Accuracy and Quality of Clinical Decision Rules for Syncope in the Emergency Department: A Systematic Review and Meta-analysis

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Study objective: We assess the methodological quality and prognostic accuracy of clinical decision rules in emergency department (ED) syncope patients.

Methods: We searched 6 electronic databases, reviewed reference lists of included studies, and contacted content experts to identify articles for review. Studies that derived or validated clinical decision rules in ED syncope patients were included. Two reviewers independently screened records for relevance, selected studies for inclusion, assessed study quality, and abstracted data. Random-effects meta-analysis was used to pool diagnostic performance estimates across studies that derived or validated the same clinical decision rule. Between-study heterogeneity was assessed with the I^2 statistic, and subgroup hypotheses were tested with a test of interaction.

Results: We identified 18 eligible studies. Deficiencies in outcome (blinding) and interrater reliability assessment were the most common methodological weaknesses. Meta-analysis of the San Francisco Syncope Rule (sensitivity 86% [95% confidence interval {CI} 83% to 89%]; specificity 49% [95% CI 48% to 51%]) and the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score (sensitivity 95% [95% CI 88% to 98%]; specificity 31% [95% CI 29% to 34%]). Subgroup analysis identified study design (prospective, diagnostic odds ratio 8.82 [95% CI 3.5 to 22] versus retrospective, diagnostic odds ratio 2.45 [95% CI 0.96 to 6.21]) and ECG determination (by evaluating physician, diagnostic odds ratio 25.5 [95% CI 4.41 to 148] versus researcher or cardiologist, diagnostic odds ratio 4 [95% CI 2.15 to 7.55]) as potential explanations for the variability in San Francisco Syncope Rule performance.

Conclusion: The methodological quality and prognostic accuracy of clinical decision rules for syncope are limited. Differences in study design and ECG interpretation may account for the variable prognostic performance of the San Francisco Syncope Rule when validated in different practice settings. [Ann Emerg Med. 2010;56:362-373.]

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INTRODUCTION

Syncope is a symptom of cerebral hypoperfusion[1] and is defined as a short, sudden, self-terminating episode of transient loss of consciousness with failure to maintain postural tone.[1,2] In the United States, it accounts for 0.6% of hospital admissions[3] and up to 1.4% of all emergency department (ED) visits.[4-8]

Patients with syncope who present to the ED can be classified as "stable" or "unstable," depending on their initial presentation (eg, ongoing chest pain, upper gastrointestinal bleeding), vital signs (eg, hypotension, hypoxia), or ECG abnormalities (eg, ischemic changes).[9] Unstable syncope patients represent up to 70% of serious clinical events (myocardial infarction, arrhythmias, hemorrhage) in syncope patients who present to the ED.[5,10,11]

On the other hand, the evaluation and diagnosis of stable ED patients with syncope is more challenging. Most patients are well-appearing and asymptomatic on arrival,[12] and there are often no witnesses to the event. Emergency physicians are often unable to obtain a detailed and accurate history of the event. Finally, there are myriad possible causes, from benign to life threatening, that may present as syncope. The concern for occult myocardial infarction and transient unidentified arrhythmias in "stable" patients with syncope may lead to

Editor's Capsule Summary

What is already known on this topic

Prediction rules have been proposed to assist in the identification of syncope patients at low risk for poor short-term outcomes.

What question this study addressed

The authors performed a systematic review that included a meta-analysis of 2 syncope prediction rules for which multiple studies had been published.

What this study adds to our knowledge

Performance of the rules was variable. Outcome rates in the low-risk groups ranged from 2% to 36% and 5% to 13% in the San Francisco and the Osservatorio Epidemiologico sulla Sincope nel Lazio rules, respectively.

How this is relevant to clinical practice

Clinicians should not solely rely on a prediction rule in deciding on the disposition of emergency department patients with syncope.

hospitalization, with no clear effect on clinical outcome.[2] Evaluation and management of patients with syncope represent a significant economic burden. Between 2000 and 2005, the cost of syncope admissions exceeded $10 billion, with a median cost of hospitalization of $8,579.[3]

Time constraints and lack of available diagnostic ancillary studies for evaluation of syncope in the ED make determining the cause and prognosticating the short-term outcome a difficult task. The reported diagnostic yield of the ED evaluation is extremely variable among studies (20% to 70%).[13-16] Thus, analogous to the evaluation of patients with chest pain,[2] the focus of the ED assessment has shifted from diagnosis to risk stratification, according to clinical factors.[17]

Clinical decision rules are tools designed to assist clinicians in making decisions at the bedside. They are derived from original research and incorporate important predictors of outcome from the history, physical examination, and basic diagnostic tests. Clinical decision rules can be used to risk-stratify patients, using the probability of an adverse outcome to inform the course of action, including the need for further testing or observation.[18,19] Investigators have developed several clinical decision tools and risk scores to predict short- and long-term adverse outcomes in ED syncope patients. The primary purpose of these prediction rules is to aid clinical decisionmaking and to safely determine patient disposition.

In this review, we sought to assess the methodological quality and prognostic accuracy of studies that derived or validated clinical decision rules or risk scores that predict adverse outcomes in adult patients presenting to the ED with syncope.

MATERIALS AND METHODS

The report of this systematic review and meta-analysis is consistent with recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses,[20] as applicable to diagnostic accuracy reviews. A protocol was developed with input from methodologists with expertise in systematic reviews (M.H.M., V.M.M.) and a content expert (W.W.D.) and is available on request.

Study Design

An expert reference librarian (P.J.E.) designed and conducted a comprehensive literature search, with input from the lead author (L.A.S.). The search strategy incorporating medical subject headings and key words related to clinical prediction rules (clinical prediction guides, decision support techniques, algorithms, multivariate analyses, logistic models, risk assessment) and syncope (fainting, loss of consciousness, drop attack, near syncope). We searched the following databases: MEDLINE (1966 to November 2009), EMBASE (1988 to November 2009), CINAHL, Web of Science (1993 to 2009), Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, and the Database of Reviews of Effectiveness. No language restrictions were applied to the search strategy. The MEDLINE (Ovid interface) search strategy is displayed in Appendix E1 (available online at http://www.annemergmed.com).

Abstracts from the American College of Emergency Physicians, American Academy of Emergency Medicine, and the Society for Academic Emergency Medicine were hand searched from 2007 to 2009. Experts in syncope and clinical decision rule development were consulted for additional published or unpublished reports. We also reviewed the bibliographies of all retrieved articles to identify potentially relevant articles not identified in the electronic search strategy.

The following inclusion criteria were applied according to published methodological standards for clinical prediction rules:[21] (1) prospectively or retrospectively derived or validated clinical decision rules or risk scores that predict subsequent adverse events in patients with syncope; (2) patients presenting with syncope or near syncope to the ED (syncope was defined as a sudden transient loss of consciousness, with loss of postural tone that is brief and self-limiting and resolves without medical intervention);[1,2] (3) based on original research; and (4) inclusion of 3 or more variables from the history, physical examination, and basic diagnostic tests. To conduct a more informative review, we did not exclude studies based on the timing of outcome assessment. Clinical practice guidelines and editorials were excluded. They were, however, used as potential bibliographic sources of eligible primary studies. In view of the inconsistent definition of syncope throughout the medical literature,[22] we excluded studies including patients with other causes of transient loss of consciousness such as seizures, vertigo, hypoglycemia, dizziness, head trauma, coma, shock, and other states of altered mental status. Studies that enrolled patients

Table 1. Hierarchy of evidence for clinical decision rules. Printed with permission of Thomas McGinn.

Level 1	Rules that can be used in a wide variety of settings with confidence that they can change clinical behavior and improve patient outcomes	At least 1 prospective validation in a different population and 1 impact analysis, demonstrating change in clinician behavior with beneficial consequences
Level 2	Rules that can be used in various settings with confidence in their accuracy	Demonstrated accuracy in either 1 large prospective study including a broad spectrum of patients and clinicians or validated in several smaller settings that differed from one another
Level 3	Rules that clinicians may consider using with caution and only if patients in the study are similar to those in the clinician's clinical setting	Validated in 1 narrow prospective sample
Level 4	Rules that need further evaluation before they can be applied in the clinical setting	Derived but not validated or validated in split samples, large retrospective databases, or by statistical techniques

outside of the ED (ie, hospital ward or outpatient facilities) were excluded.

Two reviewers (L.A.S. and M.F.B.) individually screened all titles and abstracts identified from the search strategy (phase I). Selection was based on potential relevance to the review and according to the predetermined inclusion and exclusion criteria. Reviewers were not blinded to the names of the authors, institutions, journal of publication, or results. Full articles were obtained for all titles and abstracts considered to be potentially relevant by at least one reviewer.

Two reviewers (L.A.S. and M.F.B.) working independently assessed the full-text articles for eligibility (phase II). Disagreements were resolved by consensus or by consulting a third coinvestigator (E.P.H.). We calculated chance-adjusted agreement for full-text inclusion by using κ statistics with 95% confidence intervals (CIs).

Quality assessment of the clinical decision rules and risk scores was performed at the level of the rule itself and at the level of each study. The rules were classified according to a hierarchy of evidence for clinical decision rules (Table 1).[23] Each rule was assigned a level (1 to 4) according to the strength of evidence. The individual studies were appraised with methodological standards for the development of clinical decision rules in emergency medicine.[21] Answers were dichotomized as "yes" and "no/unclear." Two reviewers (L.A.S. and M.F.B.) independently evaluated the quality of each included study, and chance-adjusted agreement was determined (κ, 95% CI).

Two authors (L.A.S. and M.F.B.) independently abstracted data with a standardized data abstraction form. We abstracted the following data from each article: year of publication, setting, objective, predictor variables included, population characteristics (age, sex, medical history, and admission rate), outcome measures, prevalence of adverse outcomes, and duration of follow-up. We also abstracted data needed for 2×2 contingency table analysis.

We contacted the corresponding author and last author for unclear or missing data and confirmed the correctness of the email address by a MEDLINE search of recent articles. If data were presented as a linear risk score, the author was contacted to provide enough information to convert it to a binary risk system. If a study had insufficient data for meta-analysis and no response was obtained after we sent 2 e-mails, made a telephone call, and wrote to the corresponding author and last author, the study was excluded from the quantitative synthesis. Data were entered into Microsoft Office Excel 2003 (Microsoft, Redmond, WA).

Primary Data Analysis

Because of the anticipated clinical heterogeneity between available clinical decision rules (different predictor variables, length of follow-up, and outcome measures), meta-analysis was restricted a priori to studies that derived or validated the same clinical decision rule. Diagnostic test characteristics were calculated with publicly available Meta-DiSc statistical software (Unit of Clinical Biostatistics of the Ramon y Cajal Hospital).[24] Using random-effects meta-analyses, we pooled the sensitivities, specificities, likelihood ratios, and diagnostic odds ratios and estimated 95% CIs for the outcomes of clinical decision rules with 2 or more studies. The diagnostic odds ratio of a test describes the ratio of the odds of a positive result in patients with disease compared with patients without disease.[25] Inconsistency among studies was assessed with the I^2 statistic, which indicates the proportion of variability in study estimates because of between-study heterogeneity. I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively.[26]

Sensitivity Analyses

We performed a priori subgroup analyses to explain potential heterogeneity among included studies. We hypothesized that heterogeneity in prognostic performance could arise from differences in study design, outcome period, ECG definition, ECG determination, and inclusion of unstable syncope patients. We tested these hypotheses with a test for interaction.[27] Sensitivity analysis were conducted with a bivariate random-effects model in which the sensitivities and specificities were simultaneously analyzed to derive pooled likelihood ratios, rather than pooling the likelihood ratios directly across studies.[28]

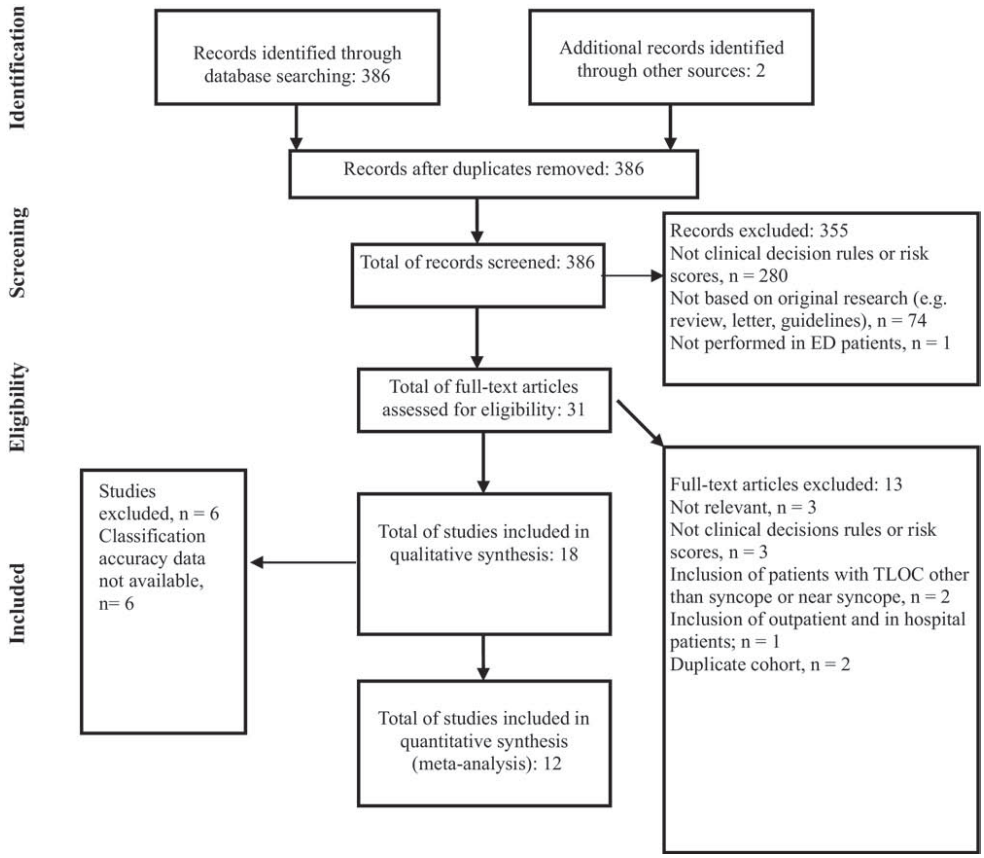

Figure 1. Flow diagram of study selection process.

RESULTS

The electronic search strategy identified 388 records (Figure 1). Two articles (accepted for publication) were obtained from the primary authors.[29,30] Two duplicate records were removed. Three hundred fifty-five records did not meet inclusion criteria and were excluded. The full text of 31 potentially eligible articles was obtained for review. Full-text review identified 18 studies meeting inclusion criteria (κ=0.84, 95% CI 62 to 100), representing 9 different clinical decision rules and risk scores. Sufficient data to construct a 2×2 contingency table were directly available from the article in 10 studies,[5-7,10,31,33,34,36,37] and additional data were provided by the authors for 2 studies.[32,36] The 12 studies included in the quantitative analysis represent 5 different clinical prediction tools and risk scores.

Characteristics of the included studies are shown in Tables 2 and 3. The 18 studies comprised a total of 10,994 patients. Nine studies were conducted in the United States,[5-7,10,34,36-38] 1 in Canada,[35] 3 in Italy,[29,32,39] 2 in Australia,[33,40] 2 in the United Kingdom,[30,41] and 1 in Switzerland.[16] There were 5 derivation studies,[6,34,36,37,39] 9 validation studies,[5,7,10,29,31,33,35,40,41] and 4 derivation/validation studies.[16,30,32,38] Three studies validated more than one rule.[29,30,41] Overall, there were 5,708 patients from derivation studies and 5,286 patients from validation studies. Thirteen studies assessed outcomes within 30 days of the index visit[5-7,10,29-31,33-37,41] 1 study predicted outcomes within 6 months,[40] 2 studies predicted outcomes within 1 year,[32,38] and 1 study did not specify the duration of follow-up.[16]

There were 4,510 patients (41%) admitted to the hospital. There were 1,437 (13%) patients who had an adverse outcome, including 832 (15%) in the derivation cohorts and 605 (11%) in the validation cohorts. Three hundred eighty-four patients (3%) experienced an adverse outcome that was identified after the initial ED evaluation. In the San Francisco Syncope Rule studies (n=5,468) there were 522 (10%) adverse outcomes, and in the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score studies, there were 148 (9%) outcomes. The mean age of patients in the included studies ranged from 50 to 79 years. Seven studies included patients younger than 18 years.[5,6,30,32,35,38,41] The weighted mean age of the 11,032 patients included in the qualitative analysis was 62 years, and 5,908 (55%) were women. Of the studies that reported elements from the medical history, a total of 42% patients had hypertension, 23% coronary artery disease, 8% congestive heart failure, and 12% diabetes mellitus.

The hierarchy of evidence for clinical decision rules[23] is described in Table 1. Of the 9 clinical decision rules and risk scores included, none were classified as level 1 evidence. Two clinical decision rules[6,32] met criteria for level 2 evidence, and the remaining clinical decision rules or risk scores were

Table 2. General study information (n=18).

Study	Population	Predictor Variables Included	Outcome Measures	Outcome Period
Cardiac ischemia in syncope				
Georgeson et al, 1992[37]	251 ED patients (men >30 y, women >40 y) with syncope and no chest pain but complaints consistent with ACS, from six hospitals in the US.	ECG, arm, neck, shoulder, or throat pain, Hx of exercise-induced angina and rales	Acute cardiac ischemia	48 h
Risk stratification of syncope				
Martin et al, 1997[38]*	252 ED patients with syncope from a single academic institution in the United States for derivation; 374 ED patients with syncope for internal validation (same institution)	ECG, Hx of ventricular arrhythmia, Hx of CHF and age >45 y	Arrhythmia or 1-y mortality	1 y
Risk score to predict arrhythmias in unexplained syncope				
Sarasin et al, 2003[16]*	175 adult ED patients with unexplained syncope from a single academic hospital in Switzerland for derivation; 267 adult ED patients with unexplained syncope from tertiary care hospital in the United States for validation	ECG, Hx of CHF and age >65 y	Cardiac arrhythmias	Not specified
OESIL Risk Score				
Colivicci et al, 2003[32]*	270 ED patients (>12 y) with syncope from 6 community hospitals in Italy; 328 ED syncope patients from 2 hospitals in Italy for validation	ECG, age >65 y, Hx of cardiac dz, and no prodrome	Death from any cause	12 mo
OESIL validation: Hing and Harris, 2005[40]	100 adult ED patients with syncope from a single tertiary referral hospital in Australia	ECG, age >65 y, Hx of cardiac dz, and no prodrome	Adverse cardiac outcome: ischemic heart disease, arrhythmias, and cardiac death	3–6 mo
ROSE pilot study (OESIL, SFSR): Reed et al, 2007[41]	99 ED patients (≥16 y) with syncope from a single hospital in the United Kingdom	SFSR: ECG, dyspnea, systolic BP <90, Hct <30%, and Hx of CHF: OESIL: ECG, age >65 y, Hx of cardiac dz, and no prodrome	Death, AMI, arrhythmias, PE, hemorrhage, stroke, subarachnoid hemorrhage, acute procedure	1 wk, 1 mo, and 3 mo
SFSR				
SFSR derivation: Quinn et al, 2004[6]	684 ED patients with syncope or near syncope from a single large academic hospital in the United States	ECG, dyspnea, Hct <30%, systolic BP <90, and Hx of CHF	Death, MI, arrhythmia, PE, stroke, subarachnoid hemorrhage, hemorrhage, ED return visit and hospitalization	7 days
SFSR validation: Quinn et al, 2006[5]	791 ED patients with syncope or near syncope from a single large academic hospital in the United States	ECG, dyspnea, Hct <30%, systolic BP <90, and Hx of CHF	SFSR outcome measures	30 days
SFSR external validation: Sun et al, 2007[10]	477 adult ED patients with syncope or near syncope from a single urban academic hospital in the United States	ECG, dyspnea, Hct <30%, systolic BP <90, and Hx of CHF	SFSR outcome measures	7 days
SFSR validation: Cosgriff et al, 2007[33]	89 adult ED patients with syncope or near syncope from a teaching hospital in Australia	ECG, dyspnea, Hct <30%, systolic BP <90, and Hx of CHF	SFSR outcome measures	7 days
SFSR external validation: Birnbaum et al, 2008[31]	713 ED adult patients with syncope or near syncope from a single urban academic hospital	ECG, dyspnea, Hct <30%, systolic BP <90, and Hx of CHF	SFSR outcome measures	7 days

Table 2. Continued.

Study	Population	Predictor Variables Included	Outcome Measures	Outcome Period
SFSR application: Schladenhaufen et al, 2008[7]	517 elderly ED patients (≥65 y) with syncope or near syncope from a community teaching hospital	ECG, dyspnea, Hct <30%, systolic BP <90, and Hx of CHF	SFSR outcome measures	7 days
SFSR external validation: Thiruganasambandamoorthy et al, 2010[35]	505 ED patients (≥16 y) with syncope from a single center urban hospital in Canada	ECG, dyspnea, Hct <30%, systolic BP <90, and Hx of CHF	SFSR outcome measures	30 days
SFSR and OESIL validation: Dipaola et al (in press)[29]	488 adult ED patients with syncope within previous 48 h from 2 general hospitals in Italy	SFSR: ECG, dyspnea, systolic BP <90, Hct <30%, and Hx of CHF: OESIL: ECG, age >65 y, Hx of cardiac dz, and no prodrome	Death, need for major therapeutic procedures and early readmission to the hospital	10 days
Boston Syncope Rule				
Boston Syncope Rule validation: Grossman et al, 2007[34]	293 adult ED patients with syncope from a large urban teaching hospital in the United States	ACS sign/symptoms, conduction disease, worrisome cardiac Hx, valvular heart disease, Hx of familial sudden death, abnormal vital signs, volume depletion, primary CNS event	Critical intervention or an adverse outcome	30 days
STePS				
STePS derivation: Costantino et al, 2008[39]	670 adult ED with syncope within previous 48 h from 4 general hospitals in Italy	Short term: ECG, concomitant trauma, no prodrome and male sex; long term: age >65 y, Hx of neoplastic procedures, stroke, SHD, and VA	Death, need for major therapeutic procedures and early readmission to the hospital	10 days
Syncope Risk Score				
Syncope Risk Score derivation: Sun et al, 2009[36]	2,584 older adult ED patients with syncope or near syncope from a regional managed care system of 3 hospitals in the United States	ECG, age>90 y, male, Hx of arrhythmia, triage systolic BP >160, and increased troponin I level	MI, arrhythmia, pacemaker or cardiac defibrillator placement, PE, stroke, hemorrhage, or acute procedure	30 days
ROSE Study				
ROSE derivation and validation: Reed et al, 2010[30]*	529 ED patients (≥16 y) with syncope from a single large tertiary hospital in the United Kingdom for the derivation; 538 ED patients (≥16 y) for internal validation	ECG, BNP ≥300, bradycardia ≤50, Hgb ≤9, chest pain, O sat ≤94%, and + stool for occult blood test	Death, AMI, arrhythmias, PE, hemorrhage, stroke, subarachnoid hemorrhage, acute procedure	1 mo

ACS, Acute coronary syndrome; *Hx*, medical history; *CHF*, congestive heart failure; *dz*, disease; *OESIL*, Osservatorio Epidemiologico sulla Sincope nel Lazio; *AMI*, acute myocardial infarction; *ROSE*, Risk Stratification of Syncope in the Emergency Department; *SFSR*, San Francisco Syncope Rule; *BP*, blood pressure; *PE*, pulmonary embolism; *MI*, myocardial infarction; *CNS*, central nervous system; *STePS*, Short-Term Prognosis of Syncope Study; *SHD*, structural heart disease; *VA*, ventricular arrhythmias; *BNP*, b-type natriuretic peptide; *Hgb*, hemoglobin; *O sat*, oxygen saturation.
*Derivation and validation cohorts; adult, older than 18 years.

derived but not validated[36,37,39] or applied to populations without clinicians using the rule[16,30,34,38] and constitute level 4 evidence.

The methodological quality of the derivation studies is shown in Figure 2. Interobserver reliability for the methodological quality of derivation studies was 92.5% (95% CI 84% to 100%). Blinded assessment of outcome was reported in 5 studies.[6,30,34,36,37] Explicit assessment of the reliability of the predictor variables (ie, κ statistics) was reported in 2 studies.[6,36] Three studies justified the sample size according to mathematical techniques and reported calculation of the sample size.[6,30,36]

The methodological quality of the validation studies is shown in Figure 3. Interobserver reliability for the validation studies was 84.9% (95% CI 76% to 94%). All validations except two[7,35] prospectively validated one or more clinical decision rules. One study reported having a training session for the physicians using the rule.[10] None of the studies accurately applied the clinical decision rule in their validation.

Table 3. Study characteristics (n=18).

Study (n)	Definition of Syncope	Adverse Outcomes, %	Adverse Outcomes Identified Outside ED, %	Admitted, %
Georgeson et al, 1992[37] (251)	Sudden TLOC with loss of postural tone; included patients with near syncope and found on floor	7	NS	70
Martin et al, 1997[38]* (252; 374)	Sudden TLOC with loss of postural tone and spontaneous recovery	26; 13	NS	NS
Sarasin et al, 2003[16]* (175; 267)	Sudden TLOC with loss of postural tone and spontaneous recovery	17; 18	NS	NS
Colivicci et al, 2003[32]* (270; 328)	Sudden TLOC with loss of postural tone and spontaneous recovery	11; 9	NS	NS
Hing and Harris 2005[40] (100)	Brief TLOC	23	NS	45
Reed et al, 2007[41] (99)	NS	11	NS	44
Quinn et al, 2004[6] (684)	TLOC with return to baseline neurologic function	12	NS	55
Quinn et al, 2006[5] (791)	TLOC with return to baseline neurologic function	14	7	59
Sun et al, 2007[10] (477)	Sudden TLOC	12	3	51
Cosgriff et al, 2007[33] (89)	TLOC with return to baseline neurologic function	11	NS	39
Birnbaum et al, 2008[31] (713)	Sudden TLOC	9	NS	83
Schladenhaufen et al, 2008[7] (517)	NS	19	NS	60
Thiruganasambandamoorthy et al, 2009[35] (676)	Sudden TLOC with prompt and complete recovery	10	5	12
Dipaola et al (in press)[29] (488)	Sudden TLOC with loss of postural tone and spontaneous recovery	5	5	34
Grossman et al, 2007[34] (384)	Sudden and brief TLOC with loss of postural tone and spontaneous recovery	23	4	69
Costantino et al, 2008[39] (670)	Sudden TLOC with loss of postural tone and spontaneous recovery	NS	6	33
Sun et al, 2009[36] (2,584)	Sudden TLOC	18	7	43
Reed et al, 2010[30] (550; 550)*	Sudden and brief TLOC with loss of postural tone and spontaneous recovery.	8; 7	4; 2	48, 53

TLOC, Transient loss of consciousness; *NS*, not specified.
*Derivation and validation studies.

The diagnostic accuracy of each study is shown in Table 4, as is the meta-analysis of each of the 5 included clinical decision rules.

The subgroup analyses of studies evaluating the San Francisco Syncope Rule (1 derivation and 7 validations) and the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score (1 derivation and 2 validations) are shown in Table 5. Sensitivity analysis conducted with a bivariate random-effect model gave results consistent with those of the original model, and study conclusions seemed robust to the choice of model (for example, bivariate estimates of the diagnostic accuracy of the San Francisco Syncope Rule show a sensitivity of 87% [95% CI 79% to 92%] and specificity of 48% [95% CI 38% to 59%]).

LIMITATIONS

There were a number of studies that were omitted from our meta-analysis because of incomplete prognostic accuracy data, which increases the risk of selection bias and may have affected our summary estimates of prognostic performance. A key limitation of this meta-analysis at the level of the outcome is the diversity of clinical and methodological aspects across studies. In this review, we pooled all studies from the same clinical decision rule regardless of study design, duration of follow-up, or rigor of predictor variable assessment. Pooling across studies with a high degree of clinical and statistical heterogeneity decreases the quality of the synthesized evidence. To identify potential sources of heterogeneity, we examined subgroups to look for homogeneous populations and conducted meta-regression analysis to assess whether differences in study characteristics explain variation in findings.

At the study level, there were several limitations. The absence of an appropriate reference test or criterion standard made the final diagnosis provided to a syncope patient difficult to confirm and subject to variability.[2] This, combined with the differing syncope definitions used across studies, could lead to over- or underestimation of the prognostic accuracy of the included clinical decision rules.

Forty-four percent of the derived rules[16,32,38,39] did not report blinding outcome assessors, representing a potential source of observation bias. The use of clinical decision rules in different populations or subgroups than those originally intended could have resulted in spectrum bias.

DISCUSSION

Our review has several strengths. The meta-analyses reported here combine data across studies from the same clinical decision rule to estimate their prognostic accuracy with greater precision than is possible in a single study. We took steps to minimize the potential of publication and selection bias by conducting a

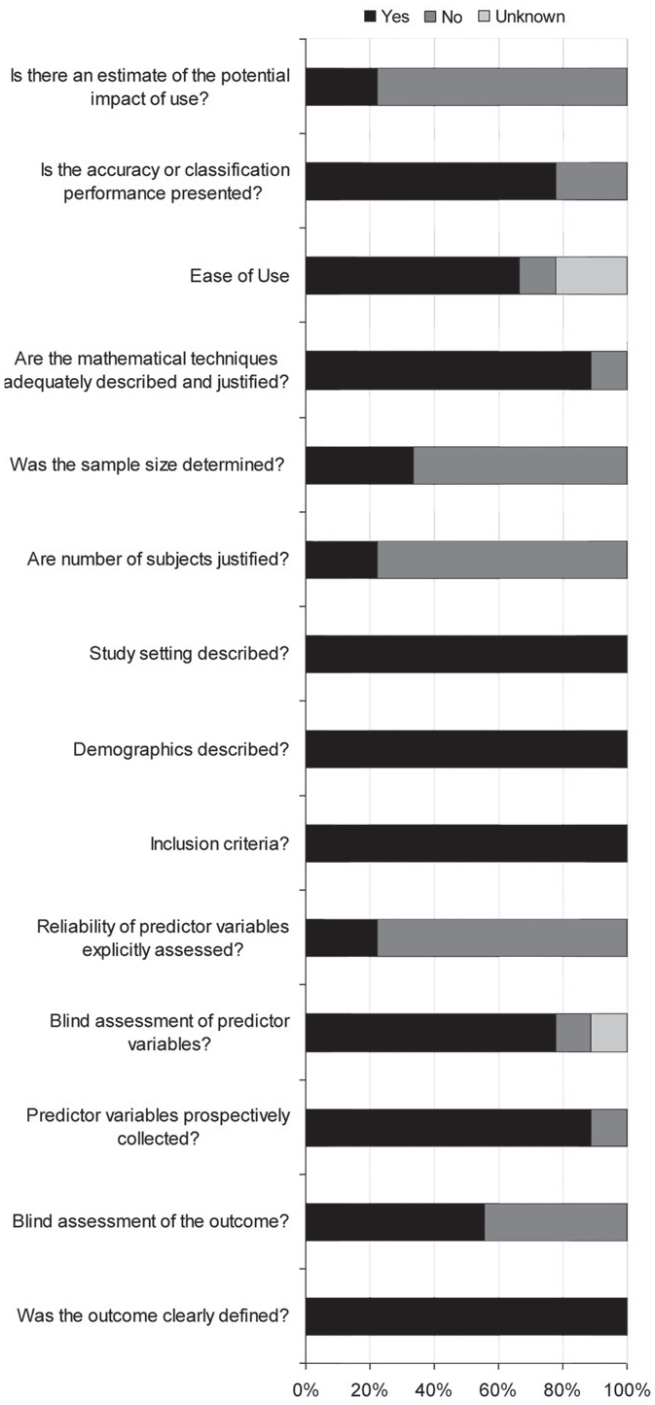

Figure 2. Methodological quality assessment of derivation studies (n=9).

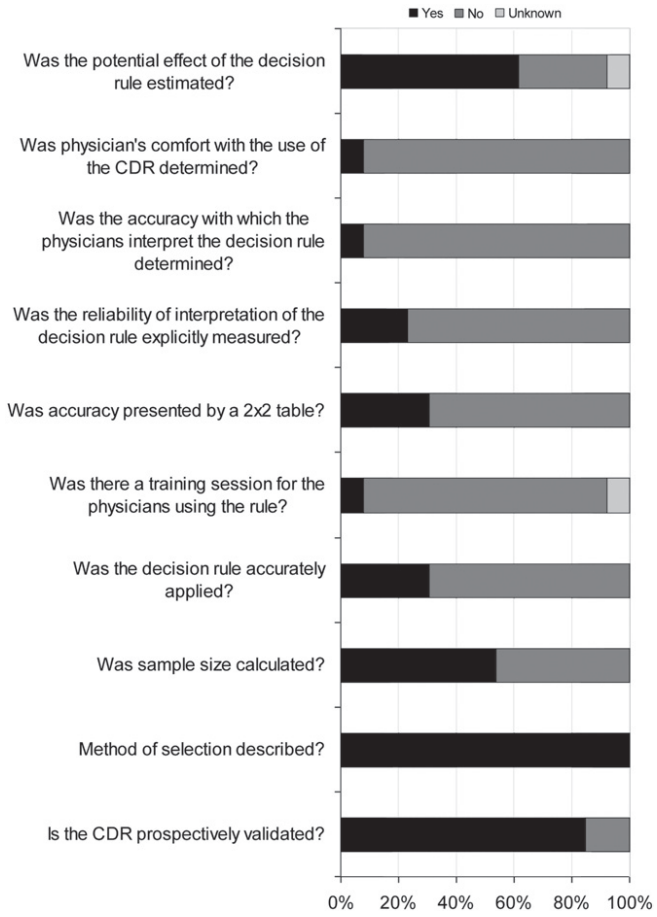

Figure 3. Methodological quality assessment of validation studies (n=13). *CDR*, Clinical decision rule.

protocol-driven review that included an exhaustive search (including extensive author contact) and explicit methodology for study selection, data extraction, and analysis.

To our knowledge, this is the first systematic review and meta-analysis to evaluate the methodological quality and prognostic accuracy of clinical prediction guides for ED patients with syncope. Overall, this review included a limited number of medium-size studies with differing degrees of methodological quality. Although the small number of included studies likely limited our ability to detect meaningful differences on subgroup analysis, differences in study design and ECG interpretation may account for the variable prognostic performance of the San Francisco Syncope Rule when validated in different practice settings.

Quality of the clinical decision rules and risk scores at the individual study level was limited, primarily because study findings have not been externally validated. Only the San Francisco Syncope Rule and the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score have been validated in more than one practice setting (level 2 evidence) and could therefore be considered for use in clinical practice.

Eight of the 9 studies had methodological weaknesses in the derivation phase. Deficiencies in outcome measure assessment (blinding) increased the risk of observation bias. Knowing that a patient had an adverse outcome, for example, may influence retrospective predictor variable assessment.[21] Only 2 studies assessed the interrater reliability of the predictor variables. Demonstration of interrater reliability is important in the derivation of clinical prediction rules because it determines

Table 4. Meta-analysis of each of the 5 included clinical decision rules.

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR Positive (95% CI)	LR Negative (95% CI)	DOR (95% CI)
SFSR					
Quinn et al, 2004[6]	96 (89–99)	62 (58–66)	2.53 (2.27–2.83)	0.06 (0.02–0.19)	41.3 (13.9–132)
Quinn et al, 2006[5]	98 (90–100)	66 (62–70)	2.89 (2.56–3.27)	0.03 (0–0.20)	101 (13.9–738)
Sun et al, 2007[10]	89 (78–96)	42 (36–48)	1.54 (1.35–1.76)	0.25 (0.12–0.55)	6 (2–15)
Cosgriff et al, 2007[33]	90 (55–100)	57 (45–68)	2.09 (1.51–2.90)	0.18 (0.03–1.14)	11.9 (1.44–98.6)
Birnbaum et al, 2008[31]	74 (61–84)	57 (53–61)	1.73 (1.45–2.06)	0.46 (0.30–0.70)	4 (2.1–6.83)
Schladenhaufen et al, 2008[7]	77 (67–85)	34 (30–38)	1.15 (1.02–1.31)	0.70 (0.48–1.02)	2 (1–3)
Thiruganasambandamoorthy et al, 2009[35]	90 (78–97)	33 (28–38)	1.34 (1.19–1.50)	0.31 (0.13–0.72)	4.3 (2.64–11.1)
Dipaola et al (in press)[29]	81 (61–93)	63 (58–67)	2.18 (1.75–2.72)	0.31 (0.14–0.67)	7.1 (2.65–19.3)
Reed et al, 2010[30]	85 (70–94)	24 (21–28)	1.12 (0.98–1.29)	0.62 (0.29–1.31)	1.8 (0.75–4.45)
Pooled results; I^2%	86 (83–89); 76	49 (48–51); 98	1.74 (1.36–2.24); 96	0.28 (0.16–0.50); 81	6 (3–14): 83
OESIL Risk Score					
Colivicci et al, 2003[32] (derivation)	100 (89–100)	22 (17–28)	1.26 (1.16–1.36)	0.07 (0–1.13)	17 (1–293)
Dipaola et al (in press)[29]	88 (70–98)	59 (54–64)	2.16 (1.81–2.58)	0.20 (0.07–0.57)	11 (3–37)
Reed et al, 2010[30]	95 (83–99)	11 (8–14)	1.06 (0.98–1.15)	0.47 (0.12–1.87)	2 (1–10)
Pooled results; I^2%	95 (88–98); 59	31 (29–34) 99	1.41 (1.03–1.92); 97	0.24 (0.11–0.54); 0	6 (2–22); 40
ROSE					
Reed et al, 2010[30] (derivation)	93 (80–97)	74 (73–74)	3.53 (2.97–3.78)	0.10 (0.035–0.266)	34.8 (11.1–108)
Reed et al, 2010[30] (validation)	87 (74–94)	66 (64–67)	2.52 (2.07–2.78)	0.20 (0.085–0.406)	12.9 (5.1–32.6)
Pooled results	90 (81–95); NA	70 (67–72); NA	2.98 (2.14–4.15); NA	0.15 (0.079–0.293); NA	20 (7.8–51.4); NA
Boston Syncope Rule					
Grossman et al, 2007[34]	97 (93–100)	62 (56–69)	2.57 (2.2–3.1)	0.05 (0.01–0.16)	54 (14–205)
Pooled results	OS	OS	OS	OS	OS
Syncope Risk Score					
Sun et al, 2009[36]	88 (82–93)	32 (30%–34)	1.3 (1.2–1.4)	0.36 (0.24–0.54)	4 (2–6)
Pooled results	OS	OS	OS	OS	OS

LR, Likelihood ratio; *DOR*, diagnostic odds ratio; *NA*, incalculable for less than three studies; *OS*, only one study.

which variables are sufficiently reliable to consider for incorporation in the rule.

Quinn et al[6] validated the San Francisco Syncope Rule in a single-center, prospective sample of 791 patients. The prognostic performance in the derivation phase was promising. However, when Sun et al[10] externally validated the San Francisco Syncope Rule, rule performance was suboptimal. In the original San Francisco Syncope Rule, syncope was defined as transient loss of consciousness with return to baseline neurologic function, and abnormal ECG was defined as any rhythm other than sinus or any new changes. Sun et al[10] defined syncope as transient loss of consciousness and abnormal ECG as any rhythm other than sinus, any bundle branch block, left-axis deviation, mono- or biventricular hypertrophy, any abnormal conduction interval except for first-degree atrioventricular block, any Q-, ST-, or T-wave change consistent with ischemia (acute or chronic), or isolated, nonspecific ST- or T-wave abnormalities. Altering the description of the patient population and the definition of important predictor variables could have resulted in differences in patient selection or misclassification of participants and therefore discordant results on validation. To assess the accuracy of a clinical prediction rule, validation studies should correctly apply the rule itself.[21]

Other studies have validated the San Francisco Syncope Rule and Osservatorio Epidemiologico sulla Sincope nel Lazio risk score by using different study designs and different individuals who interpreted the ECG (eg, researcher, cardiologist, the emergency physician caring for the patient). Prospective validation by clinicians using the rule is important to ensure that the clinical decision rule works when applied in the clinical setting.[23] It determines how the rule is being used in practice and its effect on patient care and outcome.[42] Statistical validation decreases the probability that the clinical decision rule reflects associations that are due primarily to chance; however, it does not address factors such as rule application feasibility and implementation, which can compromise its prognostic performance.[23] Subgroup analysis of San Francisco Syncope Rule studies revealed that studies with prospective designs outperformed those with retrospective designs. It is also surprising that studies in which the emergency physician caring for the patient interpreted the ECG outperformed those in which the researcher or cardiologist interpreted the ECG. It is possible that additional information available to the clinician affected subjective ECG interpretation. In addition, although there were no statistically significant differences in prognostic accuracy between San Francisco Syncope Rule studies based on these elements, the small number of studies included in the review limited our ability to detect meaningful differences. Thus, it is still possible that differences in ECG interpretation account for the variable performance of the San Francisco Syncope Rule.

Table 5. Subgroup analysis of SFSR and OESIL risk score studies.

	Sensitivity, % (95% CI); I^2%	Specificity, % (95% CI); I^2%	LR Positive (95% CI); I^2%	LR Negative (95% CI); I^2%	Diagnostic OR (95% CI); I^2%	Test for Interaction *P* Value*
SFSR						
Study design						
Prospective (n=7)[5,6,10,29-31,33]	88 (84–92); 76	54 (52–56); 98	1.93 (1.46–2.55); 96	0.22 (0.11–0.47); 79	8.82 (3.5–22); 81	.055
Retrospective (n=2)[7,35]	81 (74–87); 75	33 (30–36); 0	1.24 (1.07–1.45); 69	0.51 (0.23–1.13); 68	2.45 (0.96–6.21); 68	
Outcome period, days						
7 (n=5)[6,7,10,31,33]	86 (83–90); 82	51 (49–53); 97	1.80 (1.35–2.40); 97	0.23 (0.11–0.50); 86	7.94 (3.04–21); 87	.868
>7 (n=4)[5,29,30,35]	90 (84–94); 65	47 (45–50); 99	1.75 (1.10–2.78); 98	0.27 (0.10–0.71); 76	6.92 (1.89–25.4); 82	
ECG definition						
SFSR (n=5)[5,6,31,33,35]	90 (85–93); 83	56 (54–58); 97	2.04 (1.48–2.82); 96	0.16 (0.05–0.50); 85	13.3 (3.60–48.0); 84	.197
Other than SFSR (n=3)[7,10,29]	84 (78–89); 81	42 (40–45); 98	1.46 (1.19–1.79); 90	0.36 (0.17–0.77); 72	4.51 (1.64–12.4); 76	
ECG determination						
Evaluating physicians (n=3) [5,6,10]	95 (90–97); 56	60 (57–62); 96	2.24 (1.57–3.21); 96	0.09 (0.02–0.38); 77	25.5 (4.41–148); 82	.053
Other (eg, researcher, cardiologist) (n=5)[7,29,31,33,35]	82 (77–86); 74	45 (43–47); 98	1.53 (1.28–1.81); 88	0.42 (0.27–0.64); 49	4.03 (2.15–7.55); 61	
Patients						
Unstable (n=5)[6,7,30,31,33]	83 (78–87); 80	46 (44–48); 98	1.63 (1.12–2.37); 97	0.35 (0.16–0.64); 84	4.86 (1.69–13.9);	.689
Stable (n=4)[5,10,29,35]	89 (83–94); 77	53 (51–56); 98	1.80 (1.13–2.85); 97	0.27 (0.09–0.81); 82	6.9 (1.78–26.8); 82	
OESIL risk score						
Outcome period, mo						
12 (n=1)[32]	100 (89–100); NA	22 (17–28); NA	1.26 (1.16–1.36); NA	0.07 (0.00–1.13); NA	17 (1–293); NA	.477
<12 (n=2)[29,30]	92 (83–97); NA	34 (31–37); NA	1.51 (0.71–3.19); NA	0.27 (0.12–0.64); NA	5.25 (1.10–24.9); NA	

OR, odds ratio.
**P* values were obtained from the DOR.

We identified 2 clinical decision rules for ED syncope patients that were sufficiently developed to consider for use in practice (level 2 evidence): the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score[32] and the San Francisco Syncope Rule.[6] The San Francisco Syncope Rule represents one of the first clinical decision rules in syncope derived according to published methodological standards and the only one that predicts short-term outcomes. It was prospectively derived in 684 patients by Quinn et al[6] in 2004. Adverse outcomes, which included a large spectrum of clinical events, diagnoses, and inhospital interventions, were assessed within 7 days of the initial ED visit. The San Francisco Syncope Rule has been externally validated in several settings, with variable prognostic performance. The prevalence of adverse outcomes in patients classified as San Francisco Syncope Rule negative ranged from 2%[5] to 36%[31] across studies. In our meta-analysis, the pooled sensitivity and specificity estimates for the San Francisco Syncope Rule were lower than in the original study and showed considerable inconsistency. We did not find a statistically significant explanation for the variability of these results. However, study design (prospective versus retrospective) and ECG determination (evaluating physician versus researcher or cardiologist) approached statistical significance. Given the small number of studies included in the review and the limitations of interaction testing, we likely had insufficient power to detect potentially meaningful differences in rule performance because of these factors.[27]

In 2003, Colivicchi et al[32] derived and validated the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score. They found that an abnormal ECG result, a history of cardiovascular disease, lack of prodrome, and age older than 65 years predicted all deaths at 1 year in the 2 cohorts. Subsequent validations were not able to reproduce their results. The prevalence of adverse outcomes in patients classified as "low risk" by the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score (score of 0 to 1) ranged from 5%[30] to 13%.[29] When pooled, the Osservatorio Epidemiologico sulla Sincope nel Lazio risk score showed substantial inconsistency across studies, which could not be explained by differences in outcome period.

All the clinical prediction guides included in the review need further development before they can be routinely used in clinical practice. Future clinical decision rules for syncope should carefully define the patient population selected, clearly define a clinically important definition of abnormal ECG, and adhere to current methodological standards for clinical prediction rules.

The methodological quality and prognostic accuracy of current clinical decision rules for syncope are limited, and the prognostic performance of the San Francisco Syncope Rule and Osservatorio Epidemiologico sulla Sincope nel Lazio risk score varied between studies. Although the small number of included studies likely limited our ability to detect meaningful differences on subgroup analysis, differences in study design and ECG interpretation may account for the variable prognostic performance of the San Francisco Syncope Rule when validated in different practice settings.

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APPENDIX E1.

MEDLINE search strategy.

OVID MEDLINE 1950-Nov Week 3 2009

1 exp Syncope/

2 (faint$3 or presyncop* or unconscious* or (drop adj attack$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

3 1 or 2

4 emergency service, hospital/ or emergency medical services/ or triage/

5 (emergen$ adj3 (center$ or centre$ or unit$1 or room$1 or department$1 or service or physician$ or medicine or care or ward$1)).mp.

6 3 and (4 or 5) 658

7 limit 6 to "clinical prediction guides (optimized)"

8 exp *Syncope/di and (4 or 5)

.mp.=mp=title, original title, abstract, name of substance word, subject heading word

/=Medical Subject Heading term/controlled vocabulary

$ or *=wild card truncation, $3=up to three words adjacent

Adj=adjacent