Critical Review Form
Clinical Prediction or Decision Rule

PGY-2

Reed MJ, Newby DE, Coull AJ, Prescott RJ, Jacques KG, Gray AJ. The ROSE (risk stratification of syncope in the emergency department) study. J Am Coll Cardiol. 2010 Feb 23;55(8):713-21.

Objectives: **"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)." (p. 714)**

Methods: This single-center, prospective, observational study was conducted at the emergency department of the Royal Infirmary of Edinburgh in Scotland. A derivation cohort of patients was enrolled between March 1, 2007 and October 27, 2007, and a validation cohort was enrolled between October 27, 2007 and July 22, 2008. Patients aged 16 years or older presenting with acute syncope were eligible for enrollment. Exclusion criteria included lack of consent, lack of a relative to consent, persistent neurologic deficit concerning for stroke, previous enrollment in the study, collapse related to alcohol consumption, hypoglycemia, trauma, or seizure activity with > 15 minutes of post-ictal confusion. Data was collected using a standardized data collection form. All patients underwent BNP testing, but otherwise testing and disposition (admission, referred for outpatient investigation, discharged) were at the discretion of the treating physician.

The primary endpoint was serious outcome and all-cause death at one month. Serious outcome included: acute myocardial infarction, life-threatening arrhythmia, implantation of a pacemaker or defibrillator, pulmonary embolus, cerebrovascular accident, intracranial or subarachnoid hemorrhage, hemorrhage requiring a blood transfusion of at least 2 units, or need for acute surgical procedure or endoscopic intervention. Secondary outcomes included serious cardiovascular outcome (MI, arrhythmia, pacemaker/defibrillator implantation, or cardiac procedure) and syncope-related death. Patient follow-up at one month occurred by review of the electronic patient record system and direct contact with the patient or general practitioner. End-point assignment was conducted by two independent investigators, with disagreements resolved by three other investigators. End-points were assigned prior to development of the ROSE clinical decision rule.

Multiple logistic regression analysis was used to determine independent predictors of a serious outcome. A decision tree analysis was then used to identify those variables from logistic regression that, when combined, optimized the sensitivity of the resulting clinical decision rule.

Out of 890 potentially eligible patients presenting during the derivation enrollment period, 575 (64.6%) were screened and 550 were enrolled. After excluding 19 patients lost to follow-up and 2 patients previously enrolled, 529 patients remained in the derivation cohort. Out of 951 potentially eligible patients presenting during the validation enrollment period, 579 (60.9%) were screened. After excluding 29 patients who did not or were unable to consent, 550 patients remained in the validation cohort. Forty patients in the derivation cohort and 39 in the validation cohort had a primary outcome.

Guide		Comments
I.	***Is this a newly derived instrument* (Level IV)?**	
A.	Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).	No. Validation was performed on a separate, prospectively enrolled cohort of patients presenting to the ED with syncope.
II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	
1a	Were all important predictors included in the derivation process?	Likely yes. The authors did not provide a detailed list of factors used in the derivation process. They do report using "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." (p. 714) It is unlikely that any highly important predictors were not included.
1b	Were all important predictors present in significant proportion of the study population?	Uncertain. The authors did not provide a list of predictors used or a table detailing the proportion of patients positive for each predictor.
1c	Does the rule make clinical sense?	Somewhat. The presence of some predictors included in the rule would raise the concern for a more serious etiology of syncope, such as bradycardia, signs of GI bleeding, anemia, chest pain, and hypoxia. On the other hand, the presence of Q-waves on ECG seems less relevant; while the presence of a prior MI may provide an arrhythmogenic focus or suggest a diagnosis of heart failure, Q-waves are not specific for either of these things. The use of

		BNP to predict adverse outcomes following syncope has been studied, but not well-validated, and yet it seems the authors had a specific desire to include this in their prediction rule, regardless of how well it independently predicted a serious outcome.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	The validation cohort in this study was enrolled at a single study site, and further validation at a more heterogeneous population of patients from a variety of study sites shoulder be performed. This is therefore a Level III clinical decision rule and requires further validation.
3	*How well did the validation study meet the following criteria?*	
3a	Did the patients represent a wide spectrum of severity of disease?	Yes. All patients presenting to the ED with acute syncope were eligible for enrollment, which should result in a fairly broad spectrum of disease processes (including cardiogenic syncope, vasovagal syncope, and orthostasis). Nearly half were admitted and half sent home. A serious outcome occurred in 7.6% of the derivation group and 7% of the validation group.
3b	Was there a blinded assessment of the gold standard?	No. While the authors do note that "All derivation group end points were assigned before development of the ROSE (Risk stratification Of Syncope in the Emergency department) CDR" (p. 714), it is not specifically stated whether the investigators who assigned the end points were blinded to BNP results specifically (and seems likely that they were not) (ascertainment bias). It is possible, though not likely, that the results of BNP testing influenced end point assignment. Additionally, there is no specific gold standard for the outcomes in this study. End point assignment was performed by chart review and one-month follow-up and is potentially subjective in nature.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	No. The rule was derived specifically to fit the outcomes, the objective being to ensure a highly sensitive clinical decision rule. The predictor variables were specifically evaluated to determine how many patients with the outcome were captured, and those capturing the largest number of outcomes were then included in the rule regardless of how clinically meaningful each predictor seemed at

		face value.
3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	Uncertain. While there is no true gold standard to diagnose the etiology of syncope, it is possible that the individual predictors, including BNP, influenced the decision to perform additional testing such as ECHOcardiography, stress testing, cardiac monitoring, and cardiac catheterization. As stated before, the clinical decision rule was developed after derivation group end points were assigned, and hence could not have influence testing or end point assignment.
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	The final components of the ROSE rule were: **B**NP level ≥ 300 pg/mL **B**radycardia ≤ 50 in ED or pre-hospital **R**ectal examination with fecal occult blood **A**nemia (hemoglobin ≤ 90 g/L) **C**hest pain associated with syncope **E**CG showing Q-wave (not in lead III) **S**aturation ≤ 94% on room air • In the derivation cohort, the ROSE rule had a sensitivity of 92.5%, a specificity of 73.8%, a PPV of 22.4%, a NPV of 99.2%, a LR+ of 3.5, and LR- of 0.1. o The area under the ROC curve was 0.83 (95% CI 0.78 to 0.89). • In the validation cohort, the ROSE rule had a sensitivity of 87.2%, a specificity of 65.5%, a PPV of 16.5%, a NPV of 98.5%, a LR+ of 2.5, and LR- of 0.2. o The area under the ROC curve was 0.76 (95% CI 0.70 to 0.83).
III.	**Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:**	
1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	Poorly. • Patient selection was fairly non-biased given that all patients presenting to the ED with syncope were eligible; unfortunately, they enrolled a convenience sample rather than consecutive patients (~40% of eligible patients were not enrolled). • There was no attempt to blind investigators to results and outcomes as the rule was being derived; instead, the

		authors used decision tree analysis to select predictors that encompassed all of the serious outcomes in the derivation group. • Ten patients (~2%) in the validation cohort were lost to follow-up and hence excluded from analysis. • Only 13% of patients in the study underwent rectal exam with fecal occult blood testing.
2	What was the impact on clinician behavior and patient-important outcomes?	Not assessed. The authors did not perform an impact analysis. Based on their results, they surmised that the rule would have missed 3 patients with serious outcomes and prevented 87 admissions in the derivation cohort. In the validation cohort, the rule would have missed 5 patients with serious outcomes, and may have prevented 80 "unnecessary" admissions.

Limitations:

1. **Does not appear that consecutive patients were enrolled, but rather that this was a convenience sample. Around 35% and 40% of eligible patients were not approached for enrollment in the derivation and validation cohorts, respectively.**

2. **It is not specifically stated whether the investigators who assigned the end points were blinded to BNP results specifically (and seems likely that they were not) (ascertainment bias).**

3. **This study was derived and validated at a single center in the UK, and is currently a Level III clinical decision rule and requires further validation at additional clinical sites.**

4. **Only 13% of patients in the study underwent rectal exam with fecal occult blood testing.**

5. **While the authors surmise that use of this rule would reduce unnecessary admissions, no actual impact analysis was performed to substantiate this. Additionally, the rule did not perform all that well in validation, missing 12.8% of the serious outcomes with a LR+ of 2.5 and LR- of 0.2.**

Bottom Line:

This prospective study was designed to derive and then validate a clinical decision rule to predict 1-month serious outcomes among patients presenting to the ED with syncope. The authors derived a rule using BNP values and 6 other predictors; in validation, the rule missed 12.8% of all serious outcomes and had a very poor positive

likelhood ratio (2.5) and modestly useful negative likelihood ratio (0.2). Given the poor sensitivity and modest LR- of this CDR, it would likely be of limited clinical utility even if it were further validated.