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SYSTEMATIC REVIEW

Risk-stratification tools for emergency department patients with syncope: A systematic review and meta-analysis of direct evidence for SAEM GRACE

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Abstract

Objectives: Approximately 10% of patients with syncope have serious or life-threatening causes that may not be apparent during the initial emergency department (ED) assessment. Consequently, researchers have developed clinical decision rules (CDRs) to predict adverse outcomes and risk stratify ED syncope patients. This systematic review and meta-analysis (SRMA) aims to cohere and synthesize the best current evidence regarding the methodological quality and predictive accuracy of CDRs for developing an evidence-based ED syncope management guideline.

Methods: We conducted a systematic literature search according to the patient–intervention–control–outcome question: In patients 16 years of age or older who present to the ED with syncope for whom no underlying serious/life-threatening condition was found during the index ED visit (population), are risk stratification tools (intervention), better than unstructured clinical judgment (i.e., usual care; comparison), for providing accurate prognosis and aiding disposition decision for outcomes within 30 days (outcome)? Two reviewers independently assessed articles for inclusion and methodological quality. We performed statistical analysis using Meta-DiSc. We used GRADEPro GDT software to determine the certainty of the evidence and create a summary of the findings (SoF) tables.

Results: Of 2047 publications obtained through the search strategy, 31 comprising 13 CDRs met the inclusion criteria. There were 13 derivation studies (17,578 participants) and 24 validation studies (14,845 participants). Only three CDRs were validated in more than two studies. The San Francisco Syncope Rule (SFSR) was validated in 12 studies: positive likelihood ratio (LR+) 1.15–4.70 and negative likelihood ratio (LR−) 0.03–0.64. The Canadian Syncope Risk Score (CSRS) was validated in five studies: LR+ 1.15–2.58 and LR− 0.05–0.50. The Osservatorio Epidemiologico sulla

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Sincope nel Lazio (OESIL) risk score was validated in five studies: LR+ 1.16–3.32 and LR− 0.14–0.46.

Conclusions: Most CDRs for ED adult syncope management have low-quality evidence for routine clinical practice use. Only three CDRs (SFSR, CSRS, OESIL) are validated by more than two studies, with significant overlap in operating characteristics.

KEYWORDS
clinical decision rule, emergency department, syncope

INTRODUCTION

Syncope accounts for about 1% of all emergency department (ED) visits.[1–5] While the etiology is often benign, approximately 10% of patients have serious or life-threatening causes that may not be apparent during the initial ED assessment.[6–12] Identifying ED syncope patients with serious or life-threatening causes and requiring further diagnostic evaluation and monitoring has been a significant challenge for emergency physicians. Frequently, expensive, unnecessary, and potentially harmful investigations are undertaken for fear of missing life-threatening or otherwise serious underlying causes, particularly cardiogenic causes. Such overtesting often leads to prolonged hospitalization[13–17] and excessive resource utilization.[18]

Investigators have developed clinical decision rules (CDRs) to try and predict adverse outcomes and risk stratify ED syncope patients to minimize unnecessary resource utilization.[19] CDRs 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 history, physical examination, and basic diagnostic tests.[20]

The first-ever systematic review and meta-analysis (SRMA) to evaluate the methodological quality and prognostic accuracy of CDRs for ED patients with syncope reported limitations at outcome and study levels.[19] A key limitation of the SR at the outcome level was the diversity of clinical and methodological aspects across studies.[19] The SR study-level limitations included the absence of an appropriate syncope reference test or criterion standard and differing syncope definitions across studies.[19]

In the context of the Society for Academic Emergency Medicine (SAEM)'s Guidelines for Reasonable and Appropriate Care in the Emergency Department (GRACE) initiative,[21] because syncope is a relatively common ED presentation with life-threatening causes that may not be apparent in the ED, the current SR evaluates the direct evidence on the efficacy of CDRs to risk stratify ED syncope patients and predict adverse outcomes. Specifically, this SRMA aims to address the following question: in patients 16 years of age or older who present in the ED with syncope for whom no underlying serious or life-threatening condition is found during the index ED visit, are risk stratification tools better than unstructured clinical judgment for providing accurate prognosis and aiding disposition decision for outcomes within 30 days?

METHODS

Reporting of this SR is consistent with recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses as applicable to diagnostic accuracy reviews.[22,23] We developed a protocol for the SR with input from methodologists with expertise in systematic reviews (A.W., R.S.) and a content expert (V.T.). We registered the protocol in PROSPERO, an international prospective registry of systematic reviews (registration ID: CRD42023428455).

Population–intervention–comparator–outcome (PICO) question

The proposed PICO question is as follows: In patients 16 years of age or older who present to the ED with syncope for whom no underlying serious or life-threatening condition is found during the index ED visit (population), are risk stratification tools (intervention), better than unstructured clinical judgment (i.e., usual care; comparison), for providing accurate prognosis and aiding disposition decision for outcomes within 30 days (outcome)?

Expert reference librarians designed and conducted a comprehensive literature search with input from one of the authors (R.S.). The search strategy incorporated medical subject headings and text words related to CDRs (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: PubMed (1946 to June 2023), EMBASE (1946 to June 2023), Cumulative Index of Nursing and Allied Health (CINAHL; 1937 to June 2023), Wiley Cochrane Central Register of Controlled Trials (CENTRAL), Wiley Database of Abstracts of Reviews of Effects (DARE), Wiley Cochrane Database of Systematic Reviews, and ClinicalTrials.gov.

For the gray literature search, we conducted bibliographic searches of abstracts presented at scientific meetings published in *Academic Emergency Medicine*, *Annals of Emergency Medicine*, *Canadian Journal of Emergency Medicine*, *Emergency Medicine Journal*, *European Journal of Emergency Medicine*, *Emergency Medicine Australasia*, and *African Journal of Emergency Medicine* in English. We consulted syncope and CDR development experts for additional

published or unpublished reports. Lastly, we reviewed the bibliographies of all retrieved articles to identify potentially relevant articles not identified in the electronic search strategy.

We uploaded citations into an SR software program (DistillerSR, Ottawa, ON, Canada), followed by full-text screening. The PubMed (Ovid interface) search strategy is displayed in Appendix 1.

Eligibility criteria and study selection

Table 1 details the inclusion and exclusion criteria. To conduct a more informative review, we did not exclude studies based on the timing of outcome assessment. Although we excluded clinical practice guidelines and editorials, we used them as potential bibliographic sources of eligible primary studies.

Reviewers (S.Z., R.B., I.d., A.W., E.D., R.R., and R.A.) worked in pairs to individually screen 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 (Table 1). We did not blind reviewers to the authors' names, institutions, journals of publication, or results. We obtained full-text articles for all titles and abstracts considered potentially relevant by at least one reviewer.

Reviewers (S.Z., R.B., I.d., A.W., E.D., R.R., and R.A.) working in pairs independently assessed the full-text articles for eligibility (Phase II). Disagreements were resolved by consensus or by consulting a third author (R.S.). Reviewers (S.Z., R.B., I.d., A.W., E.D., R.R., R.A., I.R., and A.A.) working independently also 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 to perform a 2×2 contingency table for analysis.

We contacted the corresponding and last author to clarify whether the data were missing or unclear. If data were presented as a linear risk score, we contacted the author(s) to provide enough information to convert it to a binary risk system. We excluded a study from the quantitative analysis if it needed more data for meta-analysis, and we obtained no response after sending two emails to the corresponding and/or supervising author. We entered data into Microsoft Office (Microsoft Corporation [2018]; retrieved from https://office.microsoft.com/excel).

Methodological quality assessment

Developing and testing a CDR involves three steps: (1) creating or deriving the rule, (2) testing or validating the rule, and (3) assessing the rule's impact on clinician behavior (impact analysis).[26] Furthermore, the validation process may require several studies to thoroughly test the accuracy of the rule at different clinical sites.[26] Therefore, to assess the evidentiary standards supporting the use of a CDR in routine clinical practice, we performed a quality assessment of each CDR according to a published hierarchy of evidence for CDRs.[26] Reviewers (S.Z., R.B., I.d., A.W., E.D., R.R., and R.A.) working in pairs assessed the quality of each CDR independently. Disagreements were resolved by consensus or by consulting a third author (R.S.). The quality hierarchy for CDRs assigns a CDR to one of four categories depending on whether it is prospectively validated, the patient population used for its validation, and if it has been studied in an impact analysis demonstrating a change in clinician behavior with beneficial consequences (Table 2).

Data extraction

One of the authors (R.S.) extracted data using a study-specific data extraction form in Excel and checked by all co-authors. Any

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Peer-reviewed original article in English.	No published results from clinical studies
Participants 16 years and older presenting with syncope or near syncope to the ED. We defined syncope as a sudden transient loss of consciousness, with loss of postural tone that is brief and self-limiting and resolves without medical intervention.[15,16]	Clinical practice guidelines, editorials, narrative reviews and commentaries
Prospectively or retrospectively derived or validated CDRs or risk scores that predict subsequent adverse events in patients with syncope.[24]	Unobtainable or inaccessible full-text articles
CDR based on original research.[24]	Studies that enrolled 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[25]
CDR includes three or more variables from the history, physical examination, and basic diagnostic tests (such as ECG, complete blood count, and cardiac biomarkers [troponin and natriuretic peptides]).[24]	Non-ED setting (i.e., hospital wards or outpatient facilities)

Abbreviation: CDR, clinical decision rule.

TABLE 2 Hierarchy of evidence for CDRs.[19,26]

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 one prospective validation in a different population and one impact analysis, demonstrating a 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 one 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 one 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

Abbreviation: CDR, clinical decision rule.

discrepancies were resolved by discussion among all authors. Details of study characteristics, population characteristics, CDR descriptions, and operating characteristic outcome variables (true positives [TP], false positives [FP], false negatives [FN], and true negatives [TN], plus sensitivity and specificity) were extracted from the included studies.

Data synthesis

Once we created the 2×2 contingency tables for all the CDRs, we used the web application Meta-Disc 2.0 to perform statistical analysis.[27] We analyzed diagnostic test characteristics. For the meta-analyses, we used a random-effects model. We pooled the sensitivities, specificities, likelihood ratios, and diagnostic odds ratios (DORs) and estimated 95% confidence intervals (CIs) for the outcomes of CDRs with two or more external validation studies. The DOR of a test describes the ratio of the odds of a positive result in patients with the disease compared with patients without the disease.[28]

We explored heterogeneity among included studies qualitatively by comparing their characteristics and quantitatively using the I-squared (I^2) statistic.[29] We determined the clinical heterogeneity of studies based on their clinical characteristics, including the intervention, outcome assessment, and follow-up window. When similarity among studies allowed data pooling, we assessed for statistical heterogeneity using the I^2 statistic, as indicated in coupled forest plots measuring the effect of using a CDR. An I^2 of 50% or greater indicated substantial between-study heterogeneity.

Because of the anticipated clinical heterogeneity between available CDRs (different predictor variables, length of follow-up, and outcome measures), we restricted meta-analysis to a priori studies that externally validated the same CDR. We restricted meta-analysis to CDRs with two or more external validation studies. We used narrative synthesis when studies were not eligible for meta-analysis. We used coupled forest plots to present results obtained from the meta-analysis.

We used Deek's funnel plot to detect publication bias.[30] If no publication bias exists, the data obtained from each study will be distributed in an inverted funnel shape.[30] Otherwise, an asymmetric inverted funnel graph indicates the existence of sample bias in the study.[30]

Outcomes assessment

The primary outcomes of interest include death (cardiac, syncope-related, and non–syncope-related), arrhythmias, structural/ischemic heart disease, noncardiac conditions (pulmonary embolism, aortic dissection, hemorrhage/anemia requiring transfusion) at 7 days, 30 days, and 1 year from the index ED visit.

The secondary outcomes include recurrent syncope/falls resulting in major traumatic injury, pacemaker/implantable cardioverter defibrillator placement, cardiopulmonary resuscitation, subarachnoid hemorrhage, severe pulmonary hypertension, and any other serious condition that would require treatment (e.g., ectopic pregnancy, pneumothorax, sepsis).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment

We assessed the quality of the evidence for the composite outcome of all adverse events by the GRADE system: study design limitations, consistency between studies, directness (ability to generalize), precision (sufficient or precise data of results), and publication bias.[31] Five quality levels of evidence may be generated for each pooled outcome from this information: high, moderate, low, very low, and no evidence. We inputted the average values of sensitivity and specificity for each CDR at a common threshold (a score greater than 1 for each CDR) with 95% CIs, the total number of studies, and participants into the GRADEPro GDT software to assess the certainty of the evidence (CoE) and create summary of findings (SoF) tables.

RESULTS

Description of studies

We screened 2047 potential articles for inclusion by title and abstract; we retrieved 178 potentially eligible articles in full text after removing duplicates. Of the 178 full-text articles screened, 31 met the inclusion criteria (see Figure 1 for the PRISMA flowchart). The studies meeting the inclusion criteria represented 13 CDRs and risk stratification scoring systems (Table 3). The United States conducted most derivation studies for the CDRs and risk stratification scoring systems (Table 3).

There were 23 prospective and eight retrospective studies. The sample size varied between 68[41] and 5010.[12] The mean participant ages were between 44.5 years[39] and 75 years,[38] including only those older than 65. Almost all studies had equal numbers of males and females (Table S1a,b).

There were 17,578 study participants from 11 derivation studies (Table S2a,b). Six of the 11 derivation studies were validated either at the time of their derivation or externally. Five CDRs and risk stratification scoring systems (Canadian Syncope Arrhythmia Risk Score [CSARS]; history of heart Failure, history of Arrythmia, abnormal Initial ECG, elevated N-terminal-prohormone BNP (NT-ProBNP), elevated high-sensitivity Troponin T [FAINT] score; Instituto de Cardiologia–Fundação Universitária de Cardiologia [IC-FUC]; Predictors of 30-Day Serious Events in Older Patients, and Tehran Heart Center Syncope Stratifying Score [THC3S]) were derived but have not yet been validated.[12,32,34,36,37]

There were 14,845 patients from 24 validation studies (Table S1a,b). Three studies combined derivation and validation studies; there were 1407 participants in the derivation studies and 1596 participants in the validation studies.[10,37,46] Investigators validated three risk stratification scoring systems (ACP guidelines,

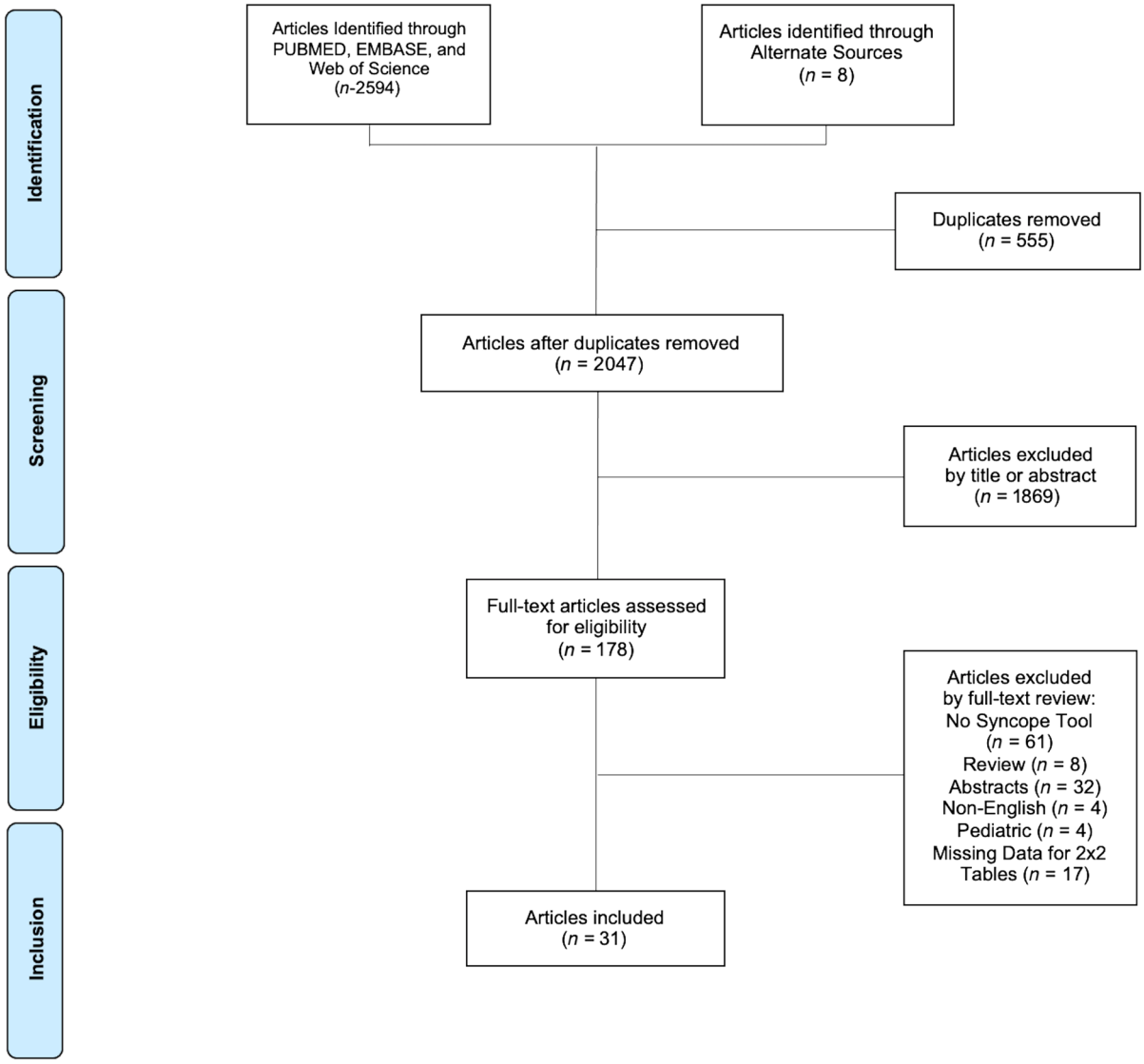

FIGURE 1 PRISMA flowchart.

TABLE 3 CDRs and risk stratification scoring systems.

CDR and risk stratification scoring system	Country where the derivation study was conducted
CSRS[11]	Canada
CSARS[12]	Canada
ACP Guidelines[32]	United States
Evaluation of Guidelines in Syncope Study (EGSYS)[33]	Italy
FAINT[34]	United States
Faint-Algorithm admission criteria (adapted from 2009 European Society of Cardiology [ESC] guidelines in Syncope)[35]	Italy
IC-FUC[36]	Brazil
OESIL[37]	Italy
Predictors of 30-Day Serious Events in Older Patients[38]	United States
ROSE[10]	United Kingdom
SFSR[6]	United States
THC3S[39]	Iran
The American College of Emergency Physicians (ACEP) Policy on Evaluating Patients with Syncope in the Emergency Department[40]	United States

Abbreviations: CDR, clinical decision rule; CSARS, Canadian Syncope Arrhythmia Risk Score; CSRS, Canadian Syncope Risk Score; FAINT, history of heart Failure, history of Arrythmia, abnormal Initial ECG, elevated N-terminal-prohormone BNP (NT-ProBNP), elevated high-sensitivity Troponin T; IC-FUC, Instituto de Cardiologia–Fundação Universitária de Cardiologia; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; ROSE, Risk Stratification of Syncope in the Emergency Department; SFSR, San Francisco Syncope Rule; THC3S, Tehran Heart Center Syncope Stratifying Score.

Faint-Algorithm admission criteria, and ACEP guidelines) without a derivation study.[32,35,40]

Our literature search found no randomized controlled trial comparing unstructured clinical judgment and a risk stratification tool in patients 16 years or older who present in the ED with syncope for whom no underlying serious or life-threatening condition is found during the index ED visit. We found one prospective observational cohort study (488 participants enrolled in two EDs) comparing the efficacy of the OESIL risk score, San Francisco Syncope Rule (SFSR), and clinical judgment in assessing the short-term (within 10 days) prognosis of severe outcomes (death, "major therapeutic procedures," and hospital readmission). The authors defined "major therapeutic procedures" as cardiopulmonary resuscitation, pacemaker or implantable cardioverter defibrillator insertion, intensive care unit admission, and acute antiarrhythmic therapy that occurred after the study participant was hospitalized from the ED or discharged.[44] The study found the OESIL risk score had a sensitivity of 88% and a specificity of 60% (admission 43%), the SFSR had a sensitivity of 81% and a specificity of 63% (admission 40%), and clinical judgment had a sensitivity of 77% and a specificity of 69% (34% admission; $p < 0.05$ vs. CDRs).[44] The study authors concluded that the OESIL risk score and SFSR "partially lacked" recognition of patients with short-term high-risk syncope because of their relatively low sensitivity.[44] Clinical judgment was more specific than the OESIL risk score and SFSR, with a significantly lower admission percentage (34%) than the OESIL risk score (43%) and SFSR (40%).[44] The authors reported that, compared to clinical judgment, the OESIL risk score would have admitted 15 and SFSR 29 more patients to avoid sending home one patient with a serious outcome.[44] However, clinical judgment failed to identify two patients who died after ED discharge; in contrast, the OESIL risk score and SFSR identified both patients who died after ED discharge.[44]

The methodological quality of the included studies

We performed quality assessments of the CDRs and risk scoring systems at the level of the rule itself and each study's level.[19] We classified the rules according to a hierarchy of evidence for CDRs (Table 2).[19,26] Using the methodological qualities of derivation and validation studies developed by McGinn et al.[26] and later codified by Serrano et al.[19] we graded each criterion as "yes," "no," or "unknown." Then, we calculated summary statistics for each criterion as a percentage "yes."

The 11 derivation studies all met the criteria "math described," "inclusion criteria," and "outcome clearly defined." "Study setting described" was identified in over 90% of studies. More than 70% of studies met the criteria "classification performance," "reliability of predictor variable," and "prospective" (Table S2a,b). Less than 50% of the derivation studies met the remaining criteria. Of note, only 30% of studies documented "Blinding of Predictor Variable" (Table S2a,b).

Of the 24 validation studies, "method of selection" had the highest score, with 87% meeting these criteria. More than 50% of the validation studies reported the following criteria: "estimate of potential effect of CDR," "2×2 tables," "accuracy of CDR interpretation," and "prospective." Less than 50% of the validation studies met the remaining criteria. Less than 10% of the validation studies reported "physicians' comfort with CDR" (Table S3a,b).

Outcomes

Regarding the primary outcome of this review, 25 studies assessed outcomes within 30 days of the index ED visit, three assessed outcomes at 6 months, and three assessed outcomes at 1 year (Table S1a,b). Only one study reported death as an outcome measure.[42] Most studies used composite outcomes (Table S1a,b). The SFSR[6] and Canadian Syncope Risk Score (CSRS)[11] reported the two most used composite outcomes. The SFSR composite outcome was defined as "serious outcomes as death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant hemorrhage, or any condition causing or likely to cause a return ED visit and hospitalization for a related event."[6] Similarly,

the CSRS composite outcome was "either arrhythmic serious conditions (any serious arrhythmias); intervention to treat arrhythmias such as pacemaker/defibrillator insertion, or cardioversion; or any death (due to an unknown cause) or non-arrhythmic serious conditions (myocardial infarction, serious structural heart disease, aortic dissection, pulmonary embolism, severe pulmonary hypertension, significant hemorrhage, subarachnoid hemorrhage, or any other serious condition causing syncope)."[11]

The incidence of composite outcomes across studies varied widely between 2.1%[12] to 51.4%[36] (Tables S4 and S5). Since the composite outcomes in individual studies contained many adverse events subcomponents, we disaggregated the composite outcome data to identify the subcomponents of interest. For example, if a study reported major adverse cardiovascular events as a composite outcome, we attempted to determine the number of events of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death separately. The number of deaths and mortality rates were reported in 29 studies, which varied between zero[9,48] and 13 deaths.[49] Mortality rates varied from 0.3%[49] to 5.1%[7,43] (Table S1a,b).

Operating characteristics of derivation studies

The weighted average incidence of composite outcomes of the 11 derivation studies was 19.6%. The CSRS study has the highest sensitivity (98%; 95% CI 93.7%–99.4%).[11] The THC3S study has the lowest sensitivity (69.2%; 95% CI 51.7%–87.0%) and highest specificity (90.3%; 95% CI 87.1%–97.0%).[39] The FAINT score has the lowest specificity (22.2%; 95% CI 20.7%–22.5%).[34] THC3S had the highest positive likelihood ratio (LR+; 7.14),[39] and OESIL had the lowest LR– (0.04[37]; Table S4). The three CDRs with at least two external validation studies (SFSR,[6] CSRS,[11] and OESIL[37]) have similar operating characteristics (Table S4).

Operating characteristics of validation studies

Of the 24 validation studies, we could create a 2×2 contingency table for 22 studies to compute the operating characteristics. We could not create a 2×2 contingency table for two studies (1224 participants) because frequency data were not published or obtainable by contacting the authors.[37,46]

The weighted average incidence of composite outcomes of the 24 validation studies was 10.3%. Only three CDRs have been validated in two or more studies (SFSR,[6] CSRS,[11] and OESIL[37]), and there is a significant overlap in the range of operating characteristics. Twelve studies have validated the SFSR with a range of LR+ 1.15–4.70 and LR– 0.03–0.64. Five studies have validated the CSRS with a range of LR+ 1.15–2.58 and LR– 0.05–0.50. Five studies have validated the OESIL risk score with a range of LR+ 1.16–3.32 and LR-0.14-0.46[43] (Table S5).

CDR predictor variables

Table S6 compares the predictor variables of the 13 identified CDRs and risk stratification scoring systems. An ECG is a predictor variable in all 13 CDRs. A history of heart disease was the second most used variable in all CDRs, except the Risk Stratification of Syncope in the Emergency Department (ROSE) rule[10] and FAINT score.[34] The definition of a syncopal event as a predictor variable varied across 10 CDRs based on whether it was associated with chest pain, shortness of breath, or a prodrome. Six CDRs include abnormal vital signs, defined by hypotension, bradycardia, and hypoxia. Five CDRs include an abnormal cardiac biomarker (troponin or B-type natriuretic peptide [BNP]), and three CDRs include low hemoglobin.

Meta-analysis

Sufficient data to construct a 2×2 contingency table were directly available from the publication in 28 studies, and the authors provided additional data for three studies. For the meta-analysis, we pooled the relative risk of the composite outcome of all adverse events for each CDR with two or more external validation studies (i.e., SFSR,[6] CSRS,[11] and OESIL[37]). Figures 2–4 show the coupled forest plots for each CDR meta-analysis, revealing significant heterogeneity ($I^2 > 50\%$) in the pooled sensitivity and specificity for all the CDRs except the OESIL[37] pooled sensitivity ($I^2 = 37.1\%$). Figure 3 shows that among the three CDRs with two or more external validation studies, the CSRS[11] has the highest pooled sensitivity (0.89 [95% CI 0.76–0.954]) and lowest pooled specificity (0.481 [95% CI 0.345–0.619]). However, the sensitivity and specificity forest plots for the three CDRs with two or more external validation studies (i.e., SFSR,[6] CSRS,[11] and OESIL[37]) show a significant overlap of the CIs and operating characteristics (Figures S1 and S2).

GRADE analysis

Tables 4 and 5 detail the GRADE assessment for the composite outcome of all adverse events when we compare the SFSR[6] and OESIL[37] to the CSRS.[11] Tables 4 and 5 show that when we compare the CSRS[11] to both SFSR[6] and OESIL,[37] there is low-quality evidence screening for all adverse events for two reasons. Firstly, indirectness (i.e., the included studies do not directly compare the CDRs of interest) limits the CoE. Secondly, the high probability of publication bias from a funnel plot with a statistically significant test for asymmetry (Egger's test; $p < 0.001$; Figure 5) limits the CoE. We compared the SFSR[6] and OESIL[37] to the CSRS[11] because the meta-analysis reveals that the CSRS[11] has the highest pooled sensitivity and lowest pooled specificity among the three CDRs with two or more external validation studies (Figure 3).

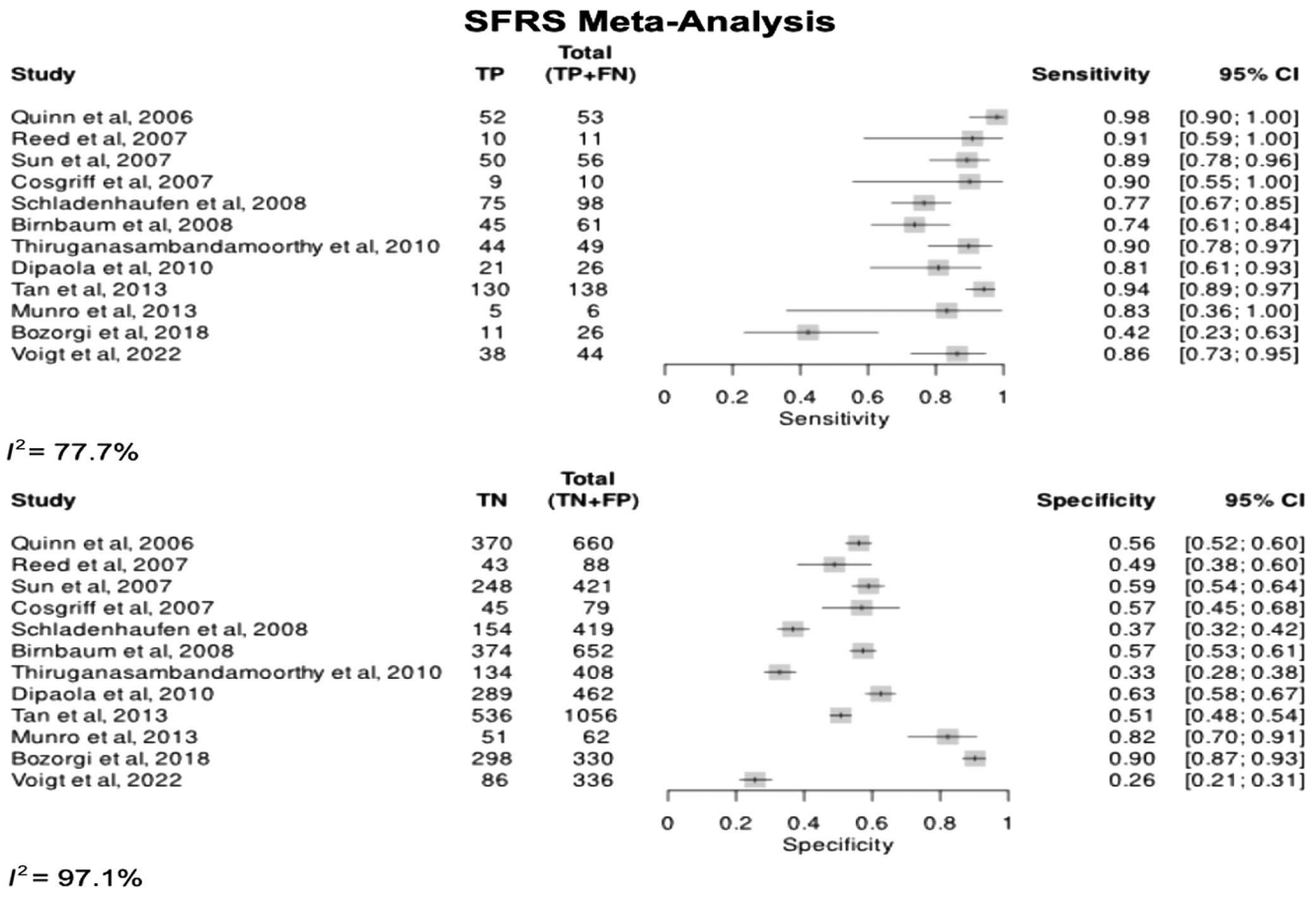

FIGURE 2 Couple forest plots of SFRS for all adverse events. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

DISCUSSION

As part of SAEM GRACE's evidence-to-decision framework, this SRMA synthesizes the best current direct evidence regarding the methodological quality and prognostic accuracy of CDRs for managing patients presenting to the ED with syncope. After a comprehensive literature search, 13 CDRs met the SRMA's inclusion criteria. Only three of the 13 CDRs (SFSR,[6] CSRS,[11] and OESIL[37]) are validated by more than two studies, with significant overlap in operating characteristics. CSRS has the highest pooled sensitivity and lowest pooled specificity.[11] Comparing the CSRS to the SFSR and OESIL reveals low-quality evidence for predicting all adverse events (a composite outcome measure) in ED patients presenting with syncope. Comparing the CSRS to the SFSR and OESIL, the factors that decrease the CoE are the indirectness of the available evidence and a strong suspicion of a high probability of publication bias.

The findings of this SRMA suggest that current CDRs may lack the necessary rigor and predictability to surpass the intuitive judgment of clinicians to risk-stratify ED syncope patients and predict adverse events because most of the CDRs examined in this SRMA demonstrate low-quality evidence for predicting all adverse events in ED syncope patients. As a rule of thumb, an LR+ below 5 seldom influences the pretest probability sufficiently to yield an actionable posttest probability.[50] In this SRMA, all the three CDRs (SFSR, CSRS, OESIL) validated by more than two studies have an LR+ below 5 for predicting all adverse events. Regarding the LR−, only a value below 0.1 produces a significant alteration in the pretest probability of the disease, enough to effectively rule it out.[50] All the three CDRs validated by more than two studies in this SRMA have an LR− above 0.1 for predicting all adverse events. The LRs of the three CDRs validated by more than two studies in the current SRMA are consistent with the conclusions of the only study (a nonrandomized study) from our literature search comparing unstructured clinical judgment and risk stratification tools for ED with syncope patients, which showed two risk stratification tools (the OESIL risk score and SFSR) had relatively low sensitivity for identifying patients with short-term high-risk syncope.[44]

GRADE use in SRs is becoming a de facto standard for high-quality SRs and is an essential component of trustworthy guidelines.[51] To the best of our knowledge, this is the first-ever SRMA to assess the evidence for ED syncope CDRs by the GRADE approach. Using GRADE in SRs and guidelines increases their reproducibility and provides a framework for conducting an SR or developing a guideline.[51] The GRADE assessments directly impact clinical practice and research, with CoE assessments highlighting where the evidence base is adequate or where more or better research is needed.[51] Using plain language in GRADE CoE assessments and recommendations makes GRADE recognizable and easy to use and interpret.[51]

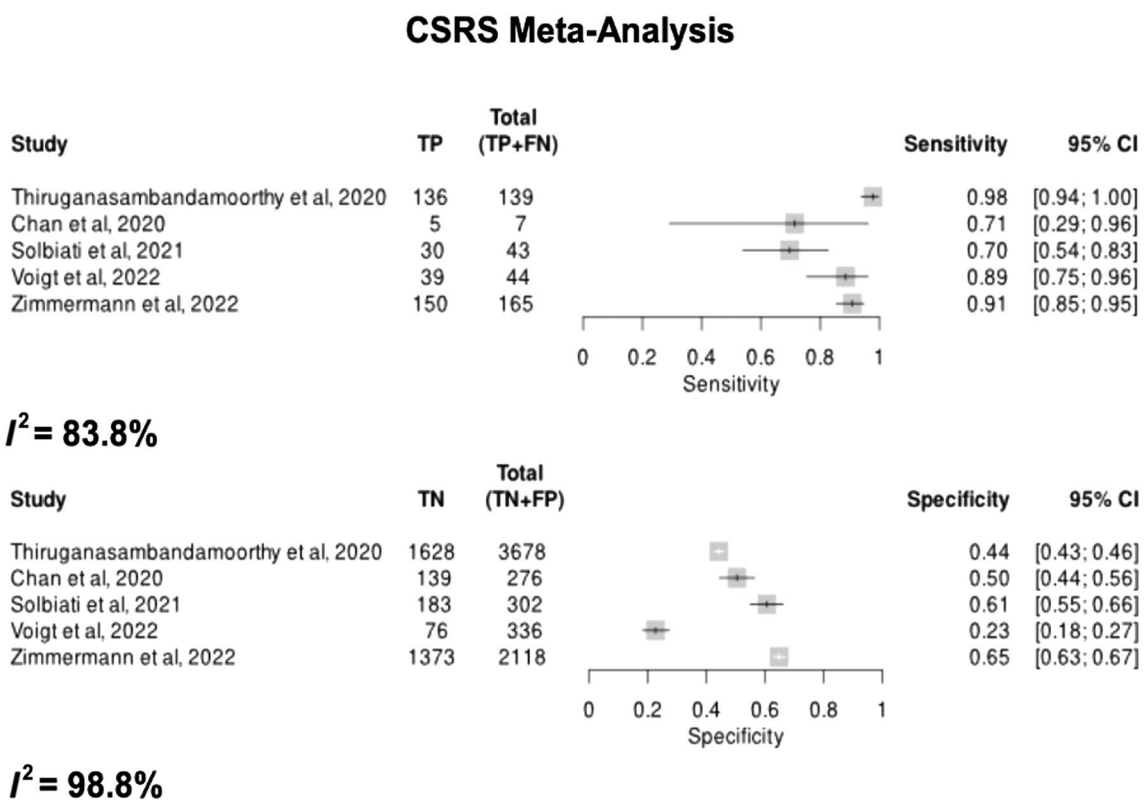

FIGURE 3 Couple forest plots of CSRS for all adverse events. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

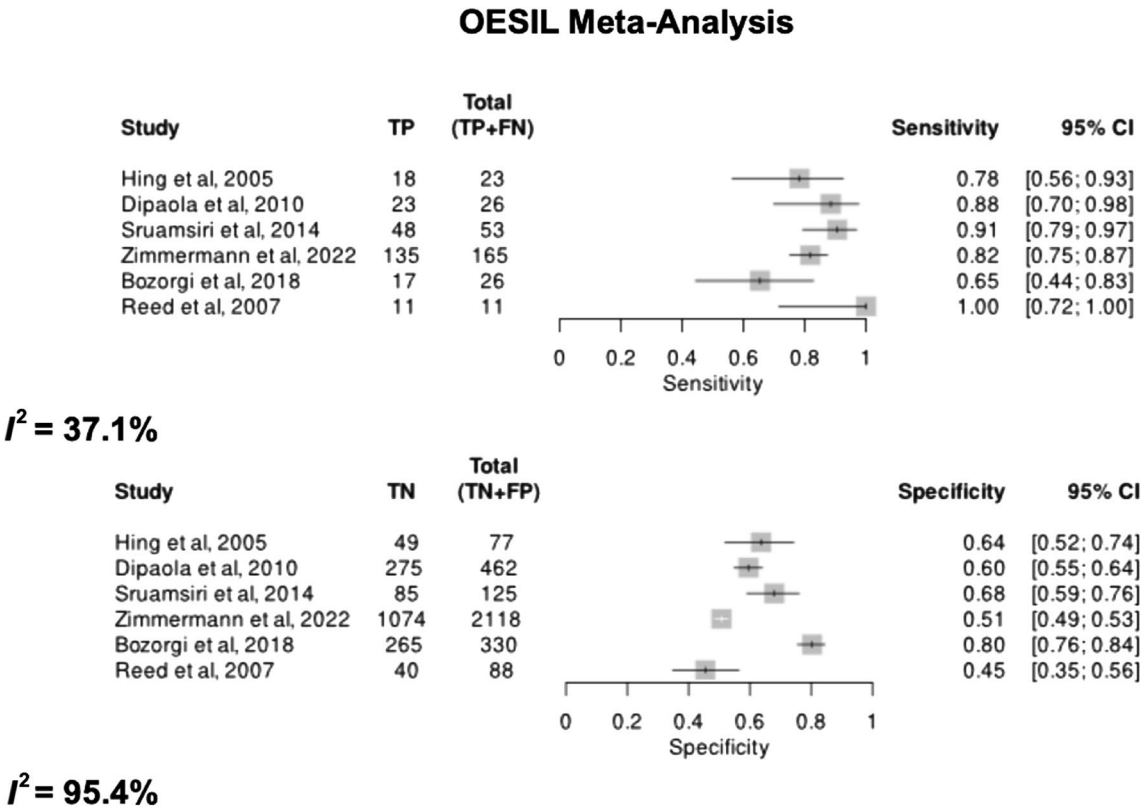

FIGURE 4 Couple forest plots of OESIL for all adverse events. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

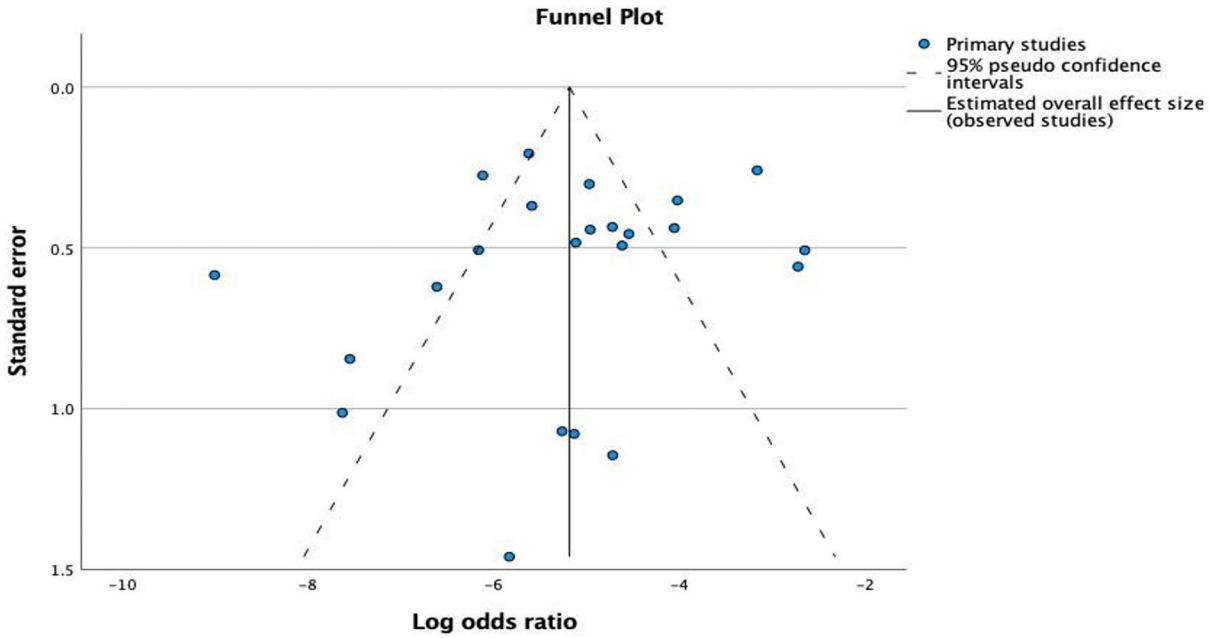

FIGURE 5 Funnel plot.

Similar to previous SRs on this topic,[19,52–54] this SRMA reveals that most CDRs are derived in ED settings, with a critical focus on the risk of potential cardiac causes as the underlying etiology of syncope. Consistent with findings from earlier reviews,[19,52–54] this SRMA demonstrates that the methodological quality and prognostic accuracy of CDRs to risk stratify ED syncope patients and predict adverse events is limited. A substantial number of the CDRs lack validation or sufficient accuracy for application to clinical practice. Given the limitations and low CoE of existing ED CDRs, there is no current evidence that they outperform clinical gestalt in predicting short-term serious outcomes following syncope. Thus, it is unclear if their routine use with clinical judgment would benefit patients.

A significant finding of this SRMA is that it identifies only three CDRs with two or more external validation studies (SFSR,[6] CSRS,[11] and OESIL[37]) and then using the GRADE approach to compare them. The SFSR[6] has more external validation studies (12) than the other two CDRs (the CSRS[11] and OESIL,[37] respectively, have five external validation studies). However, our meta-analysis showed that the CSRS has the highest pooled sensitivity and lowest pooled specificity among the three CDRs.[11] For that reason, our GRADE analysis compared the OESIL and SFSR to the CSRS as its basis. Unlike previous SRs on the topic that did not assess the body of evidence using the GRADE approach,[19,52–54] we can present the findings of these CDR comparisons in relatively easy-to-understand language for guideline developers and frontline emergency physicians. For example, although the CoE is low, reporting that the CSRS identifies slightly more TP and FP patients and slightly less FN and TN than the OESIL and SFSR makes it easy for guideline developers and frontline emergency physicians to interpret the findings of the current SRMA.

LIMITATIONS

The current SRMA identifies several limitations to the topic's current evidence base. Firstly, the ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope defines syncope as "A symptom that presents with an abrupt, transient, complete loss of consciousness, associated with the inability to maintain postural tone, with rapid and spontaneous recovery."[16] It also emphasized that "There should not be clinical features of other non-syncope causes of loss of consciousness, such as seizure, antecedent head trauma, or apparent loss of consciousness (i.e., pseudosyncope)."[16] However, distinguishing between syncope and other causes of transient loss of consciousness can be complex.[55] Consequently, it is plausible that some participants in the included CDR studies categorized as syncope patients did not have syncope. This misclassification can potentially impact a CDR's operating characteristics. Unfortunately, until more objective definitions for syncope emerge, this limitation will likely persist and hinder the broader utility of the relevant CDRs. In the meantime, using the real-world syncope definition used in the studies included in the current SMRA enhances its findings' generalizability and clinical relevance.

Secondly, the methodological quality of both derivation and validation trials falls below optimal standards, posing a significant threat to the validity of their clinical applications. For example, only a few validation studies assessed the comfort level of physicians in utilizing these CDRs—an essential aspect often integral to any derivation study.[56,57] Furthermore, many derivation studies did not provide the 2×2 tables necessary for reproducing their findings. Moreover, most validation studies failed to document crucial elements of their methodology, such as sample

TABLE 4 SoF table for comparing CSRS and SFSR to screen for all adverse events in adult ED syncope patients.

Should the CSRS vs. SFSR be used to screen for high-risk clinical conditions in adult ED syncope patients?
Patient or population: Adult ED syncope patients.
Setting: ED.
New test: SFSR | Cutoff value:
Reference test: Clinical follow-up | Threshold: Not applicable
Pooled sensitivity CSRS: 0.89 (95% CI 0.76–0.95) | Pooled specificity CSRS: 0.48 (95% CI 0.35–0.62).
Pooled sensitivity SFSR: 0.86 (95% CI 0.77–0.92) | Pooled specificity SFSR: 0.56 (95% CI 0.44–0.68).

	Number of results per 1000 patients tested (95% CI)				
	Prevalence 9.8% Typically seen in				
Test result	CSRS	SFSR	Number of participants (studies)	CoE (GRADE)	Comments
TPs (patients with high-risk clinical conditions)	87 (74–93)	84 (75–90)	398 (5)	⨁⨁◯◯ Low[a,b]	TPs are patients who will develop an adverse event after their index ED visit. The CSRS identifies slightly more (3) TP patients than the SFSR.
	Three more TPs with the CSRS				
FNs (patients incorrectly classified as not having high-risk clinical conditions)	11 (5–24)	14 (8–23)			FNs are ED patients discharged with the false reassurance of being unlikely to develop an adverse event. The CSRS identifies slightly fewer (3) FN patients than the SFSR.
	Three fewer FNs with the CSRS				
TNs (patients without high-risk clinical conditions)	433 (316–559)	505 (397–613)	6710 (5)	⨁⨁◯◯ Low[a,b]	TNs are patients who can safely be discharged from the ED because they are unlikely to develop an adverse event. The CSRS identifies fewer (72) TN patients than the SFSR.
	72 fewer TNs with the CSRS				
FPs (patients incorrectly classified as having high-risk clinical conditions)	469 (343–586)	397 (289–505)			FPs are patients falsely identified as likely to develop an adverse event and unnecessarily admitted to the hospital. The CSRS identifies more (72) FP patients than the SFSR.
	72 more FP with the CSRS				

Abbreviations: CoE, certainty of evidence; CSRS, Canadian Syncope Risk Score; FN, false negative; FP, false positive; SFSR, San Francisco Syncope Rule; SoF, summary of findings; TN, true negative; TP, true positive.

[a]The indirectness of the available evidence is serious enough to downgrade the CoE by one level because the included studies do not directly compare the CDRs of interest.

[b]We downgraded the CoE by one level because we strongly suspect a high probability of publication bias from a funnel plot with a statistically significant test for asymmetry (Egger's test; $p < 0.001$).

size analysis and the blinding of predictors and outcomes. These shortcomings collectively undermine the internal validity of the studies in question.

Thirdly, the predictive ability of a variable within a CDR is contingent on its unique qualities. Certain factors, such as gender, may demonstrate relatively stable impacts on outcomes over longer periods.[58] Conversely, the effect of some factors on outcomes changes over time. For instance, the risk of arrhythmia might be higher briefly after syncope, decreasing over time, while the risk of other outcomes could increase with a longer follow-up period.[59] Investigators need to justify and set an appropriate duration of follow-up to ensure they rigorously assess proposed outcomes and permit enough follow-up time for them to develop. Unfortunately, most studies need to catch up in this respect. The current SRMA reveals most CDRs have follow-up periods under 30 days; only a few report outcome measurement periods beyond 90 days. Therefore, the findings of most existing CDRs only apply to short-term outcomes.

Fourthly, the incidence of composite outcomes across studies varied widely between 2.1%[12] and 51.4%.[36] We would have expected that studies with longer follow-up duration would have higher incidences of their composite outcomes, yet studies with the shortest follow-up duration had composite incidences from 5.9%[35] to 29.8%,[47] and those with 1-year follow-up varied between 2.4%[42] and 41.3%.[46] This wide variability in composite outcome incidence is multifactorial, possibly related to selection bias, differential verification bias, or variations in patient populations by geography or hospital type. In addition, the heterogeneity of the elements of the studies' composite outcomes could also have contributed to the variability across the current SRMA's included studies. Finally, while GRADE provides a systematic and transparent approach to assessing the CoE, it is important to acknowledge that using GRADE will commonly involve some subjective judgments, and assessments may vary between individuals.[51,60,61]

TABLE 5 SoF table for comparing CSRS and the OESIL risk score to screen for all adverse events in adult ED syncope patients.

Should the CSRS vs. OESIL risk score be used to screen for high-risk clinical conditions in adult ED syncope patients?
Patient or population: Adult ED syncope patients.
Setting: ED.
New test: OESIL risk score | Cutoff value:
Reference test: Clinical follow-up | Threshold: Not applicable
Pooled sensitivity CSRS: 0.89 (95% CI: 0.76–0.95) | Pooled specificity CSRS: 0.48 (95% CI: 0.35–0.62).
Pooled sensitivity OESIL risk score: 0.84 (95% CI: 0.74–0.90) | Pooled specificity OESIL risk score: 0.62 (95% CI: 0.52–0.71).

	Number of results per 1000 patients tested (95% CI)				
	Prevalence 9.8% Typically seen in				
Test result	CSRS	OESIL risk score	Number of participants (studies)	CoE (GRADE)	Comments
TPs (patients with high-risk clinical conditions)	87 (74–93)	82 (73–88)	304 (6)	⨁⨁◯◯ Low[a,b]	TPs are patients who will develop an adverse event after their index ED visit. The CSRS identifies slightly more (5) TP patients than the OESIL risk score.
	Five more TPs with the CSRS				
FNs (patients incorrectly classified as not having high-risk clinical conditions)	11 (5–24)	16 (10–25)			FNs are ED patients discharged with the false reassurance of being unlikely to develop an adverse event. The CSRS identifies slightly fewer (5) FN patients than the OESIL risk score.
	Five fewer FNs with the CSRS				
TNs (patients without high-risk clinical conditions)	433 (316–559)	559 (469–640)	3200 (6)	⨁⨁◯◯ Low[a,b]	TNs are patients who can safely be discharged from the ED because they are unlikely to develop an adverse event. The CSRS identifies fewer (126) TN patients than the OESIL risk score.
	126 fewer TNs with the CSRS				
FPs (patients incorrectly classified as having high-risk clinical conditions)	469 (343–586)	343 (262–433)			FPs are patients falsely identified as likely to develop an adverse event and unnecessarily admitted to hospital. The CSRS identifies more (126) FP patients than the OESIL risk score.
	126 more FP with the CSRS				

Abbreviations: CoE, certainty of evidence; CSRS, Canadian Syncope Risk Score; FN, false negative; FP, false positive; OESIL, Osservatorio Epidemiologico sulla Sincope nel Lazio; SoF, summary of findings; TN, true negative; TP, true positive.

[a]The indirectness of the available evidence is serious enough to downgrade the certainty of evidence (COE) by 1 level because the included studies do not directly compare the CDRs of interest.

[b]We downgraded the CoE by one level because we strongly suspect a high probability of publication bias from a funnel plot with a statistically significant test for asymmetry (Egger's test; $p < 0.001$).

CONCLUSIONS

We cannot provide solid conclusions for using currently available clinical decision rules to risk stratify ED syncope patients and predict adverse events in routine clinical practice based on direct evidence in the current systematic review and meta-analysis. Firstly, only a few currently available clinical decision rules have external validation studies. Secondly, there is low-quality evidence for predicting all adverse events for the few clinical decision rules with two or more external validation studies. Based on these findings, there is a clear need for more external validation studies for most currently available clinical decision rules. Additionally, there is also a clear need for scientifically rigorous studies comparing the use of clinical decision rules and clinical judgment to risk stratify ED syncope patients and predict adverse events.

Regarding the impact of the current systematic review and meta-analysis's findings on clinical practice, clinical judgment remains a valid way of risk stratifying ED syncope patients. Regarding the utility of the current systematic review and meta-analysis's findings on emergency care research, funding the external validation and impact analysis studies of high-quality clinical decision rules should be a priority for emergency medicine research funders. Such funding is justified based on syncope as a relatively common ED presentation associated with life-threatening causes and to reduce the substantial cost implications of hospital admissions for patients unlikely to have their long-term outcomes altered by the admission.

AUTHOR CONTRIBUTIONS

Study concept and design—Abel Wakai and Richard Sinert; acquisition of the data—Shahriar Zehtabchi, Ian S. deSouza, Roshanak Benabbas, Robert Allen, Eric Dunne, Rebekah Richards, Amelie Ardilouze, and Isidora Rovic; analysis and interpretation of the data—Richard Sinert and Abel Wakai; drafting of the manuscript—Abel Wakai, Richard Sinert, Shahriar Zehtabchi, Ian S. deSouza, Roshanak Benabbas, Robert Allen, Eric Dunne, Rebekah Richards, and Amelie Ardilouze; critical revision of the manuscript for important intellectual content—Abel Wakai and Richard Sinert; statistical expertise—N/A; and acquisition of funding—Richard Sinert and Abel Wakai.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1. PUBMED (OVID INTERFACE) SEARCH STRATEGY 1

("syncope"[Mesh] OR syncope* OR faint* OR drop attack* OR vasovagal OR lipothym* OR presyncope) AND ("emergency service, hospital"[Mesh] OR "emergency medicine"[Mesh] OR emergency ward* OR emergency unit* OR emergency outpatient unit* OR emergency service* OR emergency medicine*) AND (("risk assessment"[Mesh] OR risk) AND ("decision support systems, clinical"[Mesh] OR assess* OR analy* OR evaluat* OR estimate* OR measur* OR apprais* OR scale* OR model* OR algorithm* OR metric* OR score* OR scoring* OR index* OR indices* OR count* OR stratif* OR classif* OR predict* OR prognos* OR tool* OR rule* OR aid OR aids OR hierarch* OR tier* OR decision OR cds system))

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