Review Article

Clinical scores for risk stratification of chest pain patients in the emergency department: an updated systematic review

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Abstract: Chest pain is among the most common complaint presenting to the emergency departments (EDs) worldwide. The etiology of chest pain can range from benign to life threatening causes. Therefore, it is crucial to stratify chest pain patients based on risk for development of major adverse cardiac events (MACE) in order to provide effective care and prevent overutilization of resources. Over the years, many risk stratification tools have been developed, among which, the History, Electrocardiogram (ECG), Age, Risk factors, and initial Troponin (HEART), Thrombolysis in Myocardial Infarction (TIMI), and Global Registry of Acute Coronary Events (GRACE) scores are the most widely used. This systematic review aims to provide an up-to-date summary of the latest studies on clinical scores for risk stratification of chest pain patients presenting to the ED. We conducted a search of the literature in online databases PubMed and Embase. Our search was limited to articles published between 01 January 2012 and 25 September 2017. Studies were eligible for inclusion if the reported clinical scores were used for risk stratifying ED chest pain patients. Systematic reviews, meta-analyses, case reports, and letters to the editor were excluded. Two independent reviewers screened the titles, abstracts, and full articles for the inclusion of studies. We retrieved a total of 514 articles from both databases and included 29 studies in this systematic review. The articles covered studies from over 20 countries, where more than 20 different risk scores and scoring methods were investigated. Among the various risk scores, the HEART, TIMI, GRACE, and heart rate variability (HRV)-based scores were the most widely implemented and discussed. We found that the HEART score was generally the top performer in identifying chest pain patients at high or low risk of developing MACE. Most HRV-based scoring methods had comparable performance to the HEART score while benefiting from faster score calculation without a need for laboratory testing. This could potentially be useful in accelerating existing chest pain protocols in the ED setting.

Keywords: Clinical score; risk stratification; chest pain; emergency department (ED); systematic review

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Introduction

Chest pain is a common presenting symptom in the emergency department (ED). Many chest pain patients are admitted to the hospital due to the possibility of life threatening conditions, such as acute myocardial infarction (AMI) (1). It is however, not feasible to admit all chest pain patients due to limited healthcare resources (2). Therefore, distinguishing acute coronary syndrome (ACS) from other cardiac and non-cardiac diseases is crucial (3). It is essential to quickly and accurately identify patients who are at high and low risk of developing major adverse cardiac events (MACE) in order to optimally allocate ED and hospital resources.

Risk stratification of ED chest pain patients has been extensively studied in recent years (3). However, there is currently no widely accepted risk stratification method for ED chest pain patients (4). Initial ED risk scores were adopted from those created for post-ACS risk stratification such as the Thrombolysis in Myocardial Infarction (TIMI) score (5) and the Global Registry of Acute Coronary Events (GRACE) score (6), among others (7,8). However, because these risk scoring tools were not specifically designed for ED chest pain patients, their performance in the ED has been marginal (9-13).

The History, Electrocardiogram (ECG), Age, Risk factors, and initial Troponin (HEART) score was specifically created for risk stratifying ED patients with undifferentiated chest pain (14,15). Since its inception, there have been numerous validation studies to evaluate its effectiveness in diagnosing non-ST-elevation (NSTE) ACS (16,17). In many comparison studies, the HEART score was found to be superior to most existing risk stratification tools such as the TIMI and GRACE scores (4,18-21).

Because of growing patient censuses in many EDs, it is becoming increasingly important to quickly and accurately identify high risk chest pain patients to promote efficient and effective care. The purpose of this systematic review is to present an updated investigation on various risk stratification tools that are used in the ED to categorize chest pain patients according to their risk of developing MACE.

Methods

We searched PubMed and Embase, using keywords "(score OR scoring) AND (emergency department OR emergency room) AND (chest pain OR acute coronary syndrome)". Our search was limited to English-language articles published between 01 January 2012 and 25 September 2017. Studies were eligible for inclusion if the reported clinical scores were used for risk stratifying ED chest pain patients, where one or more scoring methods were investigated. Systematic reviews, meta-analyses, case reports, letters to the editor, and articles without full text were excluded from this review. Studies with non-MACE outcomes were also excluded.

Initial literature search was conducted by N Liu. Two reviewers (N Liu and JC Ng) independently screened the titles, abstracts, and full articles for the inclusion of studies. Discrepancies were resolved through discussions among all authors to reach consensus. After screening for inclusion and exclusion criteria, data from the selected studies were extracted by N Liu. The extracted information included publication year, country of study, clinical scores investigated, sample size, study outcomes, summarized key information, and predictive performances including the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Since the aim of this systematic review was to present an updated summary of currently used risk stratification scores for ED chest pain patients, a meta-analysis was not conducted to rigorously compare the performances of various clinical scores.

Results

Our literature search identified a total of 514 articles, with 249 from PubMed database and 265 from Embase database. After removing 210 duplicated entries, we included 304 articles for abstract screening. We further excluded 243 articles due to reasons such as absence of risk stratification, non-MACE outcomes, etc. We reviewed the full-texts for the remaining 61 articles and further excluded 32 articles from the list; a final total of 29 articles were included in this systematic review (*Figure 1*).

Characteristics of the 29 selected studies are summarized in *Table 1*. Predictive performances of the clinical scores in the selected studies are presented in *Table 2*. These studies were conducted in the Asia-Pacific (n=16) and Europe (n=11) and in more than 20 countries. Majority of the studies were conducted in Singapore (n=9), the Netherlands (n=5), the United States (n=5), and Australia (n=5). Four studies involved more than one country. Outcomes in all studies were MACE within a period after discharge from the ED, ranging from 72 hours to 1 year. Thirty-day MACE was the

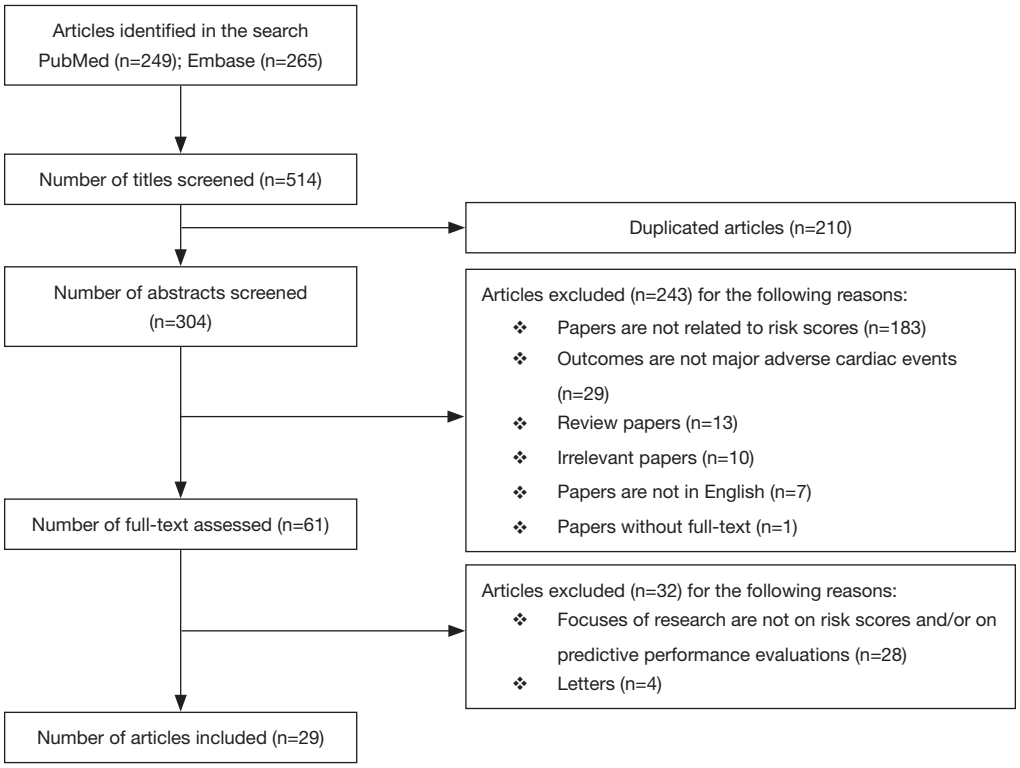

Figure 1 Flowchart of study selection.

most commonly used outcome.

Seven out of 29 studies recruited more than 2,000 patients, with Sun *et al.*'s study (19) having the largest cohort of 8,255 patients obtained from the Internet Tracking Registry of Acute Coronary Syndromes (i*trACS) (45). More than 20 different risk scores or scoring methods were reported in these studies, which can be categorized into several main groups including the HEART score and its variants and the TIMI score and its variants. Among all scores, the HEART and the TIMI scores were the most widely validated; both scores appeared in 19 studies. The GRACE score and heart rate variability (HRV) based scores were also well studied.

TIMI score

The TIMI score was introduced in 2000 (5) and has since been widely adopted to assess the risk of MACE for patients with chest pain in the ED (46). There are seven elements in the TIMI score, namely age more than 65 years, more than three coronary artery disease (CAD) risk factors (hypertension, hyperlipidemia, diabetes, family history, and smoking), significant coronary artery stenosis, severe angina symptoms, ST-deviation, elevated cardiac enzymes, and use of aspirin in the last 7 days. Each element is assigned a score of 0 or 1. Therefore, the TIMI score is between 0 and 7.

Although not specifically designed for risk stratifying ED chest pain patients, the TIMI score and its variants have been widely applied and validated on the ED cohorts (46). In this systematic review, 19 out of 29 selected studies investigated TIMI based risk scores. The standard TIMI score has been implemented in most of the studies, and the modified TIMI score was also investigated in (26) and (28). In a study conducted in Australia, Macdonald *et al.* (28) validated a modified TIMI (mTIMI) score (range 0–10) (47) and found out that mTIMI outperformed standard TIMI score but was not sufficiently sensitive to allow safe discharge of low risk patients without further investigations.

Among the comparisons with various risk scores, the TIMI score achieved moderate performance in discriminating between chest pain patients with and without MACE (18-20). Furthermore, the TIMI score and its variants were reported as unreliable in identifying low risk chest pain patients (28,31).

Table 1 Characteristics of the selected studies on clinical scores for predicting major adverse cardiac events (MACE)

Study	Year	Places	Clinical scores	Sample size	Outcomes	Key information
Goodacre *et al.* (22)	2012	UK	GRACE, TIMI	2,243	30- and 90-day MACE	GRACE score outperformed TIMI score in predicting both 30- and 90-day MACE
Fesmire *et al.* (23)	2012	USA	HEARTS$_3$, HEART, HEART (weighted)	2,206	30-day MACE	HEART (weighted) and HEARTS$_3$ scores outperformed the standard HEART score in predicting 30-day MACE
Ong *et al.* (24)	2013	Singapore	HRV	309	72-hour MACE	Heart rate variability (HRV) model has potential to be developed into a chest pain triage tool
Six *et al.* (20)	2013	Australia, China (including Hong Kong), India, Indonesia, New Zealand, Singapore, South Korea, Taiwan, Thailand	HEART, TIMI	2,906	30-day MACE	HEART score provided excellent determination of risk for 30-day MACE, comparing well with the TIMI score
Melki *et al.* (25)	2013	Sweden	HEART	410	3-month MACE	HEART score may be a useful tool for identifying low-risk chest pain patients. A simpler score including only history, troponin level, and ECG findings may be sufficient
Cullen *et al.* (9)	2013	Australia	Heart Foundation of Australia (HFA)/CSANZ, TIMI, GRACE	948	30-day MACE	All scores showed similar performance in risk stratifying ED patients with possible acute coronary syndrome (ACS). None of them showed high accuracy in predicting the absolute risk of ACS for patients
Ko *et al.* (26)	2013	Hong Kong	Modified TIMI	384	45-day MACE	Modified TIMI-based accelerated chest pain protocol (ACPP) was able to identify very low risk chest pain patients who may be suitable for early discharge without increasing risk of developing MACE
Backus *et al.* (17)	2013	Netherlands	HEART, TIMI, GRACE	2,440	6-week MACE	HEART score for chest pain patients at the emergency department provides the clinician with a quick and reliable predictor of outcome shortly after arrival of the patient
Liu *et al.* (27)	2014	Singapore	HRV, TIMI	702	72-hour MACE	HRV-based model outperformed the TIMI score
Macdonald *et al.* (28)	2014	Australia	Modified TIMI, TIMI	1,666	30-day MACE	Modified TIMI score outperformed the standard TIMI score for predicting 30-day MACE. However, it is not sufficiently sensitive to allow safe discharge without further investigations or follow-up
Liu *et al.* (29)	2014	Singapore	HRV, TIMI	564	72-hour MACE	HRV model built with machine learning outperformed TIMI score, suggesting that intelligent algorithms are potential solutions to enhance medical decision making

Table 1 (*continued*)

Table 1 (*continued*)

Study	Year	Places	Clinical scores	Sample size	Outcomes	Key information
Burkett *et al.* (30)	2014	Australia	HFA score, Goldman risk score, TIMI	281	30-day MACE	TIMI and Goldman scores performed better than the HFA score in undifferentiated ED chest pain population, but selection of cutoffs balancing sensitivity and specificity was problematic
Boubaker *et al.* (31)	2015	Tunisia	TIMI, GRACE	3,125	30-day and 1-year MACE	TIMI and GRACE scores were not valid in short- and long-term risk stratification in chest pain patients
Carlton *et al.* (32)	2015	UK	Modified Goldman, TIMI, GRACE, HEART, Vancouver Chest Pain Rule	959	30-day MACE	Risk scores in combination with a single-presentation high sensitivity troponin result has the potential to reduce the length of stay for low-risk patients and allow discharge after a single blood draw on arrival in the ED
Leite *et al.* (33)	2015	Portugal	Manchester triage system, HEART	233	6-week MACE	HEART score is an effective tool for risk stratification in the ED chest pain patients
Visser *et al.* (34)	2015	Netherlands	HEART	255	6-week MACE	HEART score and clinical gestalt had similar diagnostic accuracy for diagnosing ACS in an unselected population of patients with chest pain presenting in the ED
Heldeweg *et al.* (35)	2016	Singapore	HRV, TIMI	763	30-day MACE	HRV-based risk stratification tool performed well against the TIMI score, but needs further external validation
Sun *et al.* (19)	2016	USA, Singapore	HEART, TIMI	8,255	30-day MACE	HEART score had better discrimination than TIMI and outperforms TIMI in low-risk categories
Jain *et al.* (36)	2016	USA	HEART, TIMI	947	30-day MACE	HEART score had superior prognostic utility compared with the TIMI score
Sakamoto *et al.* (4)	2016	Singapore	HEART, TIMI, GRACE	604	30-day MACE	In high acuity chest pain patients, the HEART score was superior to the TIMI and GRACE scores in predicting 30-day MACE
Ma *et al.* (37)	2016	China	Modified HEART	1,300	3-month MACE	The modified HEART risk score was validated in chest pain patients with suspected NSTE ACS and may complement MACE risk assessment and patients triage in the ED. A prospective study of the score is warranted
Chen *et al.* (38)	2016	China	TIMI, GRACE, Banach, HEART	833	7-, 30-day, and 6-month MACE	HEART score performed better than the GRACE and Banach scores for predicting total MACE and effectiveness outcomes, whereas the Banach score best predicted safety outcomes. There was no significant difference in the area under the curve (AUC) between HEART and TIMI scores
Sakamoto *et al.* (39)	2017	Singapore	HRV, HEART, TIMI, GRACE	797	72-hour and 30-day MACE	HRV-based model was similar to HEART, and both were better than TIMI and GRACE in MACE prediction for chest pain patients

Table 1 (*continued*)

Table 1 (*continued*)

Study	Year	Places	Clinical scores	Sample size	Outcomes	Key information
McCord *et al.* (40)	2017	Europe, Australia, USA	Modified HEART, modified TIMI	661	30-day MACE	There was only a trend for the modified HEART score to have better prognostic utility when compared with a modified TIMI score. A larger study may have shown a significant difference
de Hoog *et al.* (41)	2017	Netherlands, Singapore	HEART	3,456	6-week MACE	No significant difference in overall performance and in negative predictive value of a low HEART score between Caucasian, Chinese, Indian and Malay patients presenting to the ED with symptoms suggestive of ACS
Santi *et al.* (42)	2017	Italy	Modified HEART	1,597	30-day and 6-month MACE	The modified HEART score was able to rapidly distinguish, among patients presenting at an ED with chest pain, three groups with a very different risk of MACE, and to confidently identify those patients who did not need second-line diagnostic tests and/or in-hospital observation
Streitz *et al.* (43)	2017	USA	HEART	417	6-week MACE	HEART score had an excellent prognostic accuracy for predicting 6-week MACE. Patients with low HEART scores (0–3) may be ideal candidates for discharge and outpatient follow-up
Poldervaart *et al.* (18)	2017	Netherlands	GRACE, HEART, TIMI	1,748	6-week MACE	The HEART score outperformed the GRACE and TIMI scores in discriminating between those with and without MACE in chest pain patients, and identified the largest group of low-risk patients at the same level of safety
Bank *et al.* (44)	2017	Netherlands	HEART	1,915	6-week MACE	The markedly higher 6-week MACE risk in men across all HEART risk categories should be taken into account when using the HEART score to guide clinical decision making; early discharge with a low-risk HEART score appears less safe for men than women with acute chest pain

GRACE, Global Registry of Acute Coronary Events; HEART, History, Electrocardiogram, Age, Risk factors, and initial Troponin; TIMI, Thrombolysis in Myocardial Infarction; MACE, major adverse cardiac events; ECG, electrocardiogram; HFA, Heart Foundation of Australia; CSANZ, Cardiac Society of Australia and New Zealand; ED, emergency department; NSTE, non-ST-elevation; ACS, acute coronary syndrome.

Table 2 Predictive performance of the clinical scores in the selected studies

Study	Outcome	Clinical scores	AUC	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Goodacre *et al.* (22)	30-day MACE	GRACE	0.717	–	–	–	–	–
	30-day MACE	TIMI	0.682	–	–	–	–	–
	90-day MACE	GRACE	0.726	–	–	–	–	–
	90-day MACE	TIMI	0.693	–	–	–	–	–
Fesmire *et al.* (23)	30-day MACE	HEART	0.816	–	–	–	–	–
	30-day MACE	HEARTS3	0.902	–	–	–	–	–
	30-day MACE	HEART (weighted)	0.859	–	–	–	–	–
Ong *et al.* (24)	72-hour MACE	HRV	0.835	4	88.0	68.0	19.5	98.5
Six *et al.* (20)	30-day MACE	HEART	0.830	3	96.3	31.8	17.3	98.3
	30-day MACE	TIMI	0.750	1	87.4	47.5	19.7	96.2
Melki *et al.* (25)	3-month MACE	HEART	0.890	–	–	–	–	–
Cullen *et al.* (9)	30-day MACE	HFA/CSANZ	0.750	High risk	78.0	71.5	22.5	96.8
	30-day MACE	TIMI	0.790	5	22.0	96.4	39.2	92.1
	30-day MACE	GRACE	0.830	100	69.2	76.2	23.6	95.9
Ko *et al.* (26)	45-day MACE	Modified TIMI	–	1	86.7	41.3	16.4	95.9
Backus *et al.* (17)	6-week MACE	HEART	0.830	–	–	–	–	–
	6-week MACE	TIMI	0.750	–	–	–	–	–
	6-week MACE	GRACE	0.700	–	–	–	–	–
Liu *et al.* (27)	72-hour MACE	HRV	0.812	43	82.8	63.4	–	–
	72-hour MACE	TIMI	0.637	–	–	–	–	–
Macdonald *et al.* (28)	30-day MACE	Modified TIMI	0.800	2	82.0	53.0	–	–
	30-day MACE	TIMI	0.710	2	74.0	54.0	–	–
Liu *et al.* (29)	72-hour MACE	HRV	0.837	42.3	78.9	76.5	10.5	99.0
	72-hour MACE	TIMI	0.621	1	78.9	36.7	4.2	98.0
Burkett *et al.* (30)	30-day MACE	HFA	0.540	High risk	100.0	8.4	–	–
	30-day MACE	Goldman	0.670	Low risk	69.0	51.0	–	–
	30-day MACE	TIMI	0.710	2	90.0	39.0	–	–
Boubaker *et al.* (31)	30-day MACE	TIMI	0.660	3	60.0	73.0	14.0	96.0
	30-day MACE	GRACE	0.570	109	37.0	78.0	14.0	93.0
	1-year MACE	TIMI	0.670	3	65.0	69.0	12.0	97.0
	1-year MACE	GRACE	0.650	109	52.0	77.0	15.0	95.0

Table 2 (*continued*)

Table 2 (*continued*)

Study	Outcome	Clinical scores	AUC	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Carlton *et al.* (32)	30-day MACE	Modified Goldman	–	1	98.7	43.3	13.5	99.7
	30-day MACE	TIMI	–	1	94.9	53.5	15.5	99.2
	30-day MACE	GRACE	–	80	92.3	33.8	11.1	98.0
	30-day MACE	HEART	–	3	93.7	33.9	11.3	98.3
	30-day MACE	Vancouver	–	–	100	17.5	9.8	100
Leite *et al.* (33)	6-week MACE	Manchester triage	–	–	–	–	–	–
	6-week MACE	HEART	0.880	4	90.9	63.2	26.3	97.9
Visser *et al.* (34)	6-week MACE	HEART	0.810	7	52.0	90.0	68.0	–
Heldeweg *et al.* (35)	30-day MACE	HRV	0.780	9	70.9	67.4	52.0	82.3
	30-day MACE	TIMI	0.653	2	61.8	57.2	41.9	75.0
Sun *et al.* (19)	30-day MACE	HEART	0.753	3	85.8	51.2	10.3	98.2
	30-day MACE	TIMI	0.678	1	62.8	63.8	10.2	96.3
Jain *et al.* (36)	30-day MACE	HEART	0.820	3	99.3	21.4	17.4	99.4
	30-day MACE	TIMI	0.680	–	–	–	–	–
Sakamoto *et al.* (4)	30-day MACE	HEART	0.780	4	91.6	42.2	46.7	90.1
	30-day MACE	TIMI	0.650	1	87.0	37.5	43.5	83.9
	30-day MACE	GRACE	0.620	110	60.0	54.5	42.2	71.1
Ma *et al.* (37)	3-month MACE	Modified HEART	0.840	–	–	–	–	–
Chen *et al.* (38)	7-day MACE	TIMI	0.689	2	67.1	63.4	–	–
	7-day MACE	GRACE	0.621	109	70.0	49.1	–	–
	7-day MACE	Banach	0.639	0	75.7	44.3	–	–
	7-day MACE	HEART	0.731	5	52.9	83.2	–	–
	30-day MACE	TIMI	0.700	2	66.7	64.2	–	–
	30-day MACE	GRACE	0.625	109	72.2	49.9	–	–
	30-day MACE	Banach	0.647	0	75.6	44.8	–	–
	30-day MACE	HEART	0.726	5	48.9	83.7	–	–
	6-month MACE	TIMI	0.734	2	71.1	66.3	–	–
	6-month MACE	GRACE	0.680	114	71.1	56.6	–	–
	6-month MACE	Banach	0.695	0	80.2	46.5	–	–
	6-month MACE	HEART	0.747	4	69.4	67.3	–	–

Table 2 (*continued*)

Table 2 (*continued*)

Study	Outcome	Clinical scores	AUC	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Sakamoto *et al.* (39)	72-hour MACE	HRV	0.777	0.15	74.0	70.8	92.4	36.2
	72-hour MACE	HEART	0.758	–	–	–	–	–
	72-hour MACE	TIMI	0.618	–	–	–	–	–
	72-hour MACE	GRACE	0.593	–	–	–	–	–
	30-day MACE	HRV	0.802	–	–	–	–	–
	30-day MACE	HEART	0.841	–	–	–	–	–
	30-day MACE	TIMI	0.682	–	–	–	–	–
	30-day MACE	GRACE	0.666	–	–	–	–	–
McCord *et al.* (40)	30-day MACE	Modified HEART	0.748	–	–	–	–	–
	30-day MACE	Modified TIMI	0.677	–	–	–	–	–
de Hoog *et al.* (41)	6-week MACE	HEART (Caucasian)	0.781	4	89.8	40.9	22.9	95.3
	6-week MACE	HEART (Chinese)	0.736	4	84.8	48.2	21.4	95.0
	6-week MACE	HEART (Indian)	0.784	4	86.7	50.2	20.7	96.2
	6-week MACE	HEART (Malay)	0.813	4	89.5	50.4	23.4	96.6
Santi *et al.* (42)	30-day MACE	Modified HEART	0.882	4	87.4	71.4	35.0	97.0
	160-day MACE	Modified HEART	0.880	4	87.0	72.6	38.8	96.5
Streitz *et al.* (43)	6-week MACE	HEART	0.885	4	100.0	53.0	–	–
Poldervaart *et al.* (18)	6-week MACE	GRACE	0.730	72	–	–	–	96.0
	6-week MACE	HEART	0.860	3	–	–	–	98.0
	6-week MACE	TIMI	0.800	0	–	–	–	97.0
Bank *et al.* (44)	6-week MACE	HEART (women)	0.800	4	91.6	43.7	15.3	97.9
	6-week MACE	HEART (men)	0.770	4	89.3	40.0	28.1	93.5

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; GRACE, Global Registry of Acute Coronary Events; HEART, History, Electrocardiogram, Age, Risk factors, and initial Troponin; TIMI, Thrombolysis in Myocardial Infarction; MACE, major adverse cardiac events; CSANZ, Cardiac Society of Australia and New Zealand; HRV, heart rate variability; HFA, Heart Foundation of Australia.

GRACE score

Introduced in 2001, the GRACE score is a risk stratification tool developed based on the GRACE (6,48), studying an inpatient cohort rather than an ED cohort and initially designed to look at MACE outcomes at 6 months after hospital discharge (49). There are eight elements in the GRACE score, including age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest on admission, ST-deviation, and elevated cardiac enzymes.

External validations of the GRACE score showed moderate to poor performance in stratifying ED chest pain patients in distinguishing either the MACE group or the non-MACE group (17,18,31). However, the results are mixed. In the study by Cullen *et al.* (9), the GRACE score was found to be able to identify a sizable low risk cohort with high sensitivity and NPV. Yet, a study by Singer *et al.* (50) evaluating the frequency of missed AMIs in low-risk cohorts that were identified by established risk scores demonstrated that the GRACE score had the highest percentage of missed AMI, compared to the TIMI and HEART.

HEART score

Different from the TIMI and the GRACE scores, the HEART score was specifically developed for chest pain

patients in the ED (14,20). It has been widely reported to outperform the TIMI and the GRACE scores (4,18,19). The HEART score has five prognostic factors, namely history, ECG, age, risk factors, and troponin. Each risk factor has a score of 0, 1, or 2, and the final score has a range of 0–10. The HEART score stratifies patients into three risk categories, that is, low risk [0–3], intermediate risk [4–6], and high risk [7–10]. It is noted that the HEART score was developed according to expert opinion (3), but not based on traditional multivariable regression analysis that is commonly used in clinical score derivation (51,52).

Due to its excellent performance in discriminating both high risk and low risk patients in terms of MACE development, the HEART score is the most validated score among all studied scores in this systematic review, where 19 out of 29 studies selected the HEART score as a main comparator. Comparing HEART with TIMI score in predicting 30-day MACE and 5-year all-cause mortality, Jain and colleagues (36) found that the HEART score was valuable in predicting not only short-term but also long-term outcomes for ED chest pain patients.

Other than the validations on general chest pain cohorts in the ED, the HEART score has been evaluated when several factors such as ethnicity and sex are taken into considerations. de Hoog *et al.* (41) conducted a study on a mixture of ethnic groups consisting of Caucasian, Chinese, Indian and Malay, and concluded that the overall performance of the HEART score was similar among Caucasians and Asians. Furthermore, Bank *et al.* (44) reported that male sex remained a significant factor for 6-week MACE when the HEART score was implemented for the prediction.

Based on the standard HEART score, many of its variants have been proposed and validated. Fesmire *et al.* proposed the $HEARTS_3$ score by adding three additional variables, sex, serial 2-hour ECG, and serial 2-hour delta troponin (23). The $HEARTS_3$ score reliably risk stratified patients with chest pain for MACE. Modified versions (37,40,42) of the HEART score were proposed where high-sensitivity troponin T was adopted to replace the traditional troponin element in the standard HEART score. These modifications suggested that the identified low-risk population might be directly discharged from the ED (40,42).

HRV score

HRV reflects the change in time intervals between heartbeats and has been shown to be a good predictor of MACE (53). Out of 29 studies selected in this review, Ong *et al.* (24), Liu *et al.* (29), and Sakamoto *et al.* (39) proposed several HRV-based risk scores to stratify ED chest pain patients with the purpose of making fast triage by predicting 72-hour MACE outcomes. Heldeweg *et al.* (35) developed a 30-day MACE prediction score SEDRSM by incorporating HRV, age, gender, and vitals through multivariable regression analysis. To calculate the score, all variables are discretized by proper thresholding and converted into individual scores. The range of SEDRSM is 0–37.

Liu *et al.* (29) and Liu *et al.* (27) used machine learning methods for variable selection and model derivation. In this review, most HRV-based scores were reported to outperform the TIMI score in predicting either 72-hour or 30-day MACE. Sakamoto *et al.* (39) made comparisons among the HRV score, the HEART score, the TIMI score and the GRACE score, and showed that the HRV score was superior to TIMI and GRACE scores, while achieving comparable performance with the HEART score. One advantage that the HRV-based scores have demonstrated over other clinical scores is their capability of computing the risk scores within a few minutes as only five-minute ECG records are needed for HRV parameter calculation (29).

Other scores

In addition to the above mentioned scores, several other clinical scores have been studied and evaluated, for example, the Vancouver chest pain rule (32), the Goldman risk score (30), the Heart Foundation of Australia (HFA)/Cardiac Society of Australia and New Zealand (CSANZ) guidelines (9), the Banach score (38), and the Manchester triage system (33). Cullen *et al.* (9) compared three risk scores (HFA/CSANZ, TIMI, and GRACE) and pointed out that all three scores had similar performance in predicting the risk of MACE for ED patients with chest pain. In Chen *et al.* (38), the Banach score had the largest AUC for predicting safety outcome while the HEART score had the largest AUC for predicting MACE.

Discussion

This systematic review provides an updated summary of studies on clinical scores for risk stratification of chest pain patients in the ED. The review was limited to articles published between 01 January 2012 and 25 September 2017. The initial literature search gave 514 published articles in the past 5 years that are related to risk stratification of ED

chest pain patients. After screening and detailed verification according to inclusion and exclusion criteria, 29 articles were eventually selected for further review. More than 20 risk scores or scoring methods were found in these 29 studies and among them the HEART score and the TIMI score were the most investigated risk stratification tools. The selected studies have been well distributed among more than 20 countries, covering a mixture of diverse patient cohorts. Thirty-day and 6-week MACE were the most commonly used outcomes, and long-term outcomes followed up at 6-month (38,42) were also investigated.

As one of the most common reasons for emergency hospital admission, chest pain receives much attention as it is sometimes difficult to discern the etiology quickly and accurately (3). For efficient and accurate patient care, it is essential to develop strategies for rapid rule-out or rule-in of MACE. Most chest pain scores use troponin or other laboratory tests which require time. The pathway using high sensitivity cardiac troponin may be done in a hour, but still requires two blood tests (16). Although point-of-care (POC) cardiac biomarker testing have been gaining interest in recent years and have been developed to overcome the long turnaround time of laboratory testing, POC testing is still largely unavailable in most countries (54). Therefore, there seems to still be needs for faster tools to accurately risk stratify chest pain patients presenting to the ED. Over the years, many reviews have been published, ranging from general topics related to diagnosis of ACS (8,55,56) to systematic reviews on specific risk scores (16,46). Long and Koyfman have particularly studied current controversies in evaluating low risk chest pain patients with the aids of risk scores (1). Our systematic review aimed to provide a summary of the latest studies on risk scores for ED chest pain patient, therefore the focus was not on rigorous meta-analysis of predictive performance. Instead, we targeted at listing out widely used clinical scores and scoring methods in recent years, and summarizing their key characteristics.

The HEART, TIMI, and GRACE scores are three established stratification tools to assess the risk of MACE for chest pain patients. As a score that was specifically developed for chest pain patients in the ED, the HEART score is generally considered to outperform most other risk scores in discriminating high and low risk chest pain patients. This discovery has been consistent in most of the selected studies in this review, although some studies reported that there was no significant difference in terms of diagnostic accuracy between the HEART score and the TIMI score (38) or clinical gestalt (34). The HEART score was found particularly useful for identifying ED chest pain patients who had low probability of developing MACE (16,18). Marcoon *et al.* (57) proposed using the HEART score to further risk stratify patients with low TIMI scores and they suggested that a combined use of the HEART score and the TIMI score could identify a subgroup of patients with very low risk of developing MACE.

Other than conventional clinical scores, HRV-based scores and scoring methods were widely discussed (24,29,39) with the added value of faster risk stratification of chest pain patients. HRV techniques have been applied to develop a triage tool in the ED (39) where short-term outcome (i.e., 72-hour MACE) was adopted. With this tool, quicker response to high or low risk patients is possible as laboratory tests are not required. This may potentially shorten the process of risk prediction to a few minutes (29,35,39), compared to hours of waiting time in traditional chest pain pathways (58). However, the main disadvantage of HRV is its low interpretability. Ong *et al.* (24) and Heldeweg *et al.* (35) proposed risk scores by categorizing the HRV parameters through simple thresholding. Alternatively, Sakamoto *et al.* (39) and Liu *et al.* (29) used continuous HRV parameters for predictive modelling by either traditional logistic regression or advanced machine learning methods. Although the HRV-based scores are reported to achieve good performance compared to scores such as the TIMI and GRACE scores, they need extensive external validations. Future work may combine the strengths of the HRV technique and the clinical scores to create robust, fast, and accurate scores for stratifying chest pain patients in the ED. Machine learning (59) may also play important roles in selecting significant variables (27) and improving predictive performance (60).

Limitations

This systematic review has limitations. First, this review only included studies that were published in the past 5 years. Second, the focus of the review was on studies that reported score derivations and validations. It is noted that studies on clinical pathways using the risk scores were excluded. Lastly, meta-analysis was not conducted due to the heterogeneity of the study cohorts and the outcomes in the selected articles.

Conclusions

Chest pain, as a common yet potentially life threatening

condition, deserves much attention in risk stratification and management, particularly in the ED where quick decisions are required for efficient patient care. This systematic review presents the latest studies on clinical scores that are used to categorize ED chest pain patients according to their risk of MACE. Traditional HEART, TIMI, and GRACE scores including their variants have been widely implemented and externally validated. Emerging techniques such as the HRV and machine learning were also adopted for developing risk scores where their flexibility and fast risk stratification were attractive, though low interpretability was a concern. In this review, risk score based clinical pathways were not discussed. Further investigations of existing risk scores including clinical outcomes and health economic measures are needed.

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Footnote

Conflicts of Interests: N Liu and ME Ong have a patent filing related to heart rate variability (system and method of determining a risk score for triage, application number: US 13/791,764); ME Ong has a similar patent filing unrelated to this study (method of predicting acute cardiopulmonary events and survivability of a patient, application number: US 13/047,348) and he also has a licensing agreement with ZOLL Medical Corporation for the above patented technology. The other authors have no conflicts of interest to declare.

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