several risk stratification studies in patients with syncope (1–8), but many are limited by small numbers of patients in the derivation cohort (n = 175 to 270) (1,3,4,8), whereas others have not been validated (2,7), and only 2 have looked at short-term outcome (5–7). In the large San Francisco Syncope Rule (derivation n = 684; validation n = 791) study, short-term adverse outcomes relevant to emergency practice were examined (5,6), but attempts to validate it externally have failed (9–12). Moreover, the potential role of biochemical markers in risk stratification has not been assessed. B-type natriuretic peptide (BNP) is an excellent marker of prognosis in patients with heart failure or cardiac disease (13). Given that prognosis in syncope is related to the presence of underlying heart disease (14) and that all existing syncope clinical decision rules (CDRs) include either a history of congestive heart failure (1,4–6) or underlying cardiac disease (2,3), BNP represents a promising and important biomarker that has been underinvestigated in the context of syncope.

See page 722

Definitions vary, but syncope can be defined as a "transient, self-limited loss of consciousness, usually leading to

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Manuscript received June 8, 2009; revised manuscript received September 11, 2009, accepted September 22, 2009.

JACC Vol. 55, No. 8, 2010
February 23, 2010:713–21

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CDR = clinical decision rule
CI = confidence interval
ECG = electrocardiogram
ED = emergency department
MI = myocardial infarction
OR = odds ratio
ROC = receiver-operator characteristic

falling" (15). The onset of syncope is relatively rapid, and the subsequent recovery is spontaneous, complete, and relatively prompt. The underlying mechanism is a transient global cerebral hypoperfusion (15,16). Terminology has recently been clarified (17), and "transient loss of consciousness" is now used to encompass both syncope and epileptic seizures. Often the cause for a specific event is unclear, and in these patients, transient loss of consciousness should be used.

The aims of the present study were to develop and to validate a CDR with history, examination, electrocardiogram (ECG), and biochemical markers to predict 1-month serious outcome and all-cause death in patients presenting with syncope to the emergency department (ED).

Methods

Study design and setting. This was a single-center, prospective, observational derivation and validation cohort study. The study was conducted in the Emergency Department of the Royal Infirmary of Edinburgh: a United Kingdom tertiary center with 100,000 adult attendances per annum. The study was granted ethical approval by the Multi-Centre Research Ethics Committees for Scotland A Ethics committee (06/MRE00/107) and the Lothian Regional Ethical Committee (06/S11ADMIN/151). Written consent or relative assent was obtained from all patients.

Study population. Patients 16 years of age or older presenting with acute syncope were enrolled. Exclusion criteria were no consent or relative assent, persisting neurological deficit suggestive of stroke, previous recruitment into the study, collapse related to alcohol consumption (raised alcometer reading and no other cause for syncope), hypoglycemia, trauma, or seizure activity with a >15-min witness-reported postictal phase (18).

Standardized patient assessment. Potentially eligible patients were identified in the ED triage area and assessed for study inclusion by the attending clinician (an emergency physician or nurse practitioner). A decision to enroll a patient was not later overturned. Data were collected with a structured data collection form with 32 predetermined historical variables (9 focused on clinical features, 10 on past medical history, and 13 medication-related) and 14 examinations, 24 ECGs, and 23 biochemical or hematological variables. These included all characteristics previously associated with serious outcome or used in existing CDRs and guidelines. ED tests not part of the study protocol were ordered at the discretion of the treating doctor, and patients were admitted, referred for outpatient investigation, or discharged according to current ED protocols. Point-of-care BNP testing was performed with a 2.7-ml ethylenediaminetetraacetic acid sample with a Biosite Triage point-of-care machine (Biosite Inc., San Diego, California).

Outcome measures and assessment. The primary end point was the combination of serious outcome and all-cause death at 1 month after ED presentation. Serious outcome encompassed the following: 1) acute myocardial infarction (MI) according to the universal definition (19); 2) life-threatening arrhythmia (ventricular fibrillation, sustained ventricular tachycardia [>120 beats/min], ventricular pause [>3 s], ventricular standstill, or asystole); 3) decision to implant a pacemaker or cardiac defibrillator within 1 month of index collapse; 4) pulmonary embolus (confirmed on lung perfusion scan or CT pulmonary angiography); 5) cerebrovascular accident, intracranial hemorrhage, or subarachnoid hemorrhage (demonstrated by brain imaging or lumbar puncture); 6) hemorrhage requiring a blood transfusion of ≥2 U; or 7) acute surgical procedure or endoscopic intervention. Secondary end points were cardiovascular serious outcome (acute MI, arrhythmia, pacemaker/defibrillator implantation, or cardiac procedure) and syncope-related death (death due to cause of presenting syncopal episode).

Patients were followed up 1 month after presentation through the hospital Electronic Patient Record system, hospital pacemaker records, radiological reports, and direct contact with the patient or general practitioner. A cardiologist (Jeremy Langrish) and emergency physician (M.J.R.) independently reviewed all ECGs and agreed to findings by consensus. Two investigators (M.J.R. and A.J.C.) independently reviewed all derivation clinical data and assigned end points with any disagreements resolved by consensus from 3 other investigators (D.E.N., K.G.J., and A.J.G.). All derivation group end points were assigned before development of the ROSE (Risk stratification Of Syncope in the Emergency department) CDR.

Data analysis. Nonrecruited but potentially eligible patients were identified by a daily search of all Emergency Department Electronic Patient Records with Business Objects version 6.5 (Business Objects Enterprise, San Jose, California) looking for the keywords "syncope," "collapse," "faint," "loss of consciousness," or "loc." All identified Electronic Patient Records were reviewed (M.J.R.) and classified as eligible or ineligible. Five percent were independently audited at random by a second investigator (K.G.J.).

From pilot data, we estimated approximately 1,200 eligible patients present to our ED each year and anticipated recruiting between 800 and 1,000 per annum. With an estimated 1-month event rate of 10.0% (20,21) and a sample size of 500 patients, the study has an 80% power of showing an effect ($p < 0.05$, 2-tailed), if the odds ratio (OR) for an SD change in the predictor value is 1.7. This calculation allowed for a correlation of this variable with the other covariates such that $R^2 = 0.3$. If a binary risk factor has a prevalence of 20%, there will be an 80% power to detect ($p < 0.05$, 2-tailed) an increase in the event rate if the

OR is 2.5 (nQuery Advisor, Statistical Solutions, Boston, Massachusetts). If a risk factor has a prevalence of only 10%, there is a corresponding 80% power to detect an OR of 3.2. Because of predicted loss to follow-up and missing data, we aimed to recruit a further 10% (i.e., a total of 550 patients) to each cohort.

Development of the ROSE CDR. An expert panel consisting of 6 representatives from emergency, cardiovascular, general, and geriatric medicine, and medical statistics met in January 2007 to review the selected predictor variables and definitions of all end point measures and later to develop the ROSE CDR by consensus. Initially a principal component analysis was performed to reduce the number of variables for consideration, but this approach was unhelpful. Mean values and mean differences were calculated for continuous variables for serious and nonserious outcome groups. Continuous and categorical data were assessed by *t* test and chi-square test, respectively, to determine which variables showed statistical significance (at $p < 0.10$, 2-tailed). "Missing" was considered a category for categorical variables, whereas for continuous variables mean imputation was used in conjunction with a binary dummy variable to indicate whether the numerical variable had been imputed. Cross tabulation was then performed to look for suitable cutoff points. Multiple logistic regression analysis was then performed to determine independent predictors of serious outcome, and a weighted integer risk score based on the coefficient derived from the logistic regression analysis was assigned. The combination of characteristics chosen, along with their risk score, was used to derive a total risk score that was applied to the derivation cohort. On review by the expert panel, it was decided that this approach was not sensitive enough or clinically sensible. A patient with only 1 positive predictor might not score enough to be admitted, despite a good predictor of serious outcome or death being present. A decision tree approach was therefore applied, starting with variables identified from the logistic regression. Variables that predicted adverse outcome were progressively identified to optimize the sensitivity of the rule. This approach maintained sensitivity and was therefore accepted as the ROSE CDR.

Validation of the ROSE CDR. An independent clinician (David Caesar) blinded to the ROSE CDR, assigned all validation cohort end points. Patients lost to follow-up were excluded before statistical analysis. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for the ROSE CDR in the validation cohort.

Results

Derivation cohort. Between March 1, 2007, and October 27, 2007, there were 890 (1.3%) potentially eligible patients from 70,836 presentations to the ED. Patients (n = 575; 64.6%) were screened, 13 refused to consent, and 12 were unable to consent and had no relative or caregiver who could provide assent. The derivation cohort therefore consisted of 550 patients (Fig. 1). Nineteen patients were lost to follow-up, and 2 patients had been previously enrolled into the derivation cohort and were excluded. This left 529 patients for analysis (Table 1), of whom 40 patients had a primary outcome (Table 2).

Development of the ROSE CDR. Variables found by multiple logistic regression analysis to be independent predictors of serious outcome were BNP concentration ≥300 pg/ml (Wald chi-square: 15.9, OR: 7.3), a rectal examination showing fecal occult blood (chi-square: 13.6, OR: 13.2), hemoglobin ≤90 g/l (chi-square: 11.0, OR: 6.7), Q-waves (25% of R-wave, width >0.04 s, depth >2 mm, and not in lead III; chi-square: 5.8, OR: 2.8) or left bundle branch block (chi-square: 5.3, OR: 4.8) on the presenting ECG, male sex (chi-square: 5.2, OR: 2.6), oxygen saturation ≤94% on room air (chi-square: 5.1, OR: 3.0), albumin <37 g/l (chi-square: 2.9, OR: 3.2), and white cell count $>14 \times 10^9$ cells/l (chi-square: 2.5, OR: 2.4).

With recursive partitioning to create a decision tree and to prioritize sensitivity, BNP concentration ≥300 pg/ml accounted for 13 of 40 patients with an event. This cutoff maximized its specificity without losing any sensitivity for detecting serious outcome or all-cause death. Rectal examination showing fecal occult blood accounted for a further 8 patients, hemoglobin concentration <90 g/l, and oxygen saturation ≤94% on room air accounted for 4 more patients each; and Q-wave (not in lead III) on the ECG identified 3 patients. Analysis of the remaining 8 patients showed that "chest pain associated with syncope" and "bradycardia ≤50 beats/min" accounted for a further 5 patients, leaving just 3 unidentified patients. Albumin and white cell count were not included, because they are not immediately available to the emergency clinician; male sex was removed, because it was not useful within a bundle approach.

The 3 unidentified cases were an endoscopy procedure showing severe gastro-esophageal reflux, a computed tomography guided biopsy procedure, and a pacemaker for persistent neurocardiogenic syncope. It was felt by the study investigators that these outcomes were not, in reality, life threatening although defined as "serious" by the study protocol. Figure 2 shows the finalized ROSE rule. A patient should be considered high-risk for serious outcome and admission considered if 1 or more of the 7 characteristics is present. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the ROSE rule in the derivation cohort were 92.5%, 73.8%, 22.4% and 99.2%, and 3.5 and 0.1, respectively. The rule missed 3 patients (2 of whom were admitted) compared with 5 patients with serious outcomes who were discharged from the ED (4 of whom would have been identified by the ROSE rule). The area under the receiver-operator characteristic (ROC) curve for the ROSE rule in the derivation cohort was 0.83 (95% confidence interval [CI]: 0.78 to

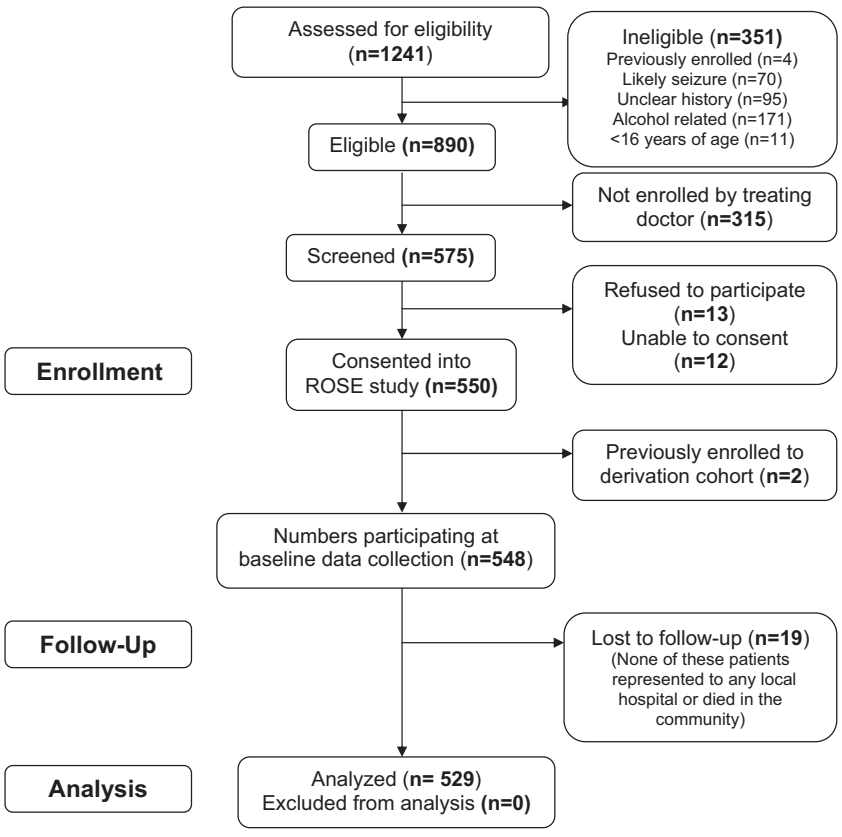

Figure 1 The ROSE Derivation STARD Diagram

A STARD (STAndards for the Reporting of Diagnostic accuracy studies) flow diagram showing recruitment of patients into the derivation cohort of the ROSE (Risk stratification Of Syncope in the Emergency department) study.

0.89). The rule would have potentially prevented 87 admissions in the derivation cohort.

Validation cohort. Between October 27, 2007, and July 22, 2008, there were 951 (1.3%) potentially eligible patients of 74,840 presentations to the ED. Patients (n = 579; 60.9%) were screened, 16 refused to consent, and 13 were unable to consent and had no relative or caregiver who could provide assent. The validation cohort therefore consisted of 550 patients (Fig. 3). Ten patients were lost to follow-up, 1 patient had previously been enrolled in the validation cohort, and 1 patient later withdrew consent. This left 538 patients for analysis (Table 1), of whom 39 patients had a primary outcome (Table 2).

Performance of the ROSE rule. The ROSE rule performed with a sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of 87.2%, 65.5%, 16.5% and 98.5%, and 2.5 and 0.2, respectively, when applied to the validation cohort missing 5 patients, raised troponin I (1.67) and possible MI, subarachnoid hemorrhage, basal ganglia hemorrhage on day 29, documented episode of ventricular tachycardia in the ED, and a gastric ulcer found on upper gastrointestinal endoscopy in a patient who did not undergo an ED rectal examination. Two of these patients were discharged by the emergency clinician (patients with subarachnoid hemorrhage and basal ganglia hemorrhage), and 1 further patient was discharged by the emergency clinician but would have been picked up by the ROSE rule. The area under the ROC curve for the ROSE rule in the validation cohort was 0.76 (95% CI: 0.70 to 0.83). Use of the ROSE rule in the validation cohort would have potentially resulted in 80 fewer admissions.

Correlation of predictors with serious outcomes. In the combined validation and derivation groups, 29 serious outcomes occurred in patients with a BNP concentration ≥300 pg/ml. Of these, 23 (79%) were cardiovascular in origin and included 7 patients requiring insertion of a pacemaker, 6 with acute MI, 5 with arrhythmia, and 5 with pulmonary embolus. Positive rectal examination picked up 9 serious outcomes, all of which were gastrointestinal bleeding or requirement for blood transfusion. Bradycardia picked up 6 serious outcomes, all of which were in patients who went on to require pacemaker insertion. Anemia identified 9 serious outcomes: 2 with acute MI, 4 requiring red cell transfusion, and 3 other serious outcomes. Chest pain identified 8 serious outcomes: 2 with a pulmonary embolus,

Table 1 Selected Characteristics of Analyzed Patients

Characteristic	Derivation Cohort	n	Validation Cohort	n
Demographic data				
Age, yrs	63.8 ± 21.2	529	62.4 ± 21.9	538
Male sex	235 (44.4)	529	245 (45.5)	538
Management				
Admitted to hospital	252 (47.6)	529	286 (53.2)	538
Medical history				
Previous history of syncope	228 (43.4)	525	214 (39.9)	537
Hypertension	206 (39.0)	528	203 (37.9)	536
Known ischemic heart disease	122 (23.1)	529	109 (20.4)	535
Previous acute myocardial infarction	55 (10.4)	529	60 (11.2)	535
Known valvular heart disease	29 (5.5)	528	31 (5.8)	536
Known history of cardiac failure	27 (5.1)	529	20 (3.7)	535
History of syncope episode				
Associated chest pain	39 (7.4)	529	47 (8.7)	538
Prodromal symptoms	326 (61.6)	529	326 (60.7)	537
Associated palpitations	20 (3.8)	529	15 (2.8)	538
Related to exertion	30 (5.7)	529	31 (5.8)	537
Examination findings				
Pulse, beats/min	76.1 ± 18.3	527	76.2 ± 17.1	537
Systolic BP, mm Hg	130.9 ± 24.0	525	129.7 ± 24.2	534
Diastolic BP, mm Hg	68.1 ± 12.7	524	67.4 ± 13.3	534
>20 mm Hg postural drop	50 (14.1)	355	38 (10.6)	358
% SpO_2 on room air	97.2 ± 2.2	517	96.8 ± 3.4	523
Heart murmur heard	65 (12.6)	516	71 (13.4)	531
Signs of heart failure	34 (6.5)	523	37 (6.9)	534
FOB present on PR if indicated	16 (19.3)	83	3 (5.3)	57
Associated trauma	167 (31.7)	526	149 (27.9)	534
Syncope cause identified in ED	234 (44.2)	529	219 (40.7)	538
Syncope cause finally identified	348 (65.8)	529	347 (64.9)	535
Arrhythmia in ED	6 (1.1)	529	4 (0.7)	538
ECG findings				
Sinus rhythm	451 (91.3)	494	460 (93.7)	491
PR >200 ms	68 (13.8)	494	56 (11.4)	491
Sinus bradycardia <50 beats/min	12 (2.4)	494	9 (1.8)	491
Pathological Q waves	120 (24.3)	494	149 (30.4)	490
Pathological Q waves not III	72 (14.6)	494	103 (21.0)	490
QTc >450 ms	71 (14.4)	494	68 (13.9)	490
QRS ≥120 ms	27 (5.5)	494	40 (8.1)	491

Values are presented as mean ± SD or n (%). Selected characteristics of the ROSE (Risk stratification Of Syncope in the Emergency department) study analyzed patients in both the derivation (n = 529) and validation (n = 538) cohorts.

BP = blood pressure; ECG = electrocardiogram; ED = emergency department; FOB = fecal occult blood; PR = per rectum examination; QTc = QT interval corrected for heart rate.

3 with acute MI, and 3 who required pacemaker insertion. Finally, Q-wave and saturation ≤94% on room air were slightly less specific but picked up mainly cardiovascular and pulmonary embolus serious outcomes.

"Missed" patients and ECG assessment. Table 3 compares patients who were enrolled with those who were eligible but not enrolled. In the derivation cohort, nonenrolled patients were younger, although there were no differences in admission or mortality rates. In the validation cohort, there were no differences between the 2 groups. The interobserver agreement of enrollment eligibility was 0.90 with a kappa value of 0.69 (95% CI: 0.60 to 0.77). Electrocardiogram interobserver agreement was between 0.94 and 1.00 for all ECG variables with kappa values between 0.85 and 1.00 for all variables except ST-segment elevation (0.66; 95% CI: 0.54 to 0.79) and ST-segment depression (0.76; 95% CI: 0.67 to 0.85).

BNP. In the derivation cohort, BNP was ≥300 pg/ml in 38 patients (7%), 13 (34%) of whom had a serious outcome or all-cause death. Mean age in those with raised BNP was 82 ± 9 years; 21 patients (55%) had previous hypertension, 15 patients (40%) had previous ischemic heart disease, 12 patients (32%) had previous MI, 12 patients (32%) had known cardiac failure, and 11 patients (29%) had signs of cardiac failure on clinical examination.

In the validation cohort, BNP was ≥300 pg/ml in 40 patients (7%), 16 patients (40%) of whom had a serious outcome or all-cause death. Mean age in those with raised

JACC Vol. 55, No. 8, 2010
February 23, 2010:713–21

Table 2 Summary of Outcome Measures

	Derivation Cohort (n = 529)	Validation Cohort (n = 538)
Primary outcome	40	39
SO	39	35
ACD	7	9
Both SO and ACD	6	5
Obvious diagnosis in ED	17	16
Secondary outcomes		
Cardiovascular SO	20	22
Syncope-related death	3	8

Summary of the main outcome measures in both the derivation and validation cohorts of the ROSE (Risk stratification Of Syncope in the Emergency department) study. The main primary end point was the combination of serious outcome (SO) and all-cause death (ACD) at 1 month after emergency department (ED) presentation. Secondary end points were syncope-related death and cardiovascular death.

BNP was 82 ± 8 years; 23 patients (58%) had previous hypertension, 19 patients (48%) had previous ischemic heart disease, 11 patients (28%) had previous MI, 7 patients (18%) had known cardiac failure, and 12 patients (30%) had signs of cardiac failure on clinical examination.

The BNP was an excellent predictor of serious outcome or all-cause death in the validation cohort. A BNP concentration ≥300 pg/ml alone predicted 16 (41%) of 39 serious outcomes or all-cause deaths, including 8 of 22 (36%) cardiovascular serious outcomes, and 8 of 9 (89%) all-cause deaths missing a patient who died of complications of a hip arthroplasty (99.8% negative predictive value for all-cause death). The area under the ROC curve of BNP with serious outcome or all-cause death was 0.81 (95% CI: 0.74 to 0.88). The areas under the ROC curves of BNP with cardiovascular serious outcome or all cause-death were 0.79 (95% CI: 0.69 to 0.88) and 0.93 (95% CI: 0.85 to 1.00), respectively.

Discussion

We have derived and validated a CDR that is safe and simple to use. The ROSE rule consists of 7 variables easily remembered by the pneumonic "BRACES" (Fig. 2). It potentially avoids 149 unnecessary admissions at the expense of missing 4 more patients with a serious outcome and no deaths for every 1,000 patients presenting with syncope. If incorporated into clinical practice it could potentially save 136,000 admissions and $734 million in hospital stay costs annually in the U.S. (22). A resource-use impact analysis study would be necessary to confirm this.

Syncope is an important problem that cardiologists see on a daily basis in their clinical practices. It is well-established that cardiac causes of syncope are the most serious and are associated with the worst outcome (23). However, at present, it is often unclear whether a patient with syncope needs to be admitted and whether their syncope is likely to be due to a cardiac cause best managed under the care of a cardiologist.

This is the first study to use point-of-care BNP as a novel predictor of outcome in patients presenting with syncope. Increasingly, BNP is being recognized as a marker of future risk and death in a range of cardiovascular disease states (13) and not just heart failure (24). Here we have extended these observations to a broad group of patients presenting with syncope and have demonstrated that it is the single most powerful predictor of adverse outcome, particularly death. Although in the United Kingdom only 5% of EDs currently have point-of-care BNP testing (25), 44% have point-of-care testing facilities (25) and almost all have rapid access to laboratory BNP, because of National Institute of Health and Clinical Excellence recommendations (26).

One possible limitation to the utility of BNP for syncope risk stratification is that it might be identifying patients who are older and who have other evidence of structural heart disease. By contrast, BNP might be a more objective and more specific marker of heart disease than a subjective clinical history or examination.

Many EDs use protocols (25) based on international syncope guidelines (15,16,27–29) in an attempt to ensure all high-risk patients are admitted. Such guidelines can be impractical, cumbersome, and nonspecific, leading to needless admissions. The ideal CDR would be simple and reproducible, admit all patients with serious underlying pathologies, and discharge all low-risk patients. We believe the ROSE rule is currently the closest rule to achieve these aims.

Although caution must be used when interpreting comparison with other CDRs, the performance of the ROSE rule in the validation cohort was compared with the performance of existing syncope CDRs (1,3,5,6) and the short-term risk factors from the recently published STePS (Short-Term Prognosis of Syncope) study (7). These CDRs were unable to avoid admissions without a large unacceptable increase in missed serious outcomes. The only 2 rules that did not miss serious outcomes required admission of many more patients and include admission criteria such as "age over 45" (1). Our study and other recent studies (3,5–7) also suggest

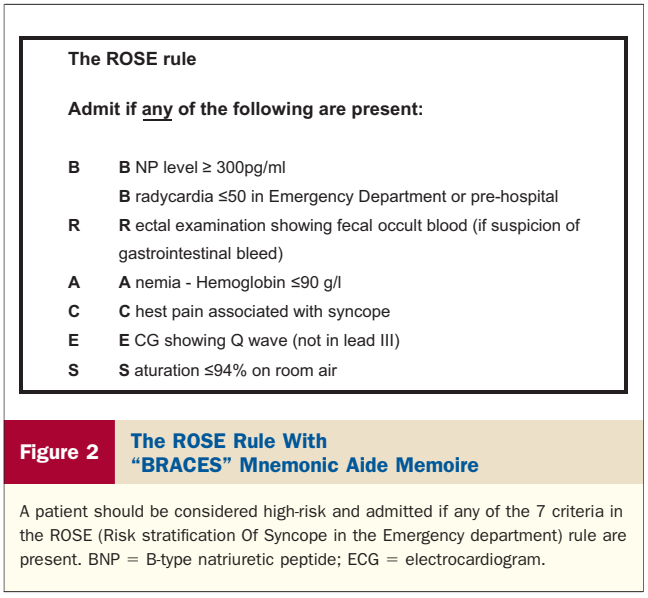

Figure 2 The ROSE Rule With "BRACES" Mnemonic Aide Memoire

A patient should be considered high-risk and admitted if any of the 7 criteria in the ROSE (Risk stratification Of Syncope in the Emergency department) rule are present. BNP = B-type natriuretic peptide; ECG = electrocardiogram.

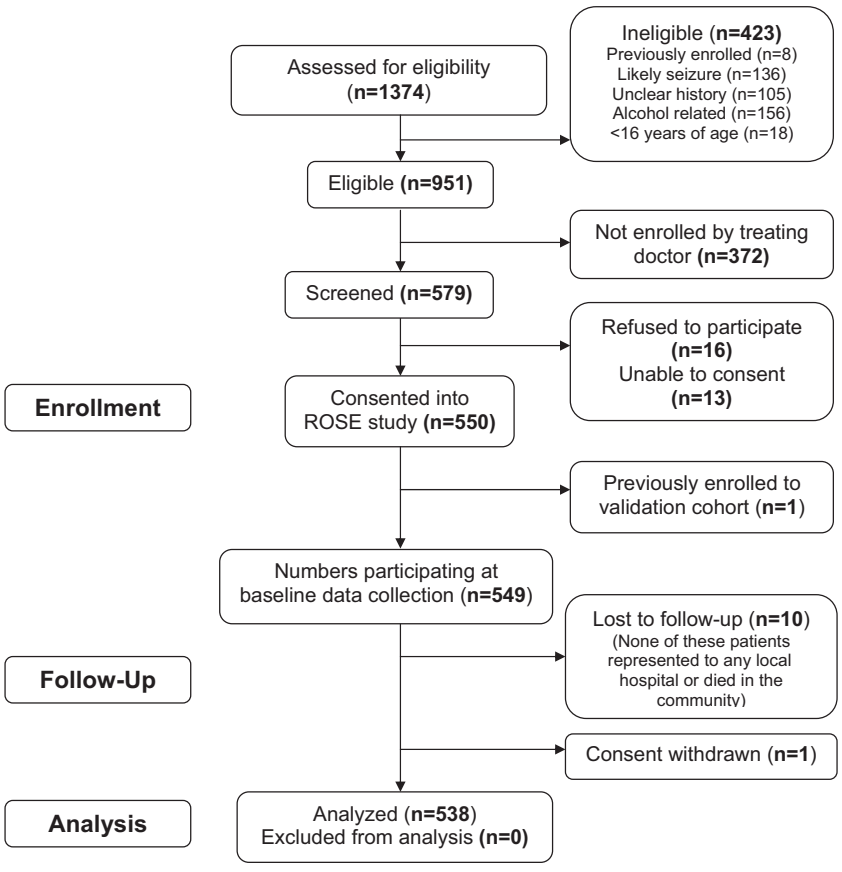

Figure 3 The ROSE Validation STARD Diagram

A STARD flow diagram showing recruitment of patients into the validation cohort of the ROSE study. Abbreviations as in Figure 1.

that risk of serious outcome is less than previously reported (14,23), and most patients do not require admission.

Our rule includes a rectal examination. We are not advocating performing such an examination on all patients presenting with syncope. During both the derivation and validation studies, rectal examination was performed in 13% of patients at the discretion of the treating physician if there was any suspicion of gastrointestinal bleeding. We suggest that this approach is used for the ROSE rule.

Study limitations. As yet it has only been derived and validated in a single United Kingdom center. Recruitment into an external validation study is currently ongoing. Secondly, although saving 149 unnecessary admissions/1,000 patients with no extra deaths, the ROSE rule misses 4 more patients with serious outcome. Although defined as serious due to our rigorous definition, many events were not life-threatening, and the clinical benefit of a large number of prevented admissions potentially outweighs the small number of missed serious outcomes.

Table 3 Comparison of Enrolled and Nonenrolled Patients

	Derivation Cohort			Validation Cohort		
	Enrolled (n = 550)	Not Enrolled (n = 340)	p Value	Enrolled (n = 550)	Not Enrolled (n = 401)	p Value
Mean age, yrs	63.9 ± 21.6	58.2 ± 24.3	0.002*	62.1 ± 22.0	59.2 ± 24.2	0.051*
Male sex	247 (44.9)	141 (41.5)	0.35†	250 (45.5)	169 (42.1)	0.34†
Admitted	254 (46.2)	178 (52.4)	0.09†	287 (52.2)	224 (55.9)	0.29†
Discharged	296 (53.8)	162 (47.6)	0.09†	263 (47.8)	177 (44.1)	0.29†
Death	7 (1.3)	10 (2.9)	0.13†	10 (1.8)	7 (1.7)	1.00†

Values are presented as mean ± SD or n (%). Comparison between enrolled patients and nonenrolled patients in both the derivation and validation cohorts of the ROSE (Risk stratification Of Syncope in the Emergency department) study. Characteristics assessed are mean age, sex, decision to admit or discharge from the emergency department, and death at 1 month after emergency department presentation. *Student *t* test (2-tailed); †chi-square with Yates' continuity correction.

Although the ROSE rule is able to detect high-risk patients, it is not clear whether the identification of risk and consequent admission affects outcome. This would require a large multicenter randomized controlled trial, with a cluster design to avoid contamination, to implement the ROSE rule to determine whether this strategy was effective and safe.

The ROSE predictive criteria including BNP might be markers of poor outcome irrespective of whether it is applied to patients presenting with syncope. This issue could be addressed by comparing outcomes with a control nonsyncopal comparator group. However, the selection, matching, and recruitment of such a comparator group would be challenging, and its absence does not detract from the important clinical question of how to manage patients with an emergency presentation of syncope.

Our CDR was derived with patients presenting with undifferentiated syncope. This was because during our pilot study (21) it became apparent that the definition of an "obvious" diagnosis differs widely between individual clinicians, and in this study, only 42% (33 of 79) of subsequent serious outcomes and deaths were apparent at initial ED assessment. A CDR should only be used in conjunction with physician judgment and after a full history and examination and bedside investigations have been performed. Clearly a CDR is not required when serious pathology is apparent; subarachnoid hemorrhage is an example. We suggest that the ROSE rule should be applied in the acute setting to patients in whom a clear diagnosis is not apparent after initial assessment. The ROSE rule identified 85% (39 of 46) of patients whose subsequent serious outcome or death was not apparent in the ED.

Conclusions

We have derived and validated a rule that has excellent sensitivity and negative predictive value that allows for the identification of high-risk patients with an emergency presentation of syncope. The ROSE rule potentially reduces admission rates by 30% and might perform better than existing CDRs. The BNP seems to be particularly useful in the identification of serious cardiovascular outcomes and all-cause death in such patients. The use of the ROSE CDR and BNP estimation holds major promise and requires further external validation and investigation in this important group of patients.

Acknowledgments

The authors thank the staff in the Emergency Department of the Royal Infirmary of Edinburgh for their help with patient recruitment for this study; Martha Bonney for help with patient follow-up; Robert Lee for help with data cleaning; Jeremy Langrish for ECG reporting; David Caesar for validation cohort end point assignment; and all general practitioners in Lothian for their help with patient follow-up.

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Key Words: biochemistry ■ cardiovascular ■ emergency medicine ■ ischemic heart disease ■ syncope.

APPENDIX

For a table comparing ROSE rule performance with existing clinical decision rules in the validation cohort, please see the online version of this article.