

REVIEW ARTICLE

Systematic review and meta-analysis of predictors of major adverse cardiac events among patients with chest pain and a low HEART score in the emergency department

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ABSTRACT

Background: The HEART score is widely used for rapid risk stratification of patients presenting to emergency departments with chest pain. However, a small proportion of patients classified as low risk (score ≤ 3) still experience major adverse cardiac events (MACE). This review evaluated the residual MACE risk and the diagnostic performance of the HEART score ≤ 3 threshold.

Methods: A systematic review and meta-analysis was conducted using studies identified in PubMed and Embase from database inception to January 1, 2026. Eligible studies included adults (≥ 18 years) presenting with chest pain and reporting outcomes for a low HEART score group (0-3). Risk of bias was assessed using the Quality In Prognosis Studies tool. Random-effects models were used to pool event rates and diagnostic accuracy measures.

Results: Five observational studies including 4,072 participants were included. The pooled MACE rate among low-risk patients was 0.56% [95% confidence interval (CI), 0.04%-1.52%]. The pooled sensitivity was 0.90, although individual study estimates ranged from 0.03 to 1.00. Specificity was 0.39 (95% CI, 0.31-0.46; $I^2 = 90.6\%$), negative predictive value was 0.98 (95% CI, 0.27-1.00; $I^2 = 93.9\%$), and positive predictive value was 0.05 (95% CI, 0.01-0.18; $I^2 = 97.0\%$). A negative test reduced the modeled post-test probability of MACE to 4.9%.

Conclusion: Although a HEART score ≤ 3 was associated with a low pooled MACE incidence, substantial between-study variability and imprecise diagnostic performance estimates limit reliance on the threshold as a stand-alone discharge criterion. The modeled post-test probability of 4.9% reinforces the need for broader clinical assessment, including appropriate troponin testing, before routine early discharge.

Keywords: Chest pain, HEART score, major adverse cardiac events, emergency department, meta-analysis.

Introduction

Chest pain is a major cause of emergency department (ED) visits in high-income countries [1]. Distinguishing acute coronary syndrome (ACS)-related chest pain from non-cardiac causes is challenging. A delayed or missed diagnosis of ACS may lead to significant morbidity and mortality [2]. Therefore, it is crucial to correctly identify and stratify these patients to improve hospital efficiency and patient outcomes.

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Several tools and scoring systems have been established to aid in risk stratification of patients with chest pain. In 2008, the HEART score was first developed as a risk assessment tool to assist patients with chest pain in the emergency department [3]. Since its introduction in 2008, the HEART score has been the most common scoring system used in emergency departments for assessing patients with chest pain or ACS symptoms [4]. The HEART score is a simple and widely used risk-stratification tool that categorizes patients presenting with chest pain into low-, intermediate-, and high-risk groups [5]. The HEART score includes five clinical elements: history, ECG, age, risk factors, and troponin level. Each component was assigned 0, 1, or 2 points depending on its severity. The HEART score was the sum of these five elements [6].

In 2018, a study showed that the HEART score (0-3) accurately identified patients with low-risk chest discomfort within the HEART pathway. These patients are considered low risk, with a 0% rate of major adverse cardiac events (MACE) at 6 weeks and can be discharged for follow-up and further outpatient evaluation [7]. Other studies have shown that the HEART score is beneficial for different populations, including Japanese cohorts. The modified HEART and HEAR scores showed a high negative predictive value (NPV) for MACEs within 6 weeks. Prospective studies should be conducted in Japanese cohorts to examine serial troponin tests [8].

Due to the absence of a comprehensive systematic review addressing patients with a low HEART score, we conducted this review to identify and synthesize evidence on MACE among patients presenting with chest pain and a low HEART score in the ED and to evaluate the diagnostic performance of the HEART score ≤ 3 threshold.

Methods

Study design and settings

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [9]. The review protocol was prospectively registered in PROSPERO [10] (registration number: CRD420261284683).

Search strategy and information sources

A comprehensive literature search was conducted in PubMed and Embase (via Ovid and Embase.com) from database inception to January 1, 2026, to identify studies evaluating MACE and their predictors among patients presenting with chest pain and a low HEART score. The search strategy combined controlled vocabulary and free-text terms related to chest pain, HEART score, prognostic factors, risk stratification, and adverse cardiac outcomes, including MACE, myocardial infarction, unstable angina, revascularization, and cardiovascular mortality. The PubMed search strategy used the following combination of terms: (“Chest pain” OR “Patients” OR “Individuals” OR “Adults” OR “Chest pain presentation”) AND (“HEART score” OR “Low

HEART score”) AND (“Predictors” OR “Risk factors” OR “Prognostic factors” OR “Predictive variables” OR “Risk stratification”) AND (“Major adverse cardiac events” OR “MACE” OR “Myocardial infarction” OR “Unstable angina” OR “Revascularization” OR “Cardiovascular death” OR “Adverse cardiac events”). The search strategy was adapted as appropriate for each database while preserving the same core concepts. In addition, the reference lists of all included studies were manually screened, and citation tracking was performed to identify any additional eligible studies.

Eligibility criteria

Studies were eligible if they included adults aged 18 years or older who presented to the ED with chest pain, reported HEART scores and specifically identified a low-risk group with a score of 0-3, and evaluated MACE or potential predictors of MACE within that low-risk population. Prospective and retrospective observational studies and randomized controlled trials were eligible. Studies were excluded if they focused on patients with known coronary artery disease or myocardial infarction within the preceding 30 days, did not report the HEART score or did not separately analyze the low HEART score subgroup, were case reports, case series, editorials, or review articles without original data, or were published in languages other than English.

Study selection

Study selection followed a two-stage screening process. Titles and abstracts were screened against the eligibility criteria, after which potentially eligible full-text reports were reviewed for inclusion. Two reviewers performed study selection, with disagreements resolved by consensus.

Data extraction

A structured data-extraction form was developed and refined after pilot testing on a sample of the included studies. Extracted study-level information included publication details, design, setting, hospital characteristics, study period, funding, and declared conflicts of interest. Participant information included sample size, age, sex, cardiovascular risk factors, and study flow. Details of HEART score application included the low-risk definition, scoring scheme, ECG criteria, troponin assay and testing protocol, positivity thresholds, and rule-out pathway definitions. Outcome data included the primary outcome, individual MACE components, follow-up window, outcome assessment methods, adjudication procedures, and blinding. Where available, predictor analyses, statistical methods, effect measures, and extractable effect sizes were recorded. Data extraction was performed independently by two reviewers, and discrepancies were resolved by consensus.

Risk-of-bias assessment

Risk of bias was assessed using the Quality In Prognosis Studies (QUIPS) tool [11]. QUIPS evaluates six domains: study participation, study attrition, prognostic factor

measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain was rated as having low, moderate, or high risk of bias. Two reviewers completed assessments independently, with disagreements resolved by consensus.

Data synthesis and statistical analysis

Statistical analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA), and meta-analyses were conducted using Review Manager (RevMan, version 5.4; Cochrane Collaboration, London, UK) and R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Pooled proportions of MACE among patients with low HEART scores (≤ 3) and diagnostic accuracy measures, including sensitivity, specificity, positive predictive value (PPV), and NPV, were calculated using random-effects models. The Freeman-Tukey double-arcsine transformation was applied to stabilize variances in the presence of low event rates and zero-event studies [12], and pooled estimates were generated using the DerSimonian-Laird random-effects method [13]. Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic [14]. Leave-one-out sensitivity analyses were performed to evaluate the influence of individual studies on pooled estimates, while summary receiver operating characteristic (SROC) curves and Fagan's nomogram were generated to assess diagnostic performance and post-test probabilities. Two-tailed p values < 0.05 were considered statistically significant.

Results

Study selection and characteristics

Five studies comprising 4,072 participants met the eligibility criteria and were included in the systematic review, of which five studies contributed to quantitative synthesis. Study sample sizes ranged from 123 to 2,433 participants, and mean or median age ranged from 53.9 to 63.0 years. Four studies reported female participation ranging from 38.1% to 50.1%. Four studies were retrospective observational cohorts, whereas one was a prospective observational validation study [15] (Figure 1).

Study settings spanned Japan, the United States, Canada, and the Netherlands. Otsuka and Takeda [8] studied a university-hospital ED in Tokyo; Oliver et al. [7] studied an urban tertiary-care ED; Kuehner et al. [16] studied rural EDs; Jellema et al. [17] studied academic and community settings; and Backus et al. [15] studied 10 cardiac EDs in the Netherlands. Four studies defined low risk as HEART 0-3; Otsuka and Takeda also evaluated HEART ≤ 3 [8]. Study characteristics are summarized in Table 1.

MACE events in the low HEART score group

Four studies comprising 1,629 patients with HEART scores of ≤ 3 contributed to the pooled MACE analysis, with 17 events overall. The random-effects pooled MACE proportion was 0.0056 (95% CI, 0.0004-0.0152),

corresponding to an estimated event rate of 0.56%. Heterogeneity was moderate ($I^2 = 63.1\%$; $p = 0.043$). Event rates were low across individual studies: Otsuka and Takeda [8] and Jellema et al. [17] each reported 1 event among 318 patients, Kuehner et al. [16] reported no events among 123 patients, and Backus et al. [15] reported 15 events among 870 patients (Figure 2).

Leave-one-out sensitivity analysis

Sequential omission of Otsuka and Takeda [8], Kuehner et al. [16], or Jellema et al. [17] produced similar pooled estimates and persistent heterogeneity. In contrast, exclusion of Backus et al. [15] reduced heterogeneity to $I^2 = 0\%$, indicating that this large prospective multicenter study was the principal driver of between-study variability (Figure 3).

Diagnostic accuracy of the HEART score ≤ 3 threshold for MACE

Sensitivity

The pooled sensitivity was 0.90, but the 95% CI ranged from 0.01 to 1.00, indicating very low precision. Otsuka and Takeda [8] and Oliver et al. [7] each reported a sensitivity of 1.00, whereas Jellema et al. [17] and Backus et al. [15] reported markedly lower sensitivities of 0.03 and 0.04, respectively. Although the statistical heterogeneity estimate was $I^2 = 0\%$, the individual estimates ranged from 0.03 to 1.00; therefore, the pooled value should be interpreted cautiously (Figure 4).

Specificity

The pooled specificity was 0.39 (95% CI, 0.31-0.46), indicating limited discrimination among patients who did not experience MACE. Individual specificity ranged from 0.27 in Jellema et al. [17] to 0.48 in Otsuka and Takeda [8]. Heterogeneity was high ($I^2 = 90.6\%$; $p < 0.0001$) (Figure 5).

Positive predictive value

The pooled PPV was 0.05 (95% CI, 0.01-0.18). Individual PPV estimates ranged from 0.01 in Backus et al. [15] to 0.29 in Otsuka and Takeda [8]. Heterogeneity was substantial ($I^2 = 97.0\%$; $p < 0.0001$) (Figure 6).

Negative predictive value

The pooled NPV was 0.98 (95% CI, 0.27-1.00), but the very wide confidence interval and substantial heterogeneity ($I^2 = 93.9\%$; $p < 0.0001$) limit the certainty of this pooled estimate. Individual NPV estimates ranged from 0.42 in Jellema et al. [17] to 1.00 in Otsuka and Takeda [8] and Oliver et al. [7] (Figure 7).

Summary receiver operating characteristic analysis

The SROC plot demonstrated two distinct clusters rather than a single coherent performance pattern. Otsuka and Takeda [8] and Oliver et al. [7] formed a high-sensitivity

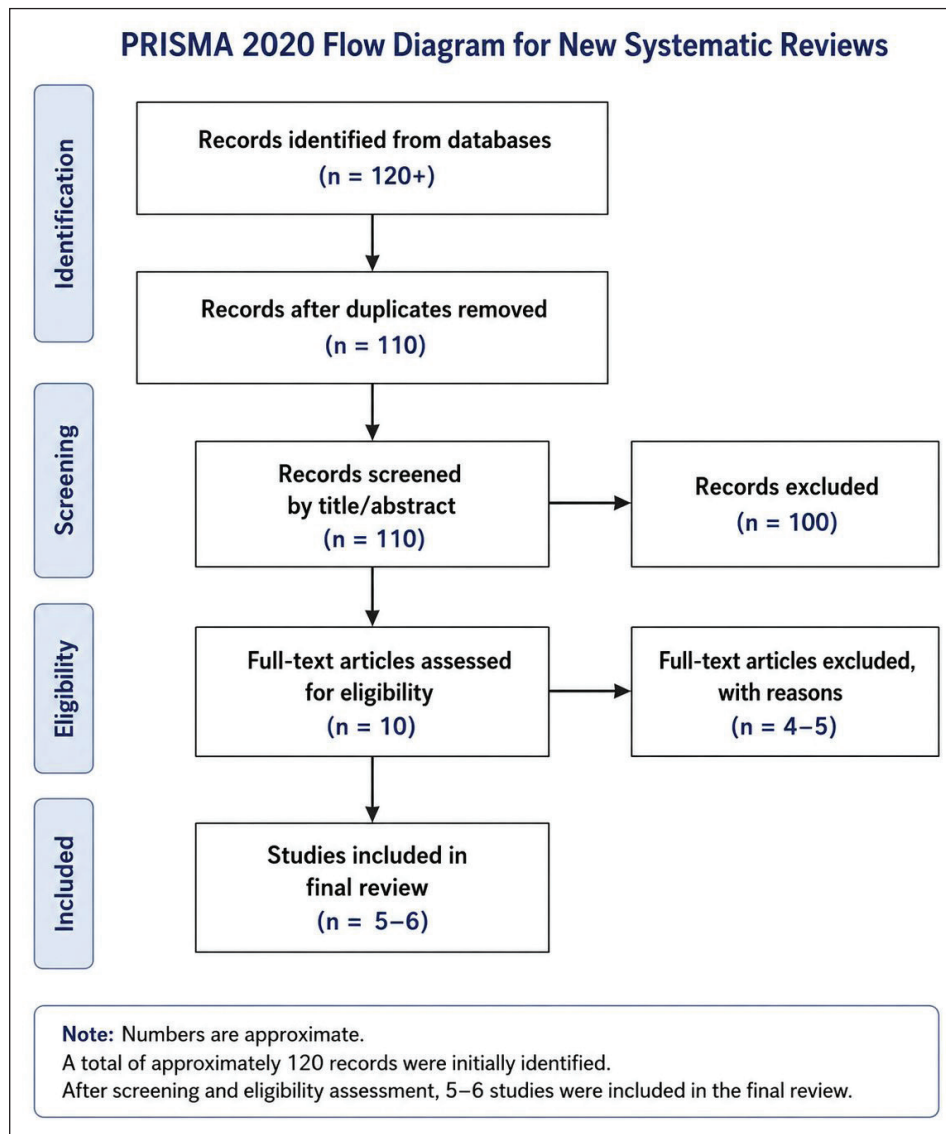


Figure 1. PRISMA flow diagram of study selection.

cluster (sensitivity 1.00), whereas Jellema et al. [17] and Backus et al. [15] formed a low-sensitivity cluster (0.03 and 0.04, respectively). This separation suggests important clinical or methodological differences among studies and argues against interpreting the pooled sensitivity as a stable property of the HEART ≤ 3 threshold across settings (Figure 8).

Fagan's nomogram

Fagan's nomogram used a pre-test MACE probability of 17.2%, a positive likelihood ratio of 1.47, and a negative likelihood ratio of 0.250. A positive test increased the modeled post-test probability to 23.4%, whereas a negative test reduced it to 4.9%. The 4.9% post-test probability after a negative result remains clinically important and was therefore emphasized in the interpretation of the findings (Figure 9).

Risk of bias

Three studies were judged to have low risk of bias across all QUIPS domains. Kuehner et al. [16] and Otsuka and

Takeda [8] had moderate risk related to confounding, and Kuehner et al. [16] also had moderate risk in study participation. No included study was judged to have high risk of bias. The domain-level distribution and study-level judgments are shown in Figures 10 and 11.

Discussion

Principal findings

This systematic review and meta-analysis included five observational studies with 4,072 patients presenting to the ED with chest pain. Four studies contributed to pooled analyses. The pooled MACE proportion among patients with HEART scores ≤ 3 was 0.56% (95% CI, 0.04%-1.52%), although heterogeneity was moderate and was largely driven by the prospective multicenter study by Backus et al. [15].

Diagnostic performance was less consistent than the pooled event rate alone suggests. Sensitivity estimates separated into two markedly different clusters: Otsuka and Takeda [8] and Oliver et al. [7] reported sensitivity

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Study	Year	Country	Design	Setting	Age, years	Female, %	Prior CAD/ MI, %	Diabetes, %	HTN, %	Smoking, %	Low-risk definition	Funding
Otsuka & Takeda [8]	2020	Japan	Retrospective observational cohort	University-hospital ED in Tokyo	63	38.1	19.2	21.9	47.9	25.3	HEAR ≤ 3 and HEART ≤ 3	Not reported
Oliver et al. [7]	2018	USA	Retrospective observational cohort	Academic urban tertiary-care ED	Mean 53.9	50.1	12.7	20.5	47.7	19.2	HEART ≤ 3	None reported
Kuehner et al. [16]	2020	Canada	Retrospective observational cohort	Rural EDs	Mean 58.8	NR	NR	12.1	33.6	21.4	HEART 0-3	None reported
Jellema et al. [17]	2014	Netherlands	Retrospective observational cohort	Two EDs: one academic and one community teaching hospital	Median 63	38.1	19.2	21.9	47.9	25.3	HEART ≤ 3	None reported
Backus et al. [15]	2013	Netherlands	Prospective observational validation cohort	Ten cardiac EDs	Mean 60.6	42.5	15.9	18.6	43.3	32.7	HEART 0-3	None reported

CAD, coronary artery disease; ED, emergency department; HEAR, History, ECG, Age, Risk factors; HEART, History, ECG, Age, Risk factors; Troponin; HTN, hypertension; MI, myocardial infarction; NR, not reported.

of 1.00, whereas Jellema et al. [17] and Backus et al. [15] reported values of 0.03 and 0.04. The SROC plot therefore did not show a single smooth performance pattern. This clustering may reflect differences in study design, case mix, troponin assays, or outcome ascertainment, and it supports cautious interpretation of the pooled sensitivity estimate.

The Fagan analysis provided an additional clinically relevant perspective. Starting from a pre-test probability of 17.2%, a negative result reduced the modeled post-test probability to 4.9%. The pre-test probability used in the Fagan analysis was derived from the overall event prevalence across studies and should be interpreted as a modeling parameter rather than the observed event rate among patients with HEART scores of ≤ 3 . Because this residual probability remains above commonly used low-risk thresholds for discharge pathways, the HEART score of ≤ 3 threshold should not be interpreted in isolation from the broader clinical context and troponin testing.

Comparison with existing literature

The pooled specificity of 39% (95% CI, 31%-46%) was broadly consistent with previous meta-analyses. Fernando et al. [18] reported a pooled specificity of 44.6%, Laureano-Phillips et al. [19] reported approximately 42%, and Ke et al. [20] reported approximately 50%. In contrast, earlier meta-analyses generally reported sensitivities around 96% [18–20], whereas the present analysis showed much wider study-level variation and a pooled sensitivity estimate with a very imprecise confidence interval.

Current chest-pain guidance considers patients with an estimated 30-day risk of death or MACE below 1% to be low risk and potentially suitable for discharge without urgent additional cardiac testing [21]. The 2018 American College of Emergency Physicians clinical policy also states that a low HEART score (≤ 3) predicts a 30-day MACE miss rate of approximately 0%-2% [22]. In the present analysis, however, the modeled post-test probability after a negative HEART threshold result was 4.9%, indicating that the threshold alone may not provide sufficient reassurance in every population.

Strengths

Strengths of this review include prospective protocol registration, adherence to PRISMA guidance, use of the QUIPS tool, application of a variance-stabilizing transformation for rare events, and leave-one-out sensitivity analysis to identify the study driving heterogeneity. The review also evaluated both event rates and several diagnostic performance measures, providing complementary perspectives on residual risk.

Limitations

This review has several limitations. First, only five studies were included, and only four contributed to pooled analyses, limiting precision and the robustness of subgroup or meta-regression analyses. Second, substantial heterogeneity was present across several diagnostic estimates. Third, all included studies were

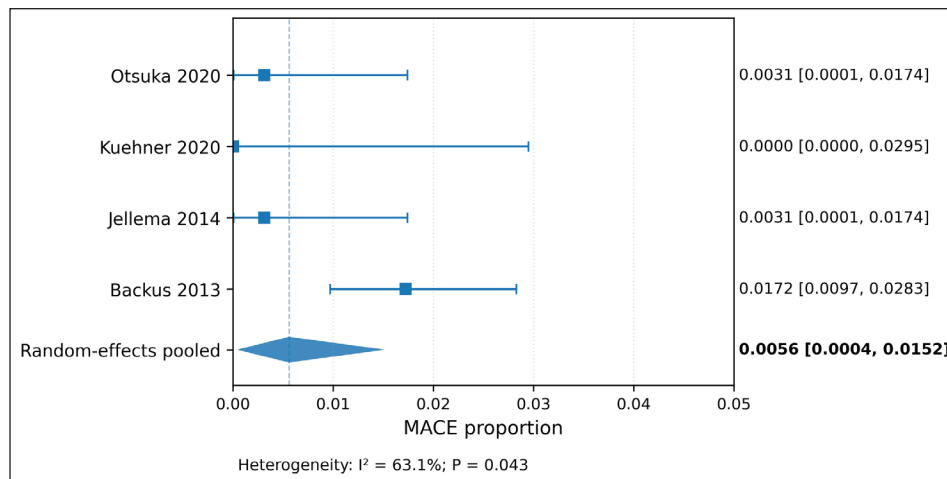


Figure 2. Forest plot of the pooled proportion of major adverse cardiac events among patients with a low HEART score (≤ 3).

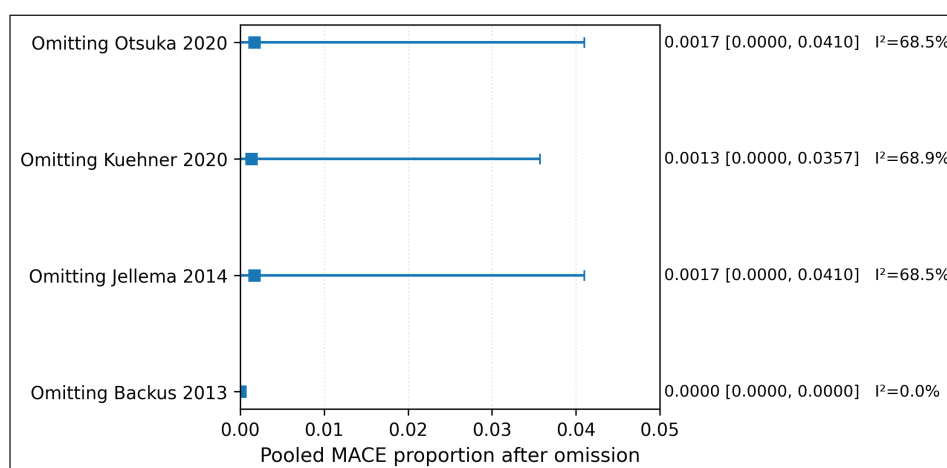


Figure 3. Leave-one-out sensitivity analysis for the pooled proportion of MACE in patients with low HEART scores.

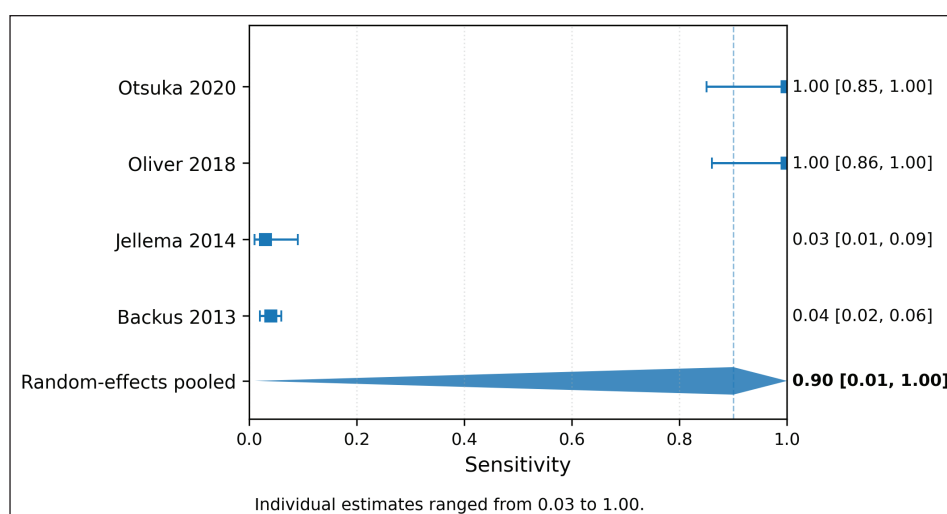


Figure 4. Forest plot of sensitivity for the HEART score threshold of ≤ 3 in relation to MACE.

observational, with four retrospective studies and one prospective study, leaving the results vulnerable to residual confounding. Fourth, the literature search

was limited to PubMed and Embase; studies indexed exclusively in databases such as Scopus, Web of Science, or the Cochrane Library may therefore have been missed.

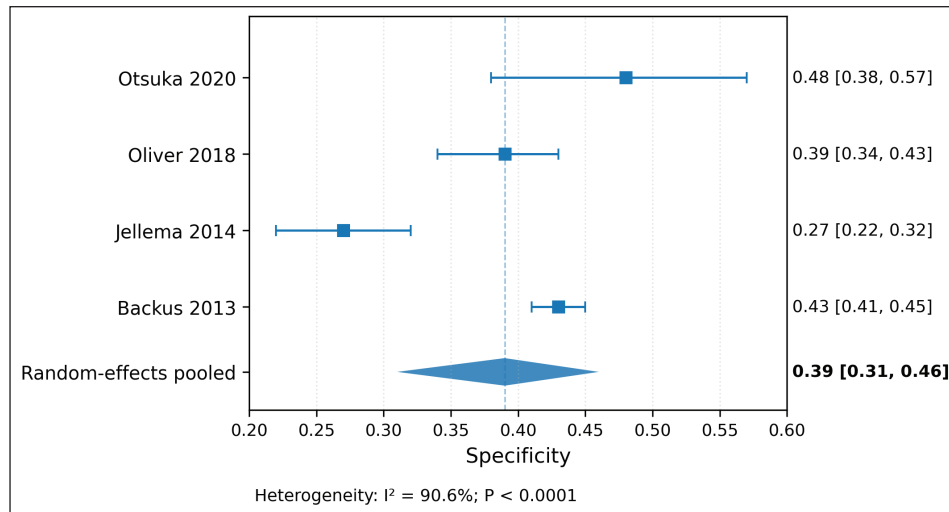


Figure 5. Forest plot of specificity for the HEART score threshold of ≤ 3 in relation to MACE.

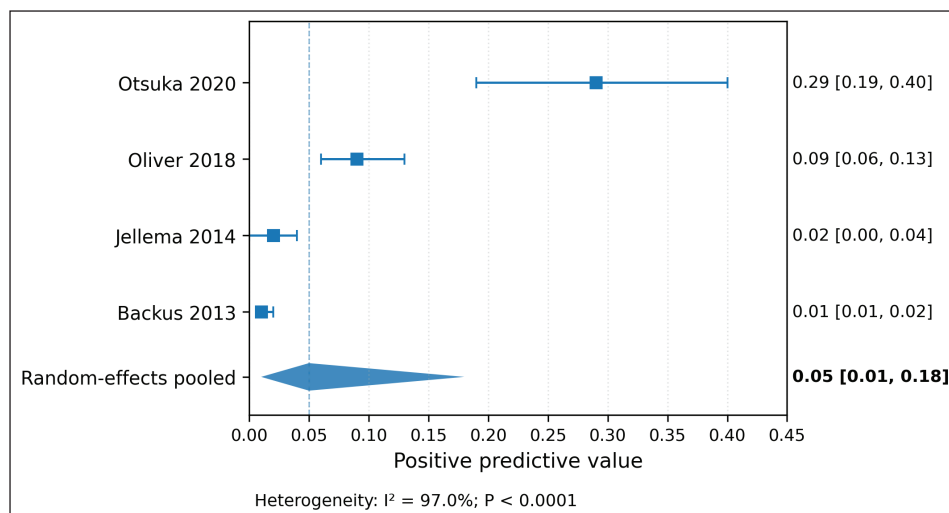


Figure 6. Forest plot of positive predictive value for the HEART score threshold of ≤ 3 in relation to MACE.

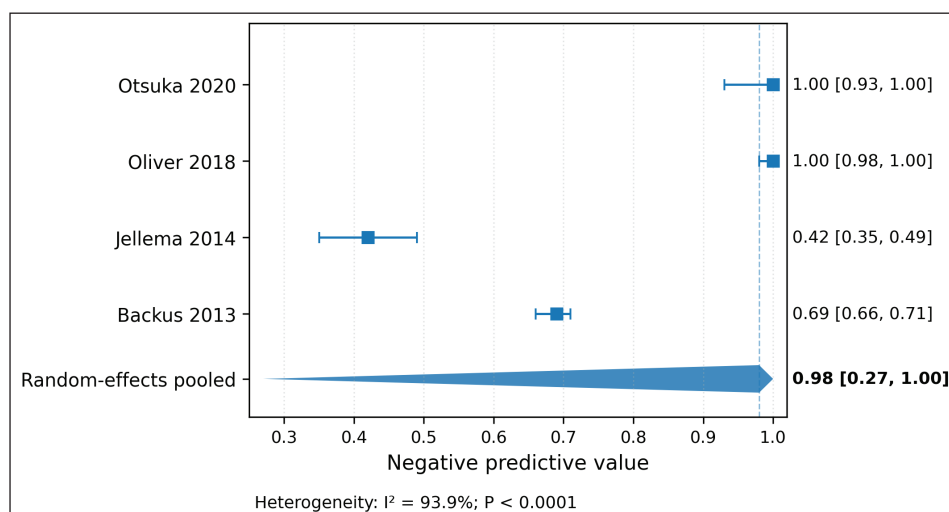


Figure 7. Forest plot of negative predictive value for the HEART score threshold of ≤ 3 in relation to MACE.

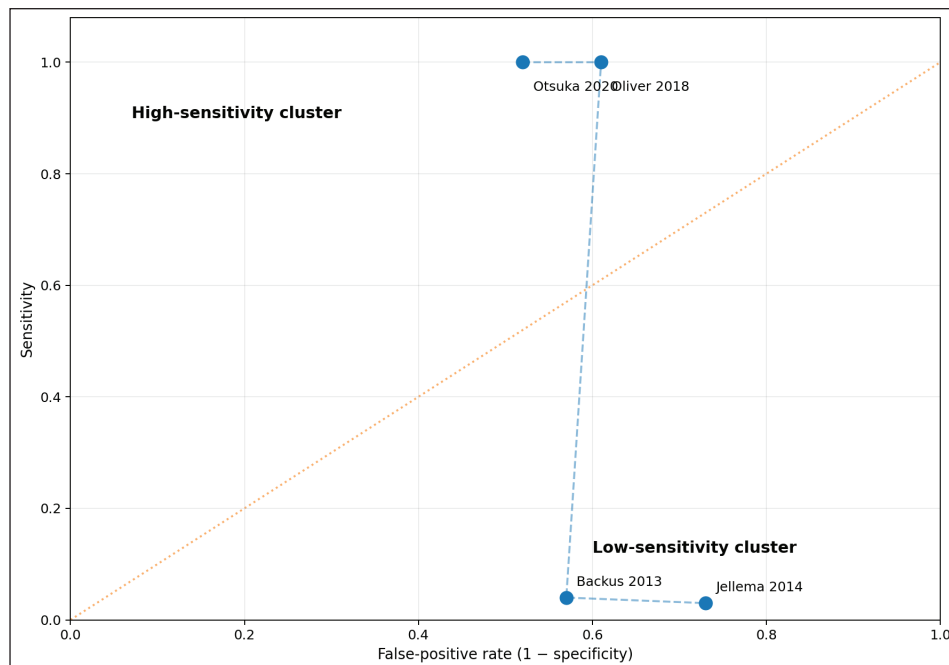


Figure 8. Summary receiver operating characteristic plot showing the two distinct clusters of study-level sensitivity and specificity estimates for the HEART score ≤ 3 threshold.

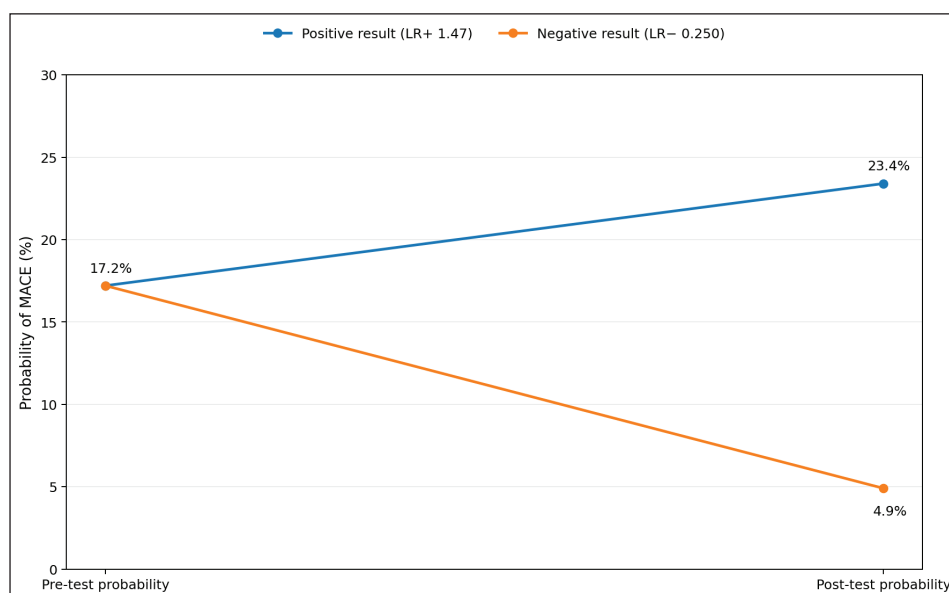


Figure 9. Fagan's nomogram summary showing pre-test probability and post-test probabilities after positive and negative HEART threshold results.

Fifth, only English-language publications were included, introducing potential language bias. Finally, publication bias cannot be excluded and was not formally assessed because of the small number of studies included.

Implications for clinical practice

The pooled MACE event rate of 0.56% supports the value of the HEART score as part of ED risk stratification, but the observed variability in sensitivity and the wide confidence interval around NPV argue against using a score ≤ 3 as a stand-alone discharge rule. The two-cluster SROC pattern further suggests that performance

may vary materially across clinical settings. Clinicians should therefore integrate the HEART score with the overall clinical assessment and appropriate serial high-sensitivity troponin testing rather than relying on the numerical threshold alone.

Future directions

Future research should validate the HEART score ≤ 3 threshold in large prospective multicenter cohorts across diverse healthcare systems, including low- and middle-income settings. Studies should also report standardized MACE definitions, troponin assay characteristics, and

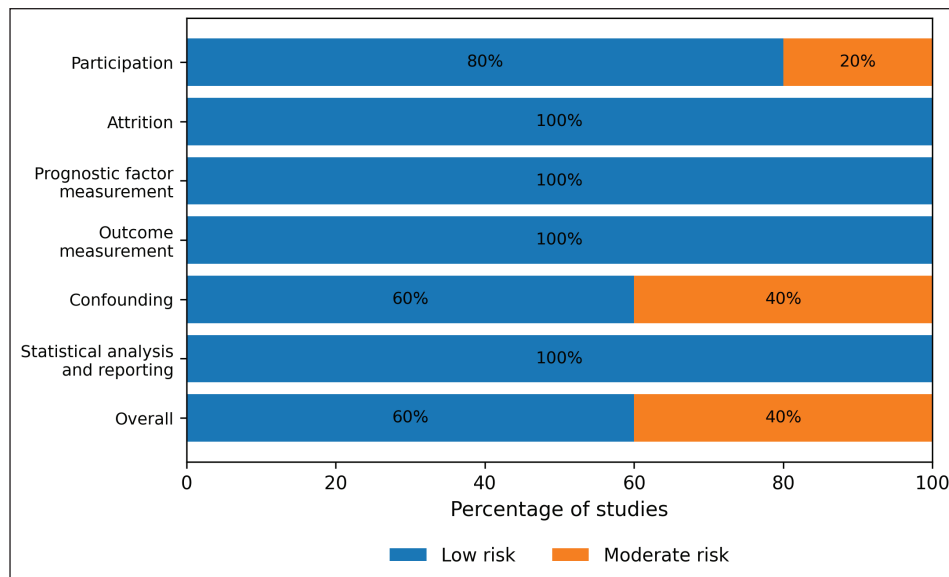


Figure 10. Summary of QUIPS risk-of-bias judgments across included studies.

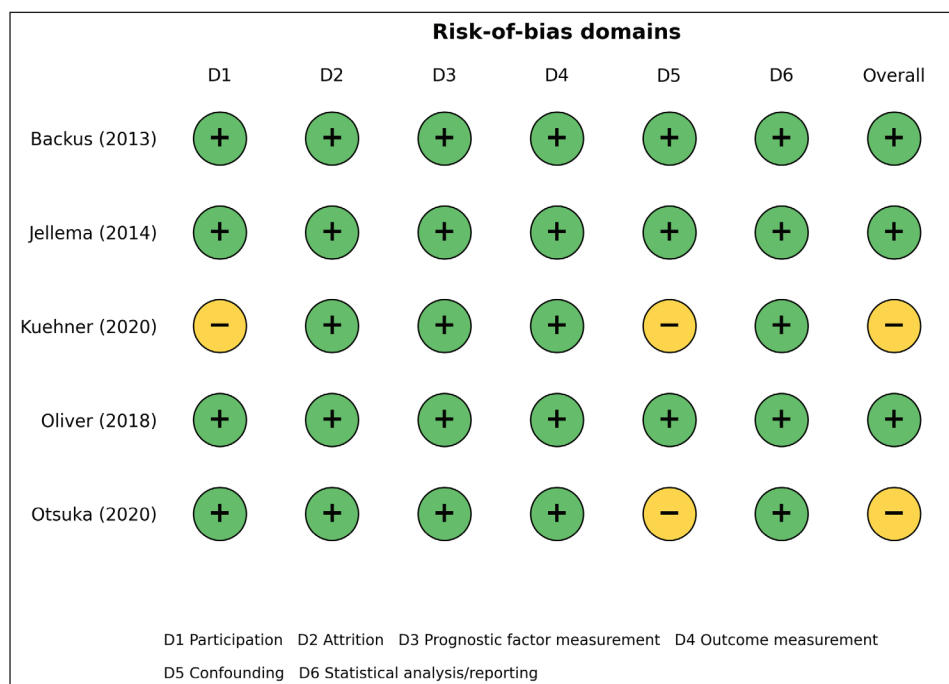


Figure 11. Study-level QUIPS risk-of-bias assessment across the six domains and overall judgment.

complete diagnostic 2×2 data to enable more reliable hierarchical diagnostic meta-analysis and exploration of sources of heterogeneity.

Conclusion

Among patients presenting to the ED with chest pain and a HEART score ≤ 3 , the pooled MACE rate was 0.56%. However, the study has markedly lower sensitivities, with low pooled specificity, and the NPV estimate was imprecise and heterogeneous because of low event counts. The SROC plot showed two distinct performance clusters, and a negative result reduced the modeled post-test MACE probability to 4.9%. These findings

support use of the HEART score as one component of risk stratification rather than as an isolated discharge criterion. Large prospective multicenter studies are needed to define the safety and generalizability of the ≤ 3 threshold.

Acknowledgments

None.

List of Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
CAD	Coronary artery disease
CI	Confidence interval

ECG	Electrocardiogram
ED	Emergency department
FN	False negative
HEAR	History, Electrocardiogram, Age, Risk factors
HEART	History, Electrocardiogram, Age, Risk factors, Troponin
MACE	Major adverse cardiac events
MI	Myocardial infarction
NPV	Negative predictive value
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
QUIPS	Quality In Prognosis Studies
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
SROC	Summary receiver operating characteristic

Conflicts of interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

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Ethical approval

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Supplementary content (if any) is available online.

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