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Prognostic Accuracy of the HEART Score for Prediction of Major Adverse Cardiac Events in Patients Presenting With Chest Pain: A Systematic Review and Meta-analysis

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A related article appears on page 261.

ABSTRACT

Objective: The HEART score has been proposed for emergency department (ED) prediction of major adverse cardiac events (MACE). We sought to summarize all studies assessing the prognostic accuracy of the HEART score for prediction of MACE in adult ED patients presenting with chest pain.

Methods: We searched MEDLINE, PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Database of Systematic Reviews from inception through May 2018 and included studies using the HEART score for the prediction of short-term MACE in adult patients presenting to the ED with chest pain. The main outcome was short-term (i.e., 30-day or 6-week) incidence of MACE. We secondarily evaluated the prognostic accuracy of the HEART score for prediction of mortality and myocardial infarction (MI). Where available, accuracy of the Thrombolysis in Myocardial Infarction (TIMI) score was determined.

Results: We included 30 studies (n = 44,202) in analysis. A HEART score above the low-risk threshold (≥4) had a sensitivity of 95.9% (95% confidence interval [CI] = 93.3%–97.5%) and specificity of 44.6% (95% CI = 38.8%–50.5%) for MACE. A high-risk HEART score (≥7) had a sensitivity of 39.5% (95% CI = 31.6%–48.1%) and specificity of 95.0% (95% CI = 92.6%–96.6%) for MACE, whereas a TIMI score above the low-risk threshold (≥2) had a sensitivity of 87.8% (95% CI = 80.2%–92.8%) and specificity of 48.1% (95% CI = 38.9%–57.5%) for MACE. A high-risk TIMI score (≥6) was 2.8% sensitive (95% CI = 0.8%–9.6%), but 99.6% (95% CI = 98.5%–99.9%) specific for MACE. A HEART score ≥ 4 had a sensitivity of 95.0% (95% CI = 87.2%–98.2%) for prediction of mortality and 97.5% (95% CI = 93.7%–99.0%) for prediction of MI.

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Conclusions: The HEART score has excellent performance for prediction of MACE (particularly mortality and MI) in chest pain patients and should be the primary clinical decision instrument used for the risk stratification of this patient population.

Chest pain is a commonly encountered presentation in the emergency department (ED), with approximately 8 million visits per year in the United States,[1] and many of these patients are ultimately admitted to hospital for observation or intervention.[2] Approximately 10% to 20% of these patients are diagnosed with an acute coronary syndrome (ACS), characterized by myocardial ischemia, and benefit from early identification and initiation of treatment, including revascularization.[3] The goal of the clinician is to differentiate between patients presenting with ACS and those with other (typically more benign) conditions. While various historical features and laboratory values may help to identify patients with true ACS, none are sufficiently accurate to be used independently.[4] As a result, 2% to 5% of patients with true ACS are inappropriately discharged from the ED annually,[5] and missed cases of ACS represent a significant proportion of malpractice claims in the United States.[6] Therefore, there is a tendency for clinicians to overinvestigate chest pain patients with further, often more invasive testing, even in low-risk patients. This practice results in increased resource utilization without improved outcomes.[7,8]

Several decision instruments to identify low-risk chest pain patients who may be suitable for discharge without further testing are currently in use. One of the most well-recognized risk scores is the TIMI (Thrombolysis in Myocardial Infarction) score, which was originally derived and validated in a population of inpatients with unstable angina and non-ST-elevation myocardial infarction (MI), to determine their 14-day risk of major adverse cardiac events (MACE). MACE is a composite outcome that includes death, MI, and revascularization (either percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]).[9,10] While the American Heart Association (AHA) and the American College of Cardiology (ACC) have recommended the TIMI score for the initial evaluation of a patient with chest pain,[11] the use of this tool for the identification of low-risk chest pain patients has been associated with conflicting results.[12–14]

To better risk stratify ED patients with chest pain, the HEART score was derived through a process involving expert opinion and review of the existing medical literature.[15] The HEART score was created specifically to identify ED patients presenting with chest pain who were at a low risk of short-term MACE, who could then be discharged from the ED with appropriate follow-up, as well as patients with high-risk of MACE, who may require immediate intervention. The five predictors included in the HEART score are: history (H), electrocardiogram (ECG, E), age (A), risk factors (R), and troponin (T; Data Supplement S1, Table S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13649/full). A HEART score of 0 to 3 identifies a patient at "low risk" of MACE and suggests consideration of discharge. Patients with a score of 4 to 6 are considered "intermediate risk," and those with a score of 7 to 10 are considered "high risk." Since its initial validation, the HEART score has been independently validated in a number of studies worldwide. Given its potential role in the risk stratification of patients with chest pain, a better understanding of the overall prognostic accuracy of this tool is needed. We conducted a systematic review and meta-analysis to summarize the prognostic accuracy of the HEART score for prediction of short-term MACE in adult patients presenting with chest pain.

METHODS

We structured this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,[16,17] the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy,[18] and existing guidelines for reviews of diagnostic accuracy.[19] We chose to perform a meta-analysis of diagnostic test accuracy rather than predictive ability, for the specific purpose of informing accuracy of screening decisions by clinicians, which is how the HEART score is primarily utilized (i.e., to rule out MACE in low-risk patients and avoid unnecessary downstream testing). When evaluating a decision instrument in the context of screening, the most important test characteristics are the sensitivity, specificity, and positive and negative likelihood ratios. Indeed, these are the characteristics that are provided

in the large majority of included studies in this meta-analysis. The study protocol was registered with PROSPERO (CRD42018087034).

Data Sources and Searches

We searched MEDLINE, PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Database of Systematic Reviews from inception until May 1, 2018. An experienced health sciences librarian assisted in the development of the search strategy. The search was conducted using the terms "HEART score," "heart-score," "HEART tool," "HEART pathway," and "HEART pathway score" (search strategy is depicted in Data Supplement S1, Figure S1). We used Science Citation Index to retrieve reports citing the relevant articles identified from our search and then entered them into PubMed. We also conducted further surveillance searches, utilizing the "related articles" feature.[20]

Study Selection

We included all English-language full-text articles describing retrospective and prospective observational studies, as well as randomized controlled trials and quasi-randomized controlled trials. We included studies meeting the following criteria: 1) enrolled adult patients (≥16 years) with suspected ACS; 2) conducted in the ED; and 3) applied the HEART score for prediction of short-term MACE (in-hospital, 28-day, 30-day, 6-week, or 3-month). We excluded studies that evaluated MACE over longer or unspecified time periods. We similarly excluded case reports, case series, and studies only evaluating the prognostic accuracy of a modified version of the HEART score. We excluded conference abstracts, as the data often change between abstracts and full-text publications. Furthermore, the data presented in these abstracts had not been verified through peer review. To be eligible for meta-analysis, each study was required to have a 2 × 2 table of true-positive, true-negative, false-positive, and false-negative counts for at least the low-risk threshold (the primary threshold of interest), either extracted from the original article or calculated from other reported information such as declared sensitivity and specificity. We contacted authors in instances where these values could not be obtained from the reported data. We excluded the study if the corresponding author did not respond after three attempts.

We screened studies using Covidence software (Melbourne, Australia). Titles were imported into Covidence directly from the search databases, and duplicates were removed. In the first phase, two reviewers (SMF, AT) independently screened the titles and abstracts of all identified citations. Disagreement was resolved by consensus; no third-party adjudication was necessary. In phase two, the same two reviewers independently assessed full texts of the selected articles from phase one. Disagreements were resolved by consensus.

Data Extraction and Quality Assessment

We used a predesigned data extraction sheet (Data Supplement S1, Table S2) to minimize the risk of transcriptional errors. Two investigators independently collected the true-positive, false-positive, false-negative, and true-negative counts of the HEART score and TIMI score (in studies where this score was also reported), total number of MACE, and stated sensitivity and specificity of HEART and TIMI (only when included) from all studies. Disagreements were resolved through consensus. All extracted data were independently verified by a third investigator.

Two reviewers (SMF, AT) independently assessed the risk of bias for the included studies, using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.[21] Disagreements were resolved through consensus. The QUADAS-2 assesses four potential areas for bias and applicability of the research question: patient selection, index test, reference standard, and flow and timing.

Data Synthesis and Analysis

We presented individual study results graphically by plotting sensitivity and specificity estimates on one-dimensional forest plots (ordered by sensitivity)[22] as well as on the receiver operating characteristic (ROC) space, to visually assess for heterogeneity. To pool the results, we applied the hierarchical summary ROC (HSROC) model[23] and obtained summary point estimates of the pairs of sensitivity and specificity, as well as diagnostic odds ratios (ORs) and likelihood ratios, with their 95% confidence intervals (CIs). The HSROC model incorporates both within-study and between-study variability. The summary point of test accuracy estimates was plotted in the ROC space together with the summary ROC curve. Whenever the number of studies was too few (seven studies or fewer), we fit a HSROC model that assumes a symmetric SROC curve (by restricting the shape parameter to be 0).[24] The analyses were conducted using MetaDAS (Version 1.3).[18,25] Univariate tests for heterogeneity in

sensitivity and specificity are not recommended by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy, as they do not account for heterogeneity explained by phenomena such as positive threshold effects.[18] Instead, it is preferable to demonstrate heterogeneity graphically through the ROC curve and forest plots and through the use of multiple subgroup and sensitivity analyses, as done previously.[26,27] We conducted subgroup analyses of studies utilizing: 6-week incidence of MACE versus 30-day incidence of MACE, ED physician-interpreted ECG versus cardiologist-interpreted ECG, and patients presenting with chest pain versus patients presenting with "suspected ACS." We conducted sensitivity analyses excluding studies with high-sensitivity troponin and those with high risk of bias.

We assessed the overall confidence in pooled diagnostic effect estimates using the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) approach (performed by BR).[28,29] The overall confidence in effect estimates were categorized into one of four levels which included high, moderate, low, or very low. A GRADE evidence profile was created using the guideline development tool (gradepro.org).

RESULTS

Search Results

Our search identified 778 citations (Figure 1) and following removal of duplicates, we screened 557 studies, from which 62 studies underwent full-text review. We included 29 distinct cohorts from 30 studies in the meta-analysis.[30–59] All included studies evaluated the prognostic accuracy of the HEART score using a low-risk threshold (score between 0 and 3). Twenty-one studies also evaluated the prognostic accuracy of the HEART score using a high-risk threshold (score between 7 and 10).[30–32,34,36,39–42,45,46,48,50–55,57–59] Eight studies additionally evaluated the prognostic accuracy of a low-risk TIMI (score of either 0 or 1) for prediction of MACE,[31,37,45,49–51,54,57] while three evaluated the prognostic accuracy of a high-risk TIMI (score of either 6 or 7).[31,45,57]

Study Characteristics

Table 1 describes the 30 included studies, and Data Supplement S1, Table S3, provides more details on individual study characteristics. Of the included studies, 40.0% were conducted in Europe, 36.7% were conducted in North America, and 16.7% were conducted in Asia. There were 17 (56.7%) retrospective cohorts, 11 (36.7%) prospective cohorts, and two (6.7%) randomized trials. Sixteen studies evaluated the HEART score for 30-day incidence of MACE,[33–36,38,40,41,43–45,50–52,54,56,57] while 13 evaluated the HEART score for 6-week incidence of MACE.[30–32,37,39,42,47–49,53,55,58,59] Most studies included only patients presenting with chest pain, while five studies included patients presenting with "suspected ACS."[33,39,41,44,57] In 14 studies, the ECG was interpreted by an ED physician,[34,36–38,40,41,43–45,51,52,55,57,58] while in seven studies the ECG was specifically interpreted by a cardiologist.[30–32,48,53,54,59] Four studies computed the HEART score using high-sensitivity troponin assays,[37,50,52,58] while the remaining studies used conventional troponin T or I assays (as used in the original study).[15]

Quality Assessment

Quality assessments using QUADAS-2 criteria are summarized in Data Supplement S1, Figure S3. Twenty studies (66.7%) had unclear risk of bias in either/both the index test (HEART/TIMI) and/or the reference standard (MACE), as it was not explicitly stated whether these values were interpreted by blinded assessors. Seventeen studies were judged to be at high risk of bias in patient selection or application of the reference standard.

Results of Synthesis

Primary Analyses: Overall Accuracy. Figure 2 depicts the forest plots of the sensitivity and specificity of HEART score ≥ 4 and TIMI score ≥ 2 (above the low-risk threshold). Summary estimates of all diagnostic accuracy measures from the HSROC model are tabulated in Table 2, with corresponding curves depicted in Figure 3. All summary estimates described are pooled values. The sensitivity of a HEART score of ≥4 for prediction of short-term MACE was 95.9% (95% confidence interval [CI] = 93.3%–97.5%), and the specificity was 44.6% (95% CI = 38.8%–50.5%). In comparison, the pooled sensitivity of a TIMI score of ≥2 for prediction of MACE was 87.8% (95% CI = 80.2%–92.8%), and the specificity was 48.1% (95% CI = 38.9%–50.5%). A high-risk HEART score (7–10) was associated with a sensitivity of 39.5% (95% CI = 31.6%–41.8%) and specificity of 95.0% (95% CI = 92.6%–96.6%) for MACE. In comparison, a high-risk TIMI score (6–7) was associated with a sensitivity of 2.8% (95% CI = 0.8%–9.6%) and specificity

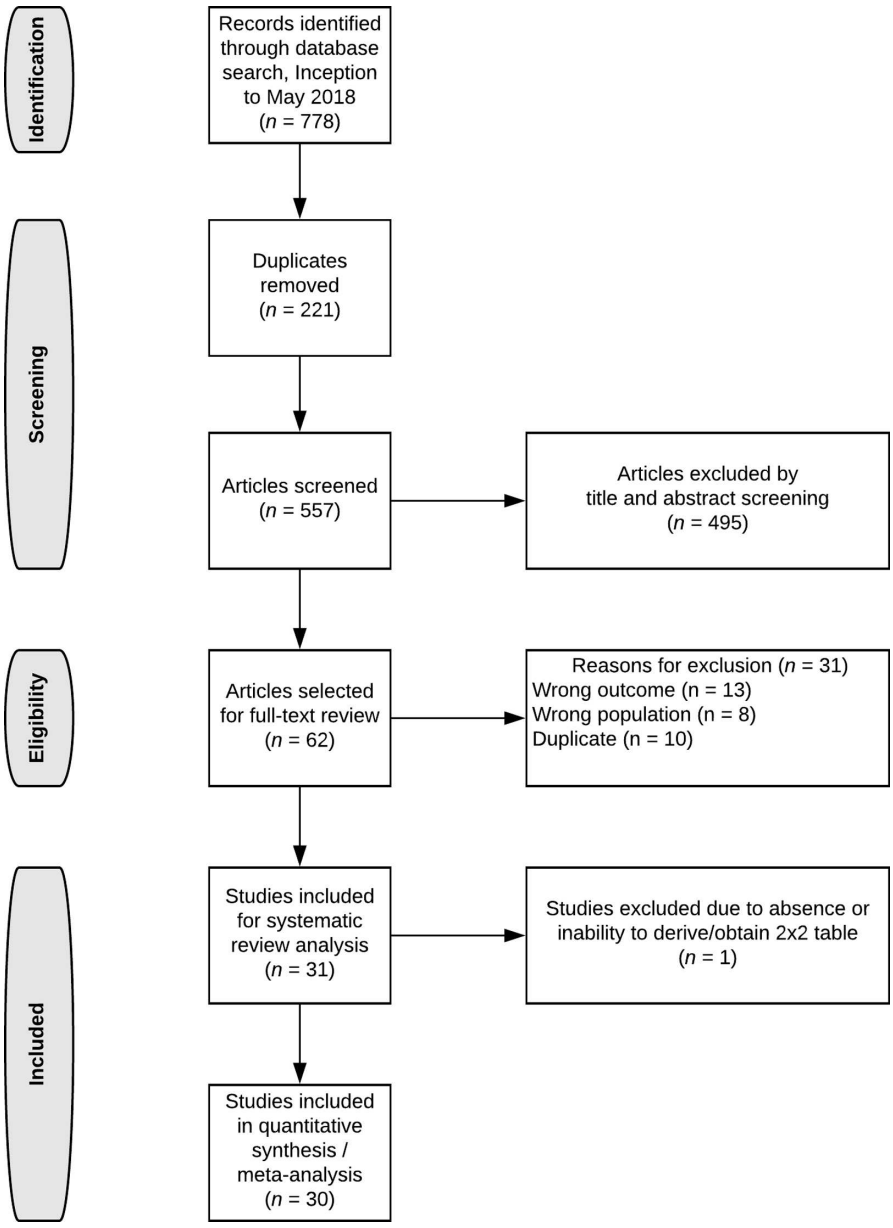


Figure 1. Flow chart summarizing evidence search and study selection.

of 99.6% (95% CI = 98.5%–99.9%). GRADE evidence profiles are included in the supplemental data (Data Supplement S1, Tables S4 and S5).

The prognostic accuracy of the HEART score for prediction of individual components of the MACE composite was also evaluated (Table 2 and Data Supplement S1, Figures S6–S11). For prediction of mortality, a HEART score above the low-risk threshold (≥4) had a sensitivity of 95.0% (95% CI = 87.2%–98.2%) and specificity of 34.2% (95% CI = 28.7%–40.2%). A high-risk HEART score (≥7) had a sensitivity of 48.4% (95% CI = 31.7%–65.4%) and specificity of 91.9% (95% CI = 88.4%–94.3%). For prediction of acute MI, a HEART score of ≥4 had a sensitivity of 97.5% (95% CI = 93.7%–99.0%) and specificity of 40.5% (95% CI = 33.6%–47.9%). A high-risk HEART score (≥7) had a sensitivity of 42.5% (95% CI = 28.9%–57.3%) and specificity of 96.9% (95% CI = 94.5%–98.3%). Finally, for prediction of coronary revascularization (i.e., PCI or CABG), a HEART score of ≥4 had a sensitivity of 89.7% (95% CI = 87.2%–91.8%) and specificity of 41.8% (95% CI = 39.4%–44.2%). A high-risk HEART score (≥7) had a sensitivity of 30.0% (95% CI = 20.2%–42.1%) and specificity of 94.5% (95% CI = 91.2%–96.6%). Prognostic accuracy of the TIMI score for prediction of individual components of the MACE composite outcome could not be evaluated due to a lack of sufficient studies.

Table 1
Characteristics of the 30 Included Studies

Description	Frequency (%)
Continent of study	
Europe	12 (40.0)
North America	11 (36.7)
Asia	5 (16.7)
Australia/Oceania	2 (6.7)
Year of publication	
2010–2014	10 (33.3)
2015–2018	20 (66.7)
Study design	
Retrospective cohort	17 (56.7)
Prospective cohort	11 (36.7)
Randomized trial	2 (6.7)
Timing of MACEs	
30-day	16 (53.3)
6-week	13 (43.3)
Presenting symptoms for inclusion	
Chest pain	25 (83.3)
Suspected ACS	5 (16.7)
Electrocardiogram interpretation	
ED physician	14 (46.7)
Cardiologist	7 (23.3)
Unknown	9 (30.0)
Troponin assay	
Conventional troponin (troponin T or troponin I)	26 (86.7)
High-sensitivity troponin	4 (13.3)

ACS = acute coronary syndrome; MACE = major adverse cardiac events.

Subgroup and Sensitivity Analyses. The results of the subgroup and sensitivity analyses to examine the prognostic accuracy of the HEART score in selected populations are depicted in Data Supplement S1, Table S6. Forest plots and HSROC curves for these analyses are displayed in Data Supplement S1, Figures S12–S27. There was no difference in pooled sensitivity among studies with ECGs interpreted by any physician compared to cardiologists specifically. Among studies evaluating only patients presenting with chest pain (as in the original HEART score study),[15] the sensitivity of a HEART score of ≥4 for MACE was 96.1% (95% CI = 93.2%–97.7%). However, there was no difference when compared to studies evaluating any patient with suspected ACS regardless of presence of chest pain. For studies only utilizing conventional troponin assays (i.e., excluding high-sensitivity troponin assays), the sensitivity of a HEART score of ≥4 for MACE was 94.9% (95% CI = 91.8%–96.9%). There were insufficient studies utilizing high-sensitivity troponin to generate pooled estimates from the HSROC model. A sensitivity analysis excluding studies with high risk of bias did not significantly alter the findings.

DISCUSSION

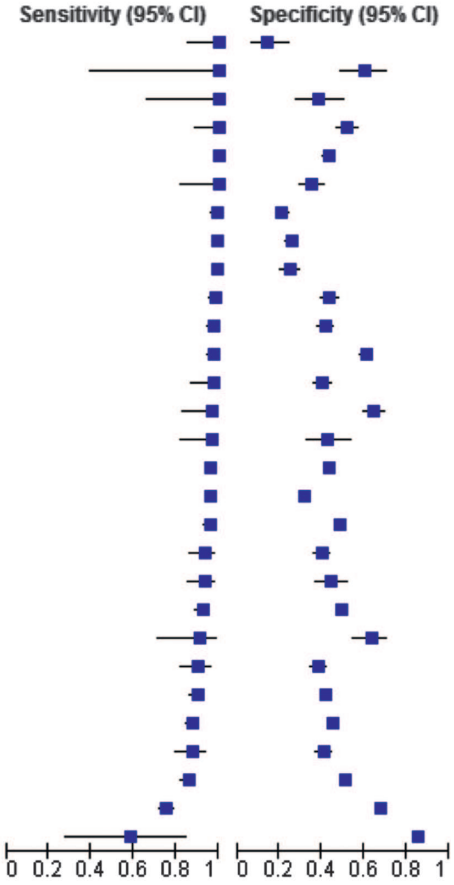
We performed a systematic review and meta-analysis to summarize the prognostic accuracy of the HEART score for prediction of short-term MACE among patients presenting with chest pain. A previous meta-analysis also evaluated the prognostic accuracy of HEART, but only included nine studies and did not investigate the accuracy of HEART for individual prediction of death and MI.[60] We condensed the findings from many external validation studies to provide a single estimate of the true prognostic performance of the score. We found a HEART score above the low-risk threshold (≥4) had high sensitivity (95.9%) for short-term MACE and was superior to the sensitivity of a TIMI score above the low-risk threshold (≥2; 87.8%). In particular, a HEART score of ≥4 had high sensitivity for both short-term mortality (95.0%) and MI (97.5%). Finally, a high-risk HEART score (≥7) had high specificity (95.0%) for short-term MACE, which was slightly lower than the specificity of a high-risk TIMI score (99.6%). Taken together, this work supports the utilization of the HEART score over the TIMI score for risk stratification of patients presenting with chest pain.

Given the difficulties associated with accurate risk stratification of patients presenting with chest pain, and the potential consequences associated with inappropriate discharge, clinicians often elect to admit patients that they believe to be at low risk of MACE.[6] As a result, the AHA/ACC guidelines have recommended that risk stratification scores should be used to aid in clinical decision making.[11] Specifically, these guidelines reference the TIMI score[9] and the Global Registry of Acute Coronary Events (GRACE) score.[61] However, neither TIMI nor GRACE was designed for ED chest pain risk stratification, but rather for prognostication among inpatients with confirmed ACS.

In a previous meta-analysis by Hess et al.,[14] the sensitivity of TIMI above the low-risk threshold (≥2) for MACE among ED patients was found to be 90.6%, which was similar to what was seen in our population (87.8%). This was despite the fact that our meta-analysis did not include any of the same citations, as none of the included studies by Hess et al. evaluated the HEART score. This suggests that the utilization of the

A

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bolvardi 2016	24	65	0	11	1.00 [0.86, 1.00]	0.14 [0.07, 0.24]
Baugh 2016	4	36	0	54	1.00 [0.40, 1.00]	0.60 [0.49, 0.70]
Willems 2014	9	49	0	31	1.00 [0.66, 1.00]	0.39 [0.28, 0.50]
Streitz 2017	31	186	0	200	1.00 [0.89, 1.00]	0.52 [0.47, 0.57]
Santi 2017	206	660	0	512	1.00 [0.98, 1.00]	0.44 [0.41, 0.47]
Patnaik 2017	19	182	0	98	1.00 [0.82, 1.00]	0.35 [0.29, 0.41]
Jain 2016	134	638	1	174	0.99 [0.96, 1.00]	0.21 [0.19, 0.24]
Mahler 2013	218	573	2	198	0.99 [0.97, 1.00]	0.26 [0.23, 0.29]
Sakamoto 2016	213	292	2	97	0.99 [0.97, 1.00]	0.25 [0.21, 0.30]
Bodapati 2016	140	303	2	233	0.99 [0.95, 1.00]	0.43 [0.39, 0.48]
Backus 2010	155	422	3	300	0.98 [0.95, 1.00]	0.42 [0.38, 0.45]
Chew 2018	206	560	5	871	0.98 [0.95, 0.99]	0.61 [0.58, 0.63]
Rainer 2017	41	335	1	225	0.98 [0.87, 1.00]	0.40 [0.36, 0.44]
Melki 2013	29	134	1	246	0.97 [0.83, 1.00]	0.65 [0.60, 0.70]
Six 2012	28	53	1	40	0.97 [0.82, 1.00]	0.43 [0.33, 0.54]
Backus 2013	392	1126	15	855	0.96 [0.94, 0.98]	0.43 [0.41, 0.45]
Six 2013	360	1726	14	806	0.96 [0.94, 0.98]	0.32 [0.30, 0.34]
Poldervaart 2017a	315	736	14	701	0.96 [0.93, 0.98]	0.49 [0.46, 0.51]
Datlow 2017	75	393	5	264	0.94 [0.86, 0.98]	0.40 [0.36, 0.44]
Visser 2015	70	100	5	80	0.93 [0.85, 0.98]	0.44 [0.37, 0.52]
Fesmire 2012	291	926	24	907	0.92 [0.89, 0.95]	0.49 [0.47, 0.52]
Leite 2015	20	56	2	96	0.91 [0.71, 0.99]	0.63 [0.55, 0.71]
Stopyra 2018	77	437	8	272	0.91 [0.82, 0.96]	0.38 [0.35, 0.42]
Bank 2017	277	936	31	671	0.90 [0.86, 0.93]	0.42 [0.39, 0.44]
de Hoog 2017	464	1616	63	1313	0.88 [0.85, 0.91]	0.45 [0.43, 0.47]
Chen 2016	79	439	11	304	0.88 [0.79, 0.94]	0.41 [0.37, 0.45]
Sun 2016	436	3780	72	3967	0.86 [0.82, 0.89]	0.51 [0.50, 0.52]
Marcoon 2013	498	2465	162	5127	0.75 [0.72, 0.79]	0.68 [0.66, 0.69]
Mahler 2011	7	159	5	899	0.58 [0.28, 0.85]	0.85 [0.83, 0.87]



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Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Poldervaart 2017b	312	997	14	425	0.96 [0.93, 0.98]	0.30 [0.28, 0.32]
Backus 2013	384	1193	23	788	0.94 [0.92, 0.96]	0.40 [0.38, 0.42]
Chew 2018	192	520	19	911	0.91 [0.86, 0.94]	0.64 [0.61, 0.66]
Rainer 2017	37	348	5	212	0.88 [0.74, 0.96]	0.38 [0.34, 0.42]
Six 2013	327	1330	47	1202	0.87 [0.84, 0.91]	0.47 [0.46, 0.49]
Sakamoto 2016	187	243	28	146	0.87 [0.82, 0.91]	0.38 [0.33, 0.43]
Marcoon 2013	493	2679	167	4913	0.75 [0.71, 0.78]	0.65 [0.64, 0.66]
Sun 2016	319	2803	189	4944	0.63 [0.58, 0.67]	0.64 [0.63, 0.65]

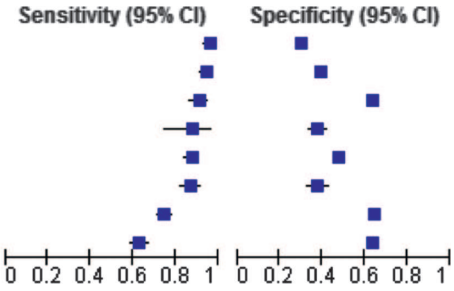

Figure 2. Forest plots of sensitivity and specificity for (**A**) HEART score above the low-risk threshold (≥4) and (**B**) TIMI score above the low-risk threshold (≥2). FN = false negative; FP = false positive; TIMI = Thrombolysis in Myocardial Infarction; TN = true negative; TP = true positive.

TIMI score among ED patients with chest pain will miss approximately one out of every 10 patients with short-term MACE. Our work demonstrates the HEART score offers superior prognostic accuracy to TIMI. A previous study has shown that the most predictive components of the TIMI score are those common to the HEART score (age, ECG changes, and troponin).[62] Therefore, after using their clinical judgment to determine a pretest probability of MACE, physicians should utilize the HEART score as the decision instrument of choice in determining a final probability of MACE in their patients presenting with chest pain (Data Supplement S1, Tables S7 and S8). For example, a patient with a pretest probability of MACE of 25% and a HEART score below the low-risk threshold (≤3) would have a posttest probability of 3.0%. That same patient with a TIMI score below the low-risk threshold (≤1) would have a posttest probability of 7.8%. It was not possible to assess the prognostic accuracy of the GRACE score, as the included studies that analyzed this score utilized different thresholds for evaluation.[31,36,49,51] These demonstrated findings have important implications for relevant guidelines and clinical policies. As mentioned, the AHA/ACC guidelines

Table 2
Summary Estimates of the Performance of the HEART Score and TIMI Score

	No. of Cohorts (No. of Patients)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Diagnostic OR (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
MACE						
HEART score ≥ 4	29 (44,202)	95.9 (93.3 to 97.5)	44.6 (38.8 to 50.5)	18.68 (12.44 to 28.06)	1.73 (1.57 to 1.90)	0.09 (0.06 to 0.14)
HEART score ≥ 7	21 (38,475)	39.5 (31.6 to 48.1)	95.0 (92.6 to 96.6)	12.40 (9.28 to 16.56)	7.89 (5.95 to 10.47)	0.64 (0.56 to 0.72)
TIMI score ≥ 2	8 (26,397)	87.8 (80.2 to 92.8)	48.1 (38.9 to 57.5)	6.68 (4.50 to 9.90)	1.69 (1.47 to 1.94)	0.25 (0.17 to 0.37)
TIMI score ≥ 6	3 (18,895)	2.8 (0.8 to 9.6)	99.6 (98.5 to 99.9)	6.69 (3.58 to 12.50)	6.53 (3.53 to 12.08)	0.98 (0.95 to 1.01)
Death						
HEART score ≥ 4	7 (9,338)	95.0 (87.2 to 98.2)	34.2 (28.7 to 40.2)	9.97 (3.64 to 27.33)	1.45 (1.32 to 1.58)	0.14 (0.06 to 0.38)
HEART score ≥ 7	5 (8,092)	48.4 (31.7 to 65.4)	91.9 (88.4 to 94.3)	10.56 (5.80 to 19.24)	5.94 (4.17 to 8.45)	0.56 (0.41 to 0.78)
MI						
HEART score ≥ 4	9 (13,032)	97.5 (93.7 to 99.0)	40.5 (33.6 to 47.9)	26.34 (10.55 to 65.76)	1.64 (1.46 to 1.84)	0.06 (0.03 to 0.15)
HEART score ≥ 7	5 (9,407)	42.5 (28.9 to 57.3)	96.9 (94.5 to 98.3)	22.88 (18.93 to 27.66)	13.58 (10.33 to 17.85)	0.59 (0.47 to 0.75)
Coronary revascularization						
HEART score ≥ 4	6 (8,391)	89.7 (87.2 to 91.8)	41.8 (39.4 to 44.2)	6.27 (4.83 to 8.14)	1.54 (1.47 to 1.62)	0.25 (0.20 to 0.31)
HEART score ≥ 7	5 (8,092)	30.0 (20.2 to 42.1)	94.5 (91.2 to 96.6)	7.33 (4.19 to 12.84)	5.43 (3.40 to 8.66)	0.74 (0.64 to 0.86)

MACE = major adverse cardiac events; MI = myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction.

currently recommend that clinicians utilize a clinical decision instrument in the risk stratification of patients with chest pain.[11] Our results suggest that the HEART score should be the preferred tool for these purposes, particularly when interested in identifying a low-risk population suitable for immediate discharge.

When evaluating patients with chest pain, the emergency physician's priority is effectively to diagnose "clinically significant" cardiac ischemia. However, as discussed extensively in the cardiovascular literature, there is no objective criterion standard to establish this diagnosis. As a result, MACE is most commonly utilized as the reference standard—a pragmatic approach to defining clinically significant ischemia based on the occurrence of adverse outcomes or need for major intervention. In this diagnostic test accuracy review, we characterized the target outcome as clinically significant cardiac ischemia, utilizing MACE as the reference standard and the HEART score as the index test.

While MACE is the most commonly utilized outcome in cardiovascular research due to its clinical importance, there is notably the potential for incorporation or verification bias—where the diagnostic test contributes to the definition of the disease. For example, consider the dilemma of evaluating the diagnostic value of troponins for identifying "clinically significant" cardiac ischemia with need for revascularization. This is a subjective diagnosis without a criterion standard and any potential outcome assessor would be likely influenced by the presence of elevated troponins. In addition, utilization of composite outcomes implicitly suggests that each component is equivalent in importance. Previous work has demonstrated that varying definitions of composite endpoints (namely MACE) in cardiovascular research studies have been associated with substantially different results and conclusions due to sample sizes being driven largely by more common, less important outcomes (i.e., PCI).[63,64] We therefore individually evaluated the prognostic accuracy of HEART for mortality, MI, and coronary revascularization. We found the sensitivity of a HEART score above the low-risk threshold (≥4) for mortality (95.0%) and MI (97.6%) was substantially better than the sensitivity for coronary revascularization (89.7%). These findings demonstrate that the HEART score offers excellent ability to identify the most objective and patient-centered components of the MACE composite (i.e., death and MI). Discussing these results with patients deemed to be low risk by the HEART score (shared decision making) may therefore have value in increasing patient knowledge and

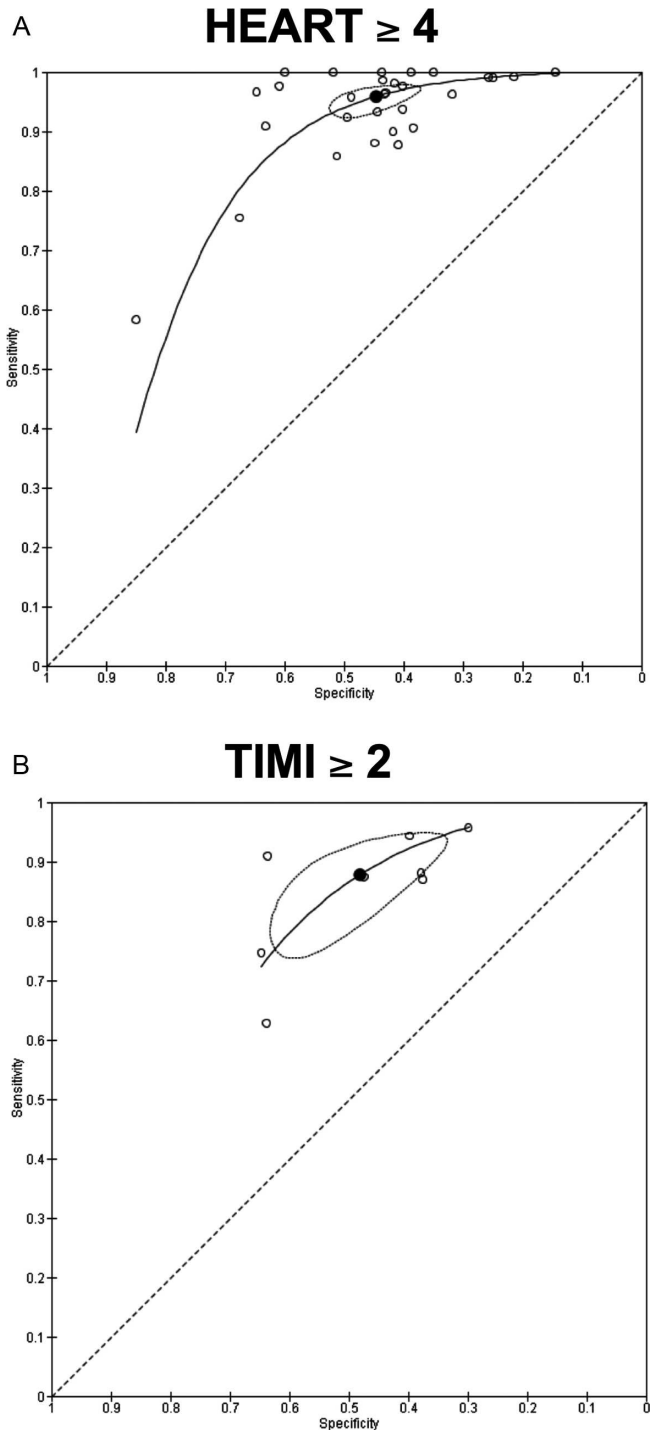

Figure 3. Hierarchical summary receiver operating characteristic curves, the bivariate summary points of (specificity, sensitivity), and the 95% confidence regions (*dotted lines*) of the summary points for (**A**) HEART score above the low-risk threshold (≥4) and (**B**) TIMI score above the low-risk threshold (≥2). FN = false negative; FP = false positive; TIMI = Thrombolysis in Myocardial Infarction; TN = true negative; TP = true positive.

engagement, while simultaneously reducing resource utilization.[65] Therefore, the utilization of shared clinical decision aids (particularly with a focus of conveying risk to patients) may increase the utilization of the HEART score by clinicians, appropriately reassure patients, and reduce unnecessary downstream testing in low-risk patients.

Finally, we performed several subgroup analyses to evaluate the accuracy of the HEART score in different clinical contexts. We found that there was no substantial difference in prediction of MACE if the ECG was interpreted by a cardiologist or by an ED physician. While the original studies on the accuracy of the HEART score had ECG interpretation performed by a cardiologist,[15,30] the primary application of the HEART score is likely to occur in the ED. Therefore, the absence of any substantial impact on prognostic accuracy of the HEART score from ED physician ECG interpretation should reinforce its use among ED clinicians. Furthermore, while the large majority of included studies used conventional troponin T and I assays for computation of the HEART score, a few of the more recent studies included a high-sensitivity troponin assay, although exclusion of these recent studies had minimal impact upon prognostic accuracy.

LIMITATIONS

This review has several strengths. It included a comprehensive search of multiple databases, clear inclusion and exclusion criteria, evaluation of multiple thresholds for each risk score, and multiple subgroup and sensitivity analyses. However, there are important limitations. Some studies were deemed to have potential high risk of bias due to inappropriate exclusion of low-risk patients, although our sensitivity analysis excluding these studies demonstrated similar performance. Additionally, we were unable to meta-analyze AUROC values, as these were not uniformly reported in most studies. However, in the evaluation of a decision instrument such as the HEART score, it can be argued that the summary estimates of sensitivity and specificity are more representative than AUROC, which does not incorporate the relative clinical consequences of false-negative and false-positive diagnoses.[66] While minimizing false positives is important in reducing downstream testing that may be of limited value in patients with chest pain, false negatives can result in death or disability. These scenarios should not be treated equally, which is an assumption of AUROC comparisons.[66] Importantly, none of the included studies compared accuracy of the HEART score to clinician gestalt. ED clinical decision instruments are rarely compared to clinician gestalt and are often not superior.[67] While the performance of the HEART score

among low-risk patients is reassuring, it is unclear whether the score identifies less patients as "low risk" compared to clinician gestalt and may ultimately lead to further downstream testing. That said, clinical gestalt should be utilized to determine pretest probability, which can then be influenced by the HEART score. In this way, clinical gestalt and decision instruments should be viewed as complementary and not competing. Finally, there was minimal evidence in the included studies surrounding the impact of the HEART score on resource utilization. Deployment of the HEART score in a stepped-wedge randomized trial did not demonstrate such savings in resource utilization,[48] although this study was limited by clinicians who were uncomfortable discharging patients with HEART scores below the low-risk threshold. Therefore, future work should focus on how use of the HEART score may impact resource utilization both in the ED and following admission or discharge.

CONCLUSION

Our systematic review and meta-analysis demonstrates that the HEART score has excellent sensitivity for identifying low-risk chest pain patients at risk of short-term major adverse cardiac events, robustly supported by findings in external validation studies across a variety of populations, settings, and study designs. A HEART score above the low-risk threshold (≥4) was associated with high sensitivity for short-term major adverse cardiac events and particularly short-term mortality and acute myocardial infarction. Our findings support the use of the HEART score among clinicians for risk stratification of patients presenting with chest pain.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13649/full

Data Supplement S1. Supplemental material.