REVIEW ARTICLE

Diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome in the emergency department setting: a systematic review

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ABSTRACT

Objective: We sought to determine the diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome (ACS) in the emergency department (ED) setting.

Methods: We searched MEDLINE, EMBASE, Web of Science and the Cochrane Database of Systematic Reviews. We contacted content experts to identify additional articles for review. Reference lists of included studies were hand searched. We selected articles for review based on the following criteria: 1) enrolled consecutive ED patients; 2) incorporated variables from the history or physical examination, electrocardiogram and cardiac biomarkers; 3) did not incorporate cardiac stress testing or coronary angiography into prediction rule; 4) based on original research; 5) prospectively derived or validated; 6) did not require use of a computer; and 7) reported sufficient data to construct a 2 ∞ 2 contingency table. We assessed study quality and extracted data independently and in duplicate using a standardized data extraction form.

Results: Eight studies met inclusion criteria, encompassing 7937 patients. None of the studies verified the prediction rule with a reference standard on all or a random sample of patients. Six studies did not report blinding prediction rule assessors to reference standard results, and vice versa. Three prediction rules were prospectively validated. Sensitivities and specificities ranged from 94% to 100% and 13% to 57%, and positive and negative likelihood ratios from 1.1 to 2.2 and 0.01 to 0.17, respectively.

Conclusion: Current prediction rules for ACS have substantial methodological limitations and have not been successfully implemented in the clinical setting. Future methodologically sound studies are needed to guide clinical practice.

Keywords: acute coronary syndrome, myocardial infarction, unstable angina, diagnosis, emergency medical services

RÉSUMÉ

Objectif : Nous avons cherché à déterminer l'exactitude diagnostique des règles de prévision clinique visant à exclure le syndrome coronarien aigu (SCA) dans les salles d'urgence.

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Submitted Sept. 25, 2007; Revised Jan. 19, 2008; Accepted Jan. 23, 2008

This article has been peer reviewed.

CJEM 2008;10(4):373-82

Méthodes : Nous avons interrogé les bases de données MEDLINE, EMBASE, Web of Science et les revues systématiques Cochrane. Nous avons communiqué avec des experts du contenu afin d'inclure des articles additionnels dans notre étude. Les listes bibliographiques des articles répertoriés ont été analysées manuellement. Nous avons appliqué les critères suivants pour la sélection des articles de notre étude : 1) recrutement de patients consécutifs à l'urgence; 2) inclusion de variables sur les antécédents ou l'examen physique, l'électrocardiogramme et les biomarqueurs cardiaques; 3) exclusion des études incluant les électrocardiographies d'effort ou les coronographies dans les règles de prévision; 4) étude fondée sur les recherches originales; 5) règles de prévision dérivées ou validées prospectivement; 6) utilisation d'un ordinateur exclue; 7) collecte de données suffisantes pour construire un tableau de contingence 2 ∞ 2. Nous avons évalué la qualité des études et extrait des données indépendamment et en double à l'aide d'un formulaire normalisé d'extraction de données.
Résultats : Huit études, regroupant 7937 patients, répondaient aux critères d'inclusion. Aucune des études ne vérifiait la règle de prévision avec un étalon de référence pour tous les patients ou un échantillon aléatoire de patients. Six études ne mentionnaient pas si les résultats obtenus avec l'étalon de référence étaient analysés en aveugle ou non. Trois règles de prévision ont été validées prospectivement. La sensibilité et la spécificité variaient de 94 à 100 % et de 13 % à 57 %, et les rapports de vraisemblance positif et négatif variaient respectivement de 1,1 à 2,2 et de 0,01 à 0,17.
Conclusion : Les règles actuelles de prévision du SCA ont des limites méthodologiques considérables et n'ont pas été mises en application avec succès en clinique. Il faut réaliser d'autres études méthodologiques solides pour orienter la pratique clinique.

Introduction

Chest pain is a diagnostic dilemma for the emergency physician. Data from the United States suggest that 2.1% of patients with acute myocardial infarction and 2.3% of patients with unstable angina are misdiagnosed,[1] with slightly higher rates reported in a recent Canadian study (4.6% and 6.4%, respectively).[2] Information obtained from the history, the initial 12-lead electrocardiogram (ECG), and a single set of cardiac markers does not have sufficient sensitivity to identify those patients who are safe for early discharge.[3,4]

To assist the American College of Cardiology and American Heart association (ACC/AHA) in developing guidelines for the diagnosis and treatment of unstable angina, the Agency for Healthcare Research and Quality (AHRQ) produced an evidence report that summarized the literature on the prediction of risk for patients with unstable angina.[5] The evidence report consisted of 3 systematic reviews: the first evaluated the diagnostic value of the clinical history, physical exam and ECG; the second evaluated cardiac troponin; and the third assessed chest pain units and emergency department (ED) protocols. Despite these 3 systematic reviews, neither the 2007 ACC/AHA Guidelines for the Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction,[6] nor the practical implementation of the 2002 AHA guidelines for the ED[7] identify a subset of patients at very low risk for acute coronary syndrome (ACS) who can be safely discharged from the ED without cardiac stress testing. As a result, many patients at low risk for ACS may undergo prolonged ED observation or extensive outpatient investigation, resulting in a greater likelihood of false positive cardiac stress testing and significant cost to the health care system.

Clinical prediction rules are clinical tools that are designed to be used at the bedside to assist physician decision-making.[8] They are derived from original research and incorporate variables from the history, physical examination and basic laboratory tests.[9] When evaluating patients with chest pain in the ED setting, clinicians rely on readily available information obtained from the history and physical examination, ECG and cardiac biomarkers. We conducted a systematic review to summarize the diagnostic accuracy of clinical prediction rules that incorporate these variables in decision-making. This review was designed to answer the question: In patients who present to the ED with chest pain, what is the diagnostic accuracy of clinical prediction rules to exclude ACS?

Methods

A protocol (available upon request) was written with input from both content experts (A.S.J. and I.G.S.) and 1 systematic review methodology expert (V.M.M.). This report adheres to the Quality of Reporting of Meta-analyses (QUOROM) guidelines as applicable to diagnostic accuracy reviews.[10]

Search strategy

The search strategy was designed and conducted by an expert reference librarian (P.E.) with input from the clinical lead. Given that clinical prediction guides are variably indexed in the literature as clinical prediction rules, clinical decision rules, risk scores, algorithms and risk stratification tools, we incorporated medical subject heading keywords and a highly sensitive validated search filter for retrieving methodologically sound clinical prediction guides in the search strategy (Appendix 1[11]). A second information specialist reviewed the search strategy and Boolean logic of the combination for errors. The electronic search included the following databases: MEDLINE (1950 to May 2007), EMBASE (1988 to 2007 week 05), Web of Science (1993 to February 2007) and Cochrane Database of Systematic Reviews (fourth quarter, 2006). The Ovid interface was used for searching MEDLINE and EMBASE. No language restrictions were applied. Adjustments were made to the search strategy to account for differences in indexing between databases.

Conference proceedings from the Canadian Association of Emergency Physicians and the Society for Academic Emergency Medicine from 2005 to 2007 were hand searched to identify abstracts that had not yet been indexed in electronic bibliographic databases. We consulted content experts (A.S.J. and J.E.H.) to identify additional published or other unpublished reports. Reference lists of included studies were searched to identify other relevant studies.

Eligibility criteria

The purpose of this review was to identify prediction rules of sufficient methodological rigour that would warrant consideration for use in clinical practice. To safeguard against intrusion of bias, inclusion criteria were chosen according to published methodological standards for clinical prediction rules, and are listed in Box 1.[8,9]

We included studies that incorporated information from commonly available tests (ECG and cardiac biomarkers) since clinicians rely on these basic investigations in conjunction with their history and physical examination in bedside decision-making. Moreover, the limitations of variables from the history, physical examination and ECG for detecting ACS are well-established.[12] Studies incorporating cardiac stress testing or coronary angiography as part of the prediction rule were excluded to reduce the risk of incorporation bias. Prediction rules that were not prospectively derived or validated were excluded.[9] Prediction rules requiring use of a computer to generate diagnostic probabilities were excluded because an in-depth review of artificial neural networks was beyond the scope of this review.

Box 1. Eligibility criteria for included studies

1. Enrolment of consecutive emergency department patients
2. Incorporation of variables from the history or physical examination, electrocardiogram and cardiac biomarkers
3. Cardiac stress testing or coronary angiography not incorporated as part of prediction rule
4. Based on original research
5. Prospectively derived or validated
6. Does not require use of a computer to generate diagnostic probabilities
7. Data available to construct a 2×2 contingency table

Study selection

Study retrieval was conducted in duplicate by 2 independent reviewers in 2 phases. In phase I, we screened titles and abstracts to identify potentially relevant articles. In phase II, we obtained the full articles and assessed them for eligibility. We determined the degree of interobserver agreement for each phase and reported κ values based on the following: for phase I "potentially eligible yes/no" agreement; for phase II, "eligible yes/no." After making independent assessments, we resolved disagreements by consensus.

Assessment of methodological quality

Although methodological criteria for clinical decision rules have been published, they have not been validated for use in systematic reviews. As such, QUADAS (Quality Assessment of Diagnostic Accuracy Studies), a validated quality assessment tool, was used.[13] Two reviewers (E.P.H. and V.T.), working independently, assessed the quality of included studies. We calculated κ values based on the total number of QUADAS criteria met and subsequently resolved all disagreements by consensus. We dichotomized answers as "yes" and "no/unclear" for κ calculations.

When assessing the methodological quality of clinical prediction rules, it is useful to classify studies based on the hierarchy of evidence for clinical prediction rules.[8] In this classification, prediction rules that have been derived but not validated constitute the lowest level of evidence (level 4), followed by studies that have been validated in only 1 narrow prospective sample (level 3), studies that have been validated broadly in multiple settings (level 2) and studies that have undergone impact analysis (level 1).

Data extraction

Working independently and in duplicate using a standardized data extraction form, we recorded the following descriptive data from every study: year and journal of publication, patient population (e.g., age, sex, cardiac risk factors

and medical history), percentage of patients in whom ECGs, cardiac biomarkers and stress tests or coronary angiograms were obtained, clinical prediction rule characteristics, duration of follow-up and outcome definitions. We extracted the necessary data to construct 2 ∞ 2 contingency tables. If data from the primary report were unclear, we contacted the corresponding author for clarification. If the corresponding author did not respond, we entered consensus data into each cell of the contingency table. Data were entered into a Microsoft Excel database (Microsoft Corp.).

Data synthesis

Sensitivity and specificity were calculated from 2 ∞ 2 contingency tables. Forest plots of sensitivity and specificity, and positive and negative likelihood ratios were constructed using Meta-DiSc software (Unit of Clinical Biostatistics of the Ramón y Cajal Hospital).[14]

Results

Study selection

Figure 1 describes the flow of candidate and eligible articles. The initial search strategy produced 720 records. After removing 46 duplicates, 674 records remained for screening in phase I. Eighty potentially eligible records were identified for further review based on review of the title and abstracts (κ = 0.95). Review of the full articles in phase II identified 8 that met inclusion criteria (κ = 0.85).[15–21] Two additional articles were selected for further review from the bibliographies of selected articles.[22,23] On full text review these were excluded because one retrospectively analyzed data that was originally collected from 2 large clinical trials[22] and the other required the use of a computer to generate diagnostic probabilities.[23] One potentially relevant article was identified through consultation with content experts. The article did not incorporate variables from the history or physical examination into the prediction tool and was therefore excluded.[24] Data were available to construct 2 ∞ 2 contingency tables for all 8 articles that met inclusion criteria. The 8 articles included in the review represent 5 different clinical prediction rules.

Characteristics of included studies

The studies included in the review were published from 2003 to 2007 and included 7937 patients in total (Table 1[15–21,25]). There were 3 studies conducted in the United States, 2 in the United Kingdom, 1 in Canada, 1 in Spain and 1 in Brazil. With the exception of 1 study that enrolled adults between 24 and 39 years of age,[19] and 2 studies that did not report cardiac risk factors,[18,20] the remaining studies reported approximately comparable baseline characteristics and cardiac risk factors.

Quality assessment

Assessment of quality based on QUADAS criteria count had an interobserver agreement of 89.3% (κ = 0.79) (Table 2[15–21,25]). None of the studies verified the results of their index test (prediction rule) against a reference standard of diagnosis (cardiac stress testing or coronary angiography) on either the whole study population or random sample thereof. A proxy reference standard of close patient follow-up for the development of adverse events was used in 7 studies.[16–21,25] The reference standard was not reported in 1 study.[15] Of the 8 studies, 6 did not clearly specify that the index test was interpreted without knowledge of results of the reference standard,[15,17,18,20,21,25] nor did it specify that the reference standard was interpreted without knowledge of the results of the index test. Table 2 lists quality assessment

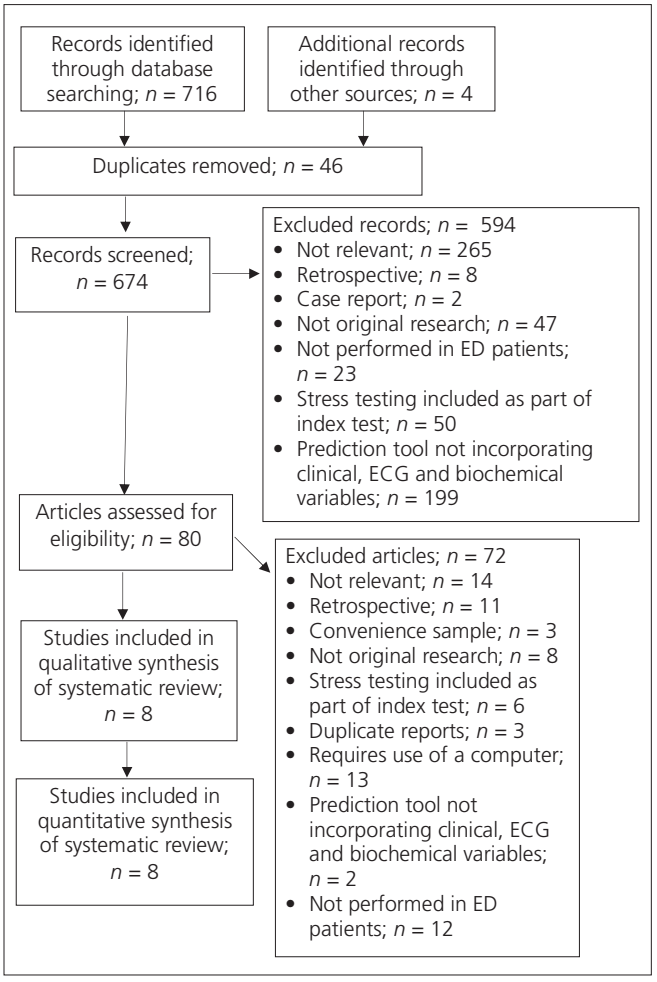


Fig. 1. Flow diagram of study selection process. ECG = electrocardiogram; ED = emergency department.

scores, diagnostic testing and prevalence of disease for each study.

Three of the prediction rules were derived but not validated (level 4 in hierarchy of evidence).[15,16,21] Bassan and colleagues[15] classified the type of chest pain according to the likelihood of ACS and based subsequent diagnostic testing on this assessment. This increased the risk of verification bias (i.e., failure to use the same gold standard on all patients), potentially overestimating diagnostic performance. In addition, it is unclear whether outcomes were assessed without knowledge of the chest pain classification and vice versa (i.e., the lack of blinding). Fernandez Portales and colleagues[21] used cardiology residents to select patients for enrolment based on a presumed diagnosis of ACS thus reducing the generalizability of their results. The clinical decision rule derived by Christenson and colleagues,[16] on the other hand, adhered to established methodology for clinical prediction rules.[9] All patients with a primary complaint of chest pain were potentially eligible, reducing the risk of selection bias. Study assistants

Table 1. Characteristics of included studies

Study (and no. of patients enrolled)	Clinical prediction guide	Variables included in prediction guide	Duration of follow-up	Outcomes
Bassan et al.[15] (1003)	Classification diagnostic tree	chest pain type, history of CAD, history of diabetes, CK-MB level, ST depression or T-wave inversion on ECG	Not reported	• AMI • Unstable angina
Chase et al.[17] (1481)	Risk score	age ≥ 65 yr, known CAD, ≥ 3 cardiac risk factors, ST-segment deviation, ≥ 2 anginal events in past 24 hr, aspirin use in past 7 d, elevated cardiac biomarkers	30 d	• All-cause mortality • AMI • Revascularization
Christenson et al.[16] (819)	Clinical prediction rule	Age < 40 yr, normal or T-wave flattening on initial ECG, initial CK-MB < 3.0 ng/mL, or initial CK-MB > 3.0 ng/mL with no change in ECG, rise in CK-MB, or rise in troponin I 0–12 hr after arrival	30 d	• AMI • Unstable angina
Conway Morris et al.[18] (1000)	Risk score	age ≥ 65 yr, known CAD, ≥ 3 cardiac risk factors, ST-segment deviation, ≥ 2 anginal events in past 24 hr, aspirin use in past 7 d, elevated cardiac marker levels	30 d	• All-cause mortality • ST-segment elevation myocardial infarction • AMI • Troponin-positive acute coronary syndrome • Revascularization
Fernandez Portales et al.[21] (321)	Risk score	6 hr troponin T > 0.04 ng/mL, age > 70 yr, cardiac history, prolonged chest pain in past 15 d, chest pain on presentation without ST-segment depression, chest pain on presentation with ST-segment depression, 6 hr troponin T > 0.04 ng/mL without ST-segment depression, 6 hr troponin T > 0.04 ng/mL with ST-segment depression	15 d	• Recurrent ischemia • Death • Heart failure
Lyon et al.[20] (1000)	Risk score	age, pulse rate at presentation, systolic blood pressure at presentation, serum creatinine level at presentation, Killip score, ST-segment depression on presenting ECG, elevated initial serum cardiac biomarker level, cardiac arrest on admission	30 d	• All-cause mortality • ST-segment elevation myocardial infarction • AMI • Troponin-positive acute coronary syndrome • Revascularization
Marsan et al.[19] (1077)	Clinical prediction rule	Absence of cardiac history , no cardiac risk factors, normal ECG, CK-MB < 5 ng/mL, troponin I < 0.3 ng/mL	30 d	• AMI • Unstable Angina
Tong et al.[25] (1236)	Risk score	age ≥ 65 yr, known CAD, ≥ 3 cardiac risk factors, ST-segment deviation, ≥ 2 anginal events in past 24 hr, aspirin use in past 7 d, elevated cardiac marker level	30 d	• All-cause mortality • AMI • Revascularization • Unstable Angina

AMI = acute myocardial infarction; CAD = coronary artery disease; CK-MB = creatine kinase; ECG = electrocardiogram.

assessed potential predictor variables without knowledge of the outcome and vice versa (adequate blinding).

Two prediction rules have been prospectively validated in 1 narrow sample (level 3).[19,20] Marsan and colleagues[19] enrolled only adults from 24 to 39 years of age, limiting the study's generalizability. Lyon and colleagues[20] enrolled all patients with chest pain, decreasing the likelihood of selection bias. However, outcome was determined from routinely available data rather than close prospective follow-up, increasing the risk of misclassification for some patients.

The Thrombolysis in Myocardial Infarction (TIMI) risk score has been prospectively validated by 3 studies (level 2).[17,18,25] Chase and colleagues[17] enrolled all patients with nontraumatic chest pain in whom an ECG was obtained, decreasing the likelihood of selection bias. However, they did not report whether the score was assessed while blinded to the outcome diagnosis and vice versa. Conway Morris and colleagues[18] validated the TIMI score in patients with chest pain deemed to be potentially cardiac in origin by the treating physician, potentially introducing selection bias. Also, the outcome relied on discharge diagnosis rather than prospective follow-up. Finally, Tong and colleagues[25] enrolled all patients with presumed cardiac chest pain that persisted longer than 30 minutes, but 237 (19%) patients were either lost to follow-up or had uninterpretable reference standard test results, potentially biasing the estimates of diagnostic performance.

Heterogeneity

We observed substantial heterogeneity between studies with regard to the variables incorporated in each clinical prediction tool, the cardiac biomarker assays used, the pretest probability of disease and the outcome measures. With the exception of 3 studies that validated the TIMI risk score,[17,18,25] each study incorporated different variables into the prediction model. The study by Bassan and colleagues[15] used CK-MB, 5 studies used cardiac troponin alone,[17,18,20,21,25] and 2 studies used both CK-MB and cardiac troponin.[16,19] Only 2 of the studies[16,19] reported the actual assay used to measure the biomarker as recommended by reporting guidelines.[26] The pretest probability of disease varied between studies, potentially contributing to variability in diagnostic performance. The outcome measures in each

Table 2. Quality assessment and extensiveness of diagnostic testing in included studies

		Test; no. (and %) of patients			Probability of disease; no. (and %) of patients			
Study; stage of development	No. of QUADAS criteria met	ECG	Cardiac markers	Stress testing or coronary angiography	Pretest probability (prevalence)	Post–positive test	Post–negative test	Comments
Bassan et al.;[15] derivation	10	556 (100)	443 (78.3)	—	269/566 (47.5)	260/388 (67)	9/578 (5.1)	117 (20.7%) discharged based on clinical and ECG assessment alone
Chase et al.;[17] validation	10	1458 (100)	1293 (85)	unclear	136/1458 (9.3)	128/983 (13)	8/475 (1.7)	TIMI Risk Score
Christenson et al.;[16] derivation	10	769 (100)	769 (100)	—	165/769 (21.5)	163/571 (28.5)	2/198 (1)	Vancouver Chest Pain Rule
Conway Morris et al.;[18] validation	9	—	—	—	137/954 (14.4)	137/723 (18.9)	0/231 (0)	TIMI Risk Score
Fernandez Portales et al.;[21] derivation	8	321 (100)	321 (100)	Coronary angiography 60 (18.7)	81/321 (25.2)	79/210 (37.6)	2/111 (1.8)	Cardiology resident enrolled patients with suspected acute coronary syndrome
Lyon et al.;[20] validation	9	—	—	—	123/734 (16.8)	123/657 (18.7)	0/77 (0)	Data to calculate a GRACE Score not available in 240 (24%) patients
Marsan et al.;[19] validation	11	1023 (100)	—	—	57/1023 (5.6)	56/724 (7.7)	1/299 (0.3%)	Study restricted to patients 24–39 years old
Tong et al.;[25] validation	9	957 (100)	957 (100)	unclear	138/957 (14.4)	135/802 (16.8)	3/155 (1.9)	TIMI Risk Score

ECG = electrocardiograms; GRACE = Global Registry of Acute Coronary Events; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; TIMI = Thrombolysis in Myocardial Infarction; — = not reported.
*Percentages were calculated based on the total number of patients analyzed in each study.

study, as well as their definitions, also varied. For these reasons, the study data were not pooled.

Diagnostic performance

Figure 2[15–21,25] shows a forest plot of sensitivity. Two studies reported sensitivities of 100%, with the remainder ranging from 94% to 99%. The forest plot for specificity is displayed in Figure 3.[15–21,25] Substantial variation between specificity estimates is evident, with most estimates falling well below the 50% range. Figure 4[15–21,25] and Figure 5[15–21,25] display forest plots of positive and negative likelihood ratios. Given that clinical prediction rules prioritize sensitivity over specificity, the positive likelihood ratios are near 1 (little diagnostic information), while the negative likelihood ratios are small. As a result, patients who are prediction-rule negative have a low posttest probability of disease.

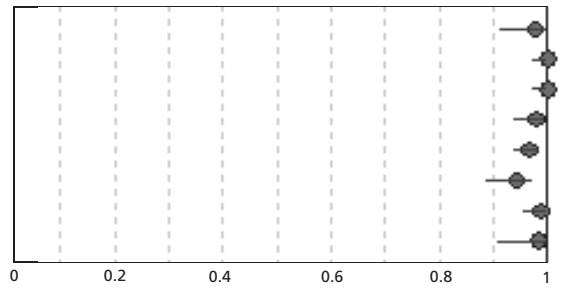
Discussion

We conducted a systematic review of prospective clinical decision rules that exclude ACS in ED patients with chest pain. Of the 8 risk prediction rules, 5 have been prospectively validated and thus could be considered for use in clinical practice.[8,9] Although the diagnostic performance of the TIMI[18] and Global Registry of Acute Coronary Events (GRACE)[20] scores was sufficient for incorporation into clinical practice, the performance of the TIMI risk score varied between studies and the GRACE score required data that was not available in all ED patients. We did not identify any prediction tool that was appropriate for incorporation into clinical practice.

All 8 studies had methodological weaknesses that could have led to the introduction of bias. Deficiencies in reference standard testing, follow-up and blinding could have led to overestimation of diagnostic performance.[15,17,18,20,21,25]

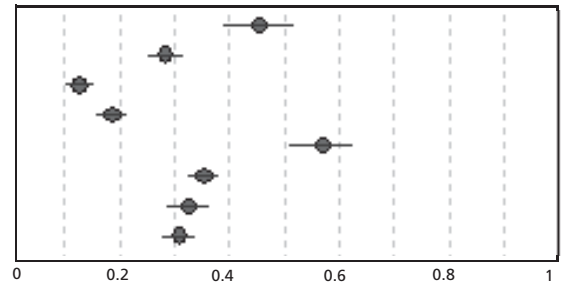
We observed considerable heterogeneity between the studies with regard to the variables incorporated in each clinical prediction tool, the cardiac biomarkers and cutoff values selected, the prevalence of disease, the outcome studied and the diagnostic performance.

Likelihood ratios (LRs), unlike positive and negative predictive values, are independent of disease prevalence, and thus useful for comparing diagnostic tests between



	Sensitivity	95% CI
Portales Fernandez et al.[21]	0.98	0.91–1.00
Conway Morris et al.[18]	1.00	0.97–1.00
Lyon et al.[20]	1.00	0.97–1.00
Tong et al.[25]	0.98	0.94–1.00
Bassan et al.[15]	0.97	0.94–0.98
Chase et al.[17]	0.94	0.89–0.97
Christenson et al.[16]	0.99	0.96–1.00
Marsan et al.[19]	0.98	0.91–1.00

Fig. 2. Forest plot of sensitivity. Point estimates of sensitivity along with 95% confidence intervals (CIs) (horizontal bars) are plotted for each study population.



	Specificity	95% CI
Portales Fernandez et al.[21]	0.45	0.39–0.52
Conway Morris et al.[18]	0.28	0.25–0.31
Lyon et al.[20]	0.13	0.10–0.15
Tong et al.[25]	0.19	0.16–0.21
Bassan et al.[15]	0.57	0.51–0.63
Chase et al.[17]	0.35	0.33–0.38
Christenson et al.[16]	0.32	0.29–0.36
Marsan et al.[19]	0.31	0.28–0.34

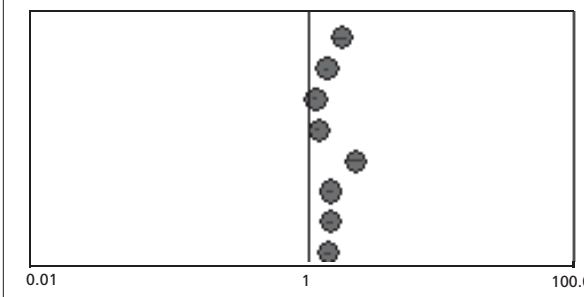
Fig. 3. Forest plot of specificity. Point estimates of sensitivity along with 95% confidence intervals (CIs) (horizontal bars) are plotted for each study population.

populations. A negative LR less than 0.1 is generally considered clinically useful.[27] The upper bound of the 95% confidence interval for the negative LR in each study included 0.1, suggesting that none of the prediction rules exclude ACS with enough certainty to be clinically useful.

Numerous risk stratification tools for ED patients with chest pain have been published. In the 1980s, Goldman and colleagues[28,29] derived and validated a computer protocol to predict myocardial infarction. However, much like other computer-derived prediction tools in emergency medicine,[4,23,30–41] it has not been broadly adopted by emergency physicians. The Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) designed by Selker and colleagues[39] is another prediction tool that has been commonly used. A multicentre controlled clinical trial found that its use reduced hospitalization among ED patients with chest pain. The ACI-TIPI instrument, however, defines low risk as less than a 10% risk for ACS, which is not low enough to forego cardiac stress testing. Also, it does not incorporate the results of cardiac biomarkers.

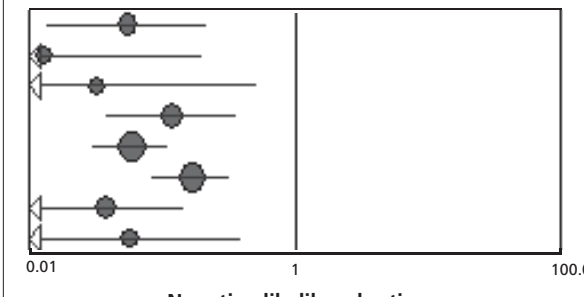
There is limited evidence to suggest what miss rate clinicians would consider acceptable. It is conceivable that this may differ between Canadian and American emergency physicians. In Canada, few ED-based observation units exist, and patients are often managed on an individualized basis.[2] Given the miss rate of 5.3%,[2] and the cost implications of broadly adopting ED observation units, a clinical prediction rule that decreases the rate of misdiagnosis in a fiscally efficient manner is likely to be acceptable to clinicians. A survey of Canadian emergency physicians indicated that most (94%) would use a clinical prediction rule for ACS, provided that it did not increase the miss rate above 2%.[42] In the United States, however, physicians' triage decisions may be influenced more by perceived medical and legal risk, and it is not known what miss rate would be acceptable to most US physicians.

In the course of the review we did not identify a prediction tool to recommend for use in clinical practice. Future studies in this area are needed to guide clinical practice and should be carefully designed to prevent intrusion of bias,[8,9] to take into account current guidelines by the European Society of Cardiology and by the American College of Cardiology[43] and standardized reporting guidelines for ED studies,[26] and to use the most sensitive cardiac troponin assays available.[44,45]



	Positive likelihood ratio	95% CI
Fernandez Portales et al.[21]	1.79	1.58–2.02
Conway Morris et al.[18]	1.39	1.33–1.45
Lyon et al.[20]	1.14	1.10–1.18
Tong et al.[25]	1.20	1.15–1.25
Bassan et al.[15]	2.24	1.96–2.56
Chase et al.[17]	1.46	1.37–1.54
Christenson et al.[16]	1.46	1.38–1.55
Marsan et al.[19]	1.42	1.35–1.50

Fig. 4. Forest plot of positive likelihood ratios. Horizontal bars represent the 95% confidence interval (CI).



	Negative likelihood ratio	95% CI
Fernandez Portales et al.[21]	0.05	0.01–0.22
Conway Morris et al.[18]	0.01	0.00–0.20
Lyon et al.[20]	0.03	0.00–0.51
Tong et al.[25]	0.12	0.04–0.36
Bassan et al.[15]	0.06	0.03–0.11
Chase et al.[17]	0.17	0.08–0.33
Christenson et al.[16]	0.04	0.01–0.15
Marsan et al.[19]	0.06	0.01–0.40

Fig. 5. Forest plot of negative likelihood ratios. Horizontal bars represent the 95% confidence interval (CI).

Limitations

Our review is primarily limited by the methodological quality of the primary studies and the relatively small number of studies meeting inclusion criteria. None of the studies verified the results of the prediction rule by using a reference standard of diagnosis on the whole sample or random selection of the sample, increasing the risk of verification bias. Although only 8 studies met inclusion criteria, we conducted a thorough literature search that was unrestricted by language. In addition, we hand searched recent conference abstracts and consulted content experts thus minimizing the potential for publication bias.

Conclusion

Chest pain is a diagnostic dilemma for the emergency physician. Current prediction rules are heterogeneous, have substantial methodological limitations and have not been successfully implemented in the clinical setting. Future methodologically sound studies are needed to guide clinical practice.

Acknowledgements: We would like to thank Dr. Maria Fernanda Bellolio Avaria for her assistance in translation. This project was conducted as part of a course on systematic reviews and meta-analysis at the University of Ottawa Epidemiology master's program. We are grateful for the assistance of Drs. David Moher and Dean Fergusson, coteachers of the course.

Competing interests: None declared.

Funding: This study was jointly funded by the American Heart Association, the Emergency Medicine Foundation and the Society for Academic Emergency Medicine.

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Appendix 1. Search strategy for MEDLINE

1. *chest pain/ or chest pain/bl, di, et, en, ep, pa, ra or (chest adj pain).mp. or chestpain.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 16582
2. (emergen$ adj3 (center$ or centre$ or unit$1 or room$1 or department$1 or service or physician$ or medicine or care or ward$1)).mp. 56706
3. emergency service, hospital/ or emergency medical services/ or triage/ 47137
4. 1 and (2 or 3) 2054
5. limit 4 to "clinical prediction guides (optimized)"[11] 415
6. exp angina pectoris/di, co, et, ep, ra or exp myocardial ischemia/di, ra, co, et, ep 123391
7. (acute adj (coronary or cardiac or myocardial or heart) adj (syndrome$ or infarct$)).mp. 40383
8. 4 and (6 or 7) 1265
9. diagnosis, differential/ or diagnostic errors/ or missed.mp. or patient discharge/ or patient readmission/ or outcome$.mp. 977299
10. 8 and 9 581
11. decision support techniques/ or multivariate analysis/ or probability/ or logistics model/ or algorithms/ or likelihood functions/ or neural networks$.mp. 168322
12. 10 and 11 89
13. 8 and 11 155
14. 5 or 12 or 13 496