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Performance of CARE rule in ruling out acute coronary syndrome in non-traumatic chest pain: an external validation study

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Abstract: **Objective:** About one out of every 10 patients with chest pain in the emergency department (ED) are finally diagnosed with acute coronary syndrome (ACS). A HEART score of ≤ 3 has been shown to rule out ACS with a low risk of major adverse cardiac events (MACE) occurrence. It has been proposed that a negative CARE rule (≤1), which stands for the first four elements of the HEART score and excludes the troponin assay requirement, may have similar rule-out reliability. This study aimed to externally validate the CARE rule.

Methods: In this multicenter, observational study a convenience sample consisting of patients over the age of 15 who had at least one troponin study were included. The performance of the CARE rule at the cut-off ≤1 for MACE prediction was assessed and compared to a HEART score of ≤3 and physicians' gestalt. MACE was defined as myocardial infarction, coronary angioplasty, coronary artery bypass graft, and all-cause mortality in 6 weeks.

Results: The data of 154 patients was analyzed. Of these, 121 patients had a negative CARE score of ≤1 and 33 individuals had a positive CARE score. Of those with a negative CARE score, only 1 (3%) experienced an adverse cardiac event while in those with a positive CARE score, 26 individuals (16.88 %) experienced MACE. The sensitivity of the CARE rule was 96.15% and the specificity was 25% with a negative likelihood ratio (LR-) of 0.15. The indices for HEART score were 88%, 59.69%, and 0.2, respectively. In comparison, physicians' gestalt had a sensitivity of 96%, specificity of 49.22%, and a LR- of 0.08. Of note, utilizing the CARE rule with a cut-off of <3 showed sensitivity of 96%, specificity of 41.86%, and a LR- of 0.1.

Conclusion: The CARE rule miss rate in MACE was more than 2% and while its performance was better than the HEART score, physicians' gestalt outperformed both rules for ruling out MACE.

Keywords: CARE Rule; Chest Pain; Clinical Decision Rules; Major Adverse Cardiac Events

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1. Introduction

Five to ten percent of all emergency department (ED) patients present with a chief complaint of chest pain (1,2). Of this population, only 13% are ultimately diagnosed with acute coronary syndrome (ACS). Given the notable prevalence of individuals presenting to the ED with chest pain, it's important for physicians to have a systematic way to separate high-risk and low-risk patients in this population to conserve resources, forgo longer ED stay times, and avoid overcrowding and its associated patient safety issues (3). Diagnostic protocols have been developed to assist with decision-making in many conditions including ACS. The HEART score, which considers a patient's history of present illness, ECG, age, risk factors, and cardiac troponin (cTn) levels, was developed in 2006 and is frequently used for this purpose. Each item can be scored 0 to 2 and patients are considered low risk if the sum remains ≤3.

Several studies have confirmed the ability of the HEART score to risk stratify patients and help physicians discharge those who are at low risk (4-6). Recent guidelines also recommend its use in the ED for risk stratification (7). However, the HEART score still requires a laboratory work up due to its inclusion of the cTn value. When the sum of the items in the HEART score, without considering cTn, is below 2 the final score is always below 4 irrespective of the cTn result. This

suggests that it may be possible for patients to be assessed and risk stratified almost instantaneously while maintaining the safety profile of the HEART score (8). We aimed to externally validate the performance of the CARE rule, initially developed and studied by Six et al. (9), in patients presenting with non-traumatic chest pain to the ED and compare its performance with physicians' gestalt.

2. Methods

2.1. Study design and setting

This is a multicenter, observational, prospective study which took place at three urban EDs beginning in September 2019 and ending in February 2020 due to the coronavirus disease 19 (COVID-19) outbreak. The EDs were all academic centers in two cities (Tehran and Qazvin) in Iran with 24/7 emergency care available. The two centers in Tehran, Imam Khomeini hospital and Sina hospital, are teaching hospitals with residents and an active ST-elevation myocardial infarction (STEMI) protocol in place. The STEMI protocol ensured a rapid electrocardiogram (ECG) after ambulance arrival which was promptly reviewed by a cardiologist at emergency medical service (EMS) dispatch center so that the patient could be transferred directly to the catheterization laboratory in case of a STEMI. In contrast, there was no STEMI protocol in the ED of Booali Sina hospital in Qazvin and emergency physicians were the first physicians to evaluate these patients and review their ECGs. The study was approved by the institutional review board at all three institutions (IR.TUMS.IKHC.REC.1397.225).

2.2. Selection of participants

Patients over the age of 15 who presented to the ED with a chief complaint of non-traumatic chest pain and who had at least one cTn level ordered were considered eligible and included. Patients were screened around the clock during the investigators' shifts. Those who did not give consent, were unable to provide a history, or could not be followed up were excluded. Patients' enrollment began in September 2019 but was prematurely terminated in February 2020 due to the COVID-19 outbreak in the country, which caused a dramatic decrease in patients presenting to the hospital with chest pain.

2.3. Measurements

During the study period, there was no structured decision-making tool in use at the study sites for chest pain, and patients would undergo a diagnostic workup according to the discretion of the treating physician. Two emergency physicians (HM and TM) and a post graduate year-2 (PGY-2) emergency medicine resident (MC) separately collected the information needed for the calculation of the CARE and HEART scores. As mentioned above, the CARE rule incorporates the same items as the HEART score with the exception of the cTn level. Considering the maximum cTn score of 2, it is proposed by designers that a score of <2 for the CARE rule would fall within the low-risk group irrespective of the cTn result (10). We also assessed physician gestalt for the probability of MACE within 6 weeks of ED presentation on a 3-level scale (low, medium, and high) using the same data used for the rules. A board-certified cardiologist (AA) who was not involved in the care of the patients and did not have access to any of their collected data, interpreted the ECGs. After reviewing admitted patients charts for MACE occurrence in the hospital, the patients with no MACE and who were deemed low-risk and discharged from the ED were contacted after 6 weeks after the index visit. Contact attempts were made up to three times on three consecutive days before the patient was considered lost to follow up and excluded from the final analysis.

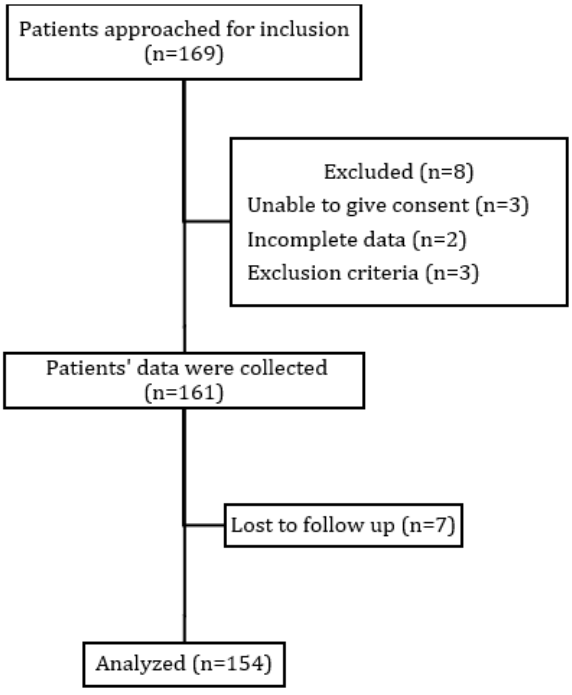

Figure 1 The flowchart of the patients studied with chest pain

The cTn used at all three medical centers, was the high sensitivity cardiac troponin I (hs-cTn I) assay (Abbot Architect® i2000 device and VIDAS®) and the cut-off values of 0.03 ng/ml and 0.19 ng/ml, which correspond to the 99th percentile of normal population, were used.

2.4. Outcomes

The primary goal of this study was to assess the performance of the CARE rule at the ≤1 cut-off for MACE prediction after 6 weeks. Secondary outcomes included performance of the HEART score ≤3 to rule out MACE during the period, and physicians' gestalt for identifying those who were "low risk" using a 3-level Likert scale which was administered to the treating physicians. MACE was a composite outcome that was assessed via structured telephone follow up after 6

Table 1 Characteristics of the patients with chest pain included in the study

Variables	Total (N=154)	MACE (N=25)	Non-MACE (N=129)	P value
Age (year), mean±SD	52.55±14.52	62.08±9.20	50.71±14.83	0.012
Male gender, n (%)	101 (65.6)	13 (52.0)	88 (68.2)	0.273
Diabetes mellitus, n (%)	35 (22.7)	10 (40.0)	25 (19.4)	0.251
Diagnosed hypertension, n (%)	57 (37.0)	13 (52.0)	44 (34.1)	0.128
Diagnosed dyslipidemia, n (%)	39 (25.3)	8 (32.0)	31 (24.0)	0.335
Active or weaned smoker < 90 days, n (%)	33 (21.4)	7 (28.0)	26 (20.2)	0.251
Obesity (BMI > 30 kg/m^2), n (%)	11 (7.1)	2 (8.0)	8 (6.2)	0.929
Intake of aspirin in last 7 days, n (%)	51 (33.1)	8 (32.0)	43 (33.3)	0.707
History of myocardial infarction, n (%)	9 (5.8)	2 (8.0)	6 (4.7)	0.381
Systolic blood pressure at admission (mmHg), mean±SD	132.26±23.28	138.15±29.32	136.16±29.35	0.251
Diastolic blood pressure at admission (mmHg), mean±SD	81.36±10.83	82.19±12.90	81.16±12.53	0.758
Heart rate at admission (beats/min), mean±SD	77.56±13.98	69.96±10.99	70.862±11.08	0.002

SD: Standard deviation; MACE: Major adverse cardiac events; BMI: Body mass index

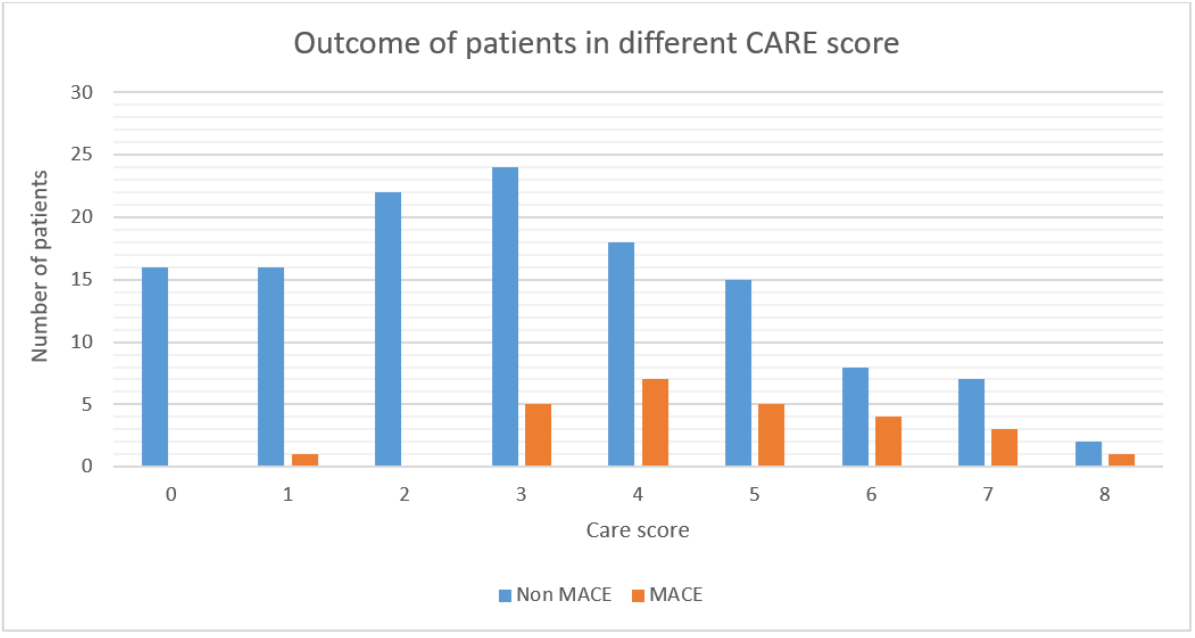

Figure 2 Distribution of MACE incidence among included chest pain patients with different CARE score
MACE: Major adverse cardiac events

weeks. It was defined as myocardial infarction (using the definition of the international consensus conference of 2012 for myocardial infarction) (10), coronary angioplasty, coronary artery bypass graft, and all-cause mortality.

2.5. Analysis

The categorical variables were presented with frequency and percent while quantitative variables were presented as mean and standard deviation or median and interquartile range according to the data distribution. Considering the lower bound of sensitivity in the original Moumneh et al. study (99%) (8) with a difference of 2%, at least 215 patients were needed in the sample size.

The performances of the rules in terms of sensitivity, specificity, and positive and negative predictive values were calculated using a 2 by 2 contingency table. The results were reported with a 95% confidence interval (CI). The area under the curve (AUC) of the receiver operating characteristic (ROC) curve were also calculated for both clinical decision rules and physician gestalt. All tests were performed using SPSS 24.0 software (IBM, Armonk, NY, USA). Post hoc power analysis was performed to calculate the power after completion of the study to assess type II error due to the adverse effects of false negatives in case of ACS.

3. Results

During the 6-month study period, 169 patients were approached and included. Eight were excluded due to exclusion criteria and incomplete data. Seven patients could not be reached via phone after 6 weeks (Figure 1). At the end, 154 patients' data were collected and analyzed. The characteristics of the included patients are shown in table 1.

Table 2 CARE and HEART scores by items among all patients and in patients with and without MACE

Rule items, Score		Total (N=154)	MACE (N=25)	Non-MACE (N=129)	P value
Characteristics of the chest pain	Highly suspicious (2)	29	7	22	0.004
	Moderately suspicious (1)	67	16	51	
	Slightly suspicious (0)	58	2	56	
Age	≥ 65 years (2)	32	9	23	0.001
	45–64 years (1)	77	16	61	
	< 45 years (0)	45	0	45	
Risk factors	≥ 3 risk factors or history of atherosclerotic disease (2)	53	11	42	0.173
	1 or 2 risk factors (1)	59	11	48	
	No known risk factor (0)	42	3	39	
ECG	Significant ST-segment deviation (2)	37	10	27	0.087
	Non-specific repolarization disturbances (1)	9	2	07	
	Normal (0)	108	13	95	
Cardiac troponin I	>3 times normal (2)	22	10	10	<0.001
	1-3 times normal limit (1)	6	3	3	
	≤ normal limit (0)	126	12	116	
CARE score, mean±SD		3.34±0.17	4.76±0.34	3.06±0.18	<0.001
HEART score, mean±SD		3.66±2.43	5.84±1.97	3.24±2.29	<0.001

ECG: Electrocardiogram; SD: Standard deviation; MACE: Major adverse cardiac events

Table 3 Performance of CARE rule, HEART score, and physicians' gestalt among patients with chest pain for MACE during the 6-week follow up

Variables	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value	Negative predictive value	Accuracy	Number of patients diagnosed as low risk (%)
	(95%CI)							
CARE rule	96.15% (80.36-99.90)	25.00% (17.77-33.42)	1.28 (1.13 - 1.45)	0.15 (0.02 - 1.08)	20.66% (18.67 - 22.81)	96.97% (82.06 - 99.56)	37.01% (29.38 - 45.16)	33 (21.43)
CARE rule at cut - off < 3	96% (79.65 - 99.90)	41.86% (33.24 - 50.87)	1.65 (1.40 - 1.95)	0.1 (0.01 - 0.66)	24.24% (21.31 - 27.44)	98.18% (88.67 - 99.73)	50.65% (42.48 - 58.79)	55 (35.71)
HEART score	88% (68.78 - 97.45)	59.69% (50.70 - 68.23)	2.18 (1.69 - 2.82)	0.2 (0.07 - 0.59)	29.73% (24.69 - 35.32)	96.25% (89.79 - 98.68)	64.29% (56.18 - 71.84)	80 (51.95)
Physicians' gestalt	96% (79.65 - 99.90)	49.22% (40.28 - 58.20)	1.89 (1.57 - 2.28)	0.08 (0.01 - 0.56)	26.97% (23.42 - 30.83)	98.44% (90.16 - 99.77)	56.86% (48.62 - 64.83)	64 (42.21)

CI: Confidence interval; MACE: Major adverse cardiac event

*Low risk thresholds defined as CARE rule <2; HEART score <4; and physicians' gestalt of low risk

Twenty-six patients (16.88%) experienced MACE in 6 weeks and two deaths occurred among all the patients. Thirty-three (21.43%) individuals had a negative CARE rule of which 1 patient experienced MACE (coronary angioplasty) after discharge in the 6-week follow up (Figure 2). The components of the CARE score for the population and MACE and non-MACE groups are shown in table 2. The sensitivity of the CARE rule was 96.15% (95% CI: 80.36,99.90) and specificity was 25% (95% CI: 17.77,33.42). The indices for HEART score were 88% (95% CI: 68.78,97.45) and 59.69% (95% CI: 50.70,68.23), respectively. In comparison, physician gestalt had a sensitivity of 96% (95% CI: 79.65,99.90) and specificity of 49.22% (95% CI: 40.28,58.20) surpassing both clinical decision-making rules.

The LR- of the CARE rule, HEART score, and the physicians' gestalt for the diagnosis of "low risk" (defined as CARE < 2, HEART < 4, and Physicians' gestalt of "low risk") were 0.15% (95% CI: 0.02-1.08), 0.20 (95% CI: 0.07,0.59), and 0.08 (95% CI: 0.01,0.56), respectively (Table 3). In addition, the AUC for the CARE rule HEART score, and gestalt were 0.74 (95% CI: 0.64,0.83), 0.80 (95% CI: 0.72,0.89), 0.83 (95% CI: 0.75,0.91), respectively (Figure 3).

It is important to note that the performance of both scores in the low-risk group was affected by one patient who had MACE. He was a 48-year-old man with no risk factors who was considered low risk in history and had negative ECG findings with a normal cTnI result. He underwent coronary angioplasty during the follow up period.

Using a new cut-off value for the CARE rule (CARE<3) would result in a sensitivity of 96% (95% CI: 79.65,99.90), specificity of 41.86% (95% CI: 33.24,50.87), LR+ of 1.65 (95% CI:1.40,1.95), LR- of 0.1 (95% CI: 0.01,0.66), positive predictive value (PPV) of 24.24% (95% CI: 21.31,27.44), and negative predictive value (NPV) of 98.18% (95% CI: 88.67,99.73). The

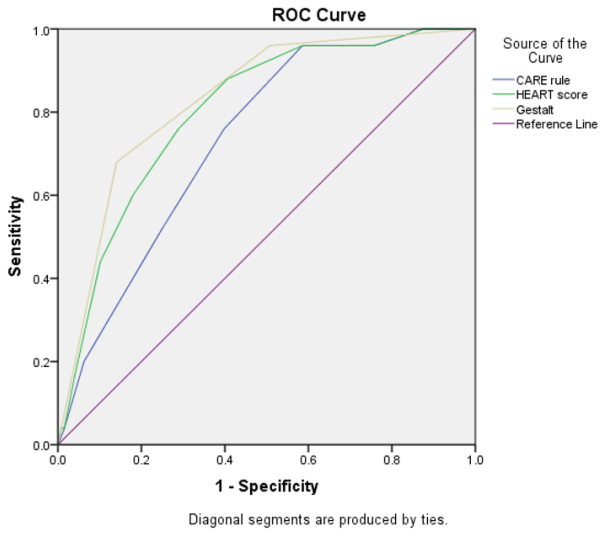

Figure 3 Receiver operating characteristic (ROC) curve for HEART score, CARE rule, and physicians' gestalt

accuracy would be 50.65% (95% CI: 42.48,58.79) at this new cut-off. The post hoc power analysis resulted in 76%.

4. Discussion

Our results showed that although the CARE rule helped the physicians with no ACS misdiagnosis, the miss rate for MACE predication was more than the acceptable limit of less than 2% (11,12). In addition, while its performance was better than the HEART score, the results of the physicians' gestalt outperformed both rules.

Due to limited resources, it is necessary to distinguish ACS from other benign causes of chest pain in those with a low risk of MACE (13). Guidelines have recommended that risk stratification scores should be used for clinical decision-making (14). The primary goal of any decision-making tool for ACS is to lower the miss rate (ideally less than about 2%) (11,12) through higher sensitivity and NPV with low LR-. Initial risk scores for risk stratification such as TIMI (thrombolysis in myocardial infarction) and GRACE (Global registry of acute coronary events) scores were adopted from admitted patients (15). The HEART score was proposed in 2006 for the ED and validated in numerous studies afterward. Although the results were variable due to factors such as a difference in clinical settings and the application of new generations of the cTnI assay, meta-analyses showed acceptable results (16,17). Our results fell within the results of previous studies but did not show the acceptable performance of this rule in our population. Moumneh et al. first introduced the CARE rule for ACS exclusion in a prospective study (8). They examined the tool for MACE prediction in a 6-week period. Among 641 patients, CARE rule was negative in 200 (31.2%) and none suffered a MACE during the timeframe of the study [0% (0.0,1.9)]. Considering the sample size and narrow confidence interval, which was below 2%, the CARE rule was proposed as a reliable tool. Multiple studies have also evaluated the performance of this rule. In a study by Stopyra et al., authors retrospectively reviewed paramedics' prehospital reports to assess the rule performance in MACE prediction in a 30-day period (18). Among 747 patients, the results for sensitivity, NPV, and LR- were 78.8% (95% CI: 68.6,86.9), 94.3% (95% CI: 91.2,96.6), and 0.50 (95% CI: 0.28,0.72), respectively. In another study from the same institution, a preplanned secondary analysis by Smith et al. showed that in a sample of 3809 ED patients the sensitivity was improved to 97.8% (94.5% to 99.4%) with LR- of 0.179 (0.068 to 0.473) (19). In the 30-day follow up period, there were 2 deaths and 2 myocardial infarction (MI)s among the patients who were considered as low risk. Of note, the patients with acute ischemic changes on their ECG and history of cardiac diseases were excluded in the Smith et al. study in order to include patients with no obvious ischemic signs on their ECG. In comparison to our study, this would only leave patients with lower risk in the study population. This can be seen in comparing the prevalence of patients with MACE in studies which was over five times higher in our study (3.03% versus 16.88%). This difference may be due to study sites type and the patients included in this study. In that study, among patients who were stratified into the low-risk group by the rule, the prevalence of MACE was below 1% but more than 2% in the lower bound of the CI. Considering this, the authors proposed additional validation before recommendations because the miss rate might be above 2% (the acceptable miss rate by emergency physicians).

Our study attempted to refine the cut-off for the CARE rule to improve its function while maintaining specificity and sensitivity. The idea stemmed from the presumption that because of the low probability of ACS and MACE, even at this new cut-off value, a positive cTnI is unlikely in cases with a CARE rule below 2. This new value helped to include another 22 patients (14%) in the low-risk group with no additional cases of MACE. The results showed that the modified CARE rule, which we defined as a CARE score of <3, can rule out MACE among 67.30% of the cohort with a similar performance in comparison to 31.80% in the original CARE rule. Data for this new cut-off was only available in the Moumneh et al. study (8). The study showed an additional 20% of the population could be safely discharged with this change in the cut-off, without increasing the incidence of MACE.

It is prudent to evaluate clinical judgment against clinical decision-making rules. Clinician gestalt has been previously assessed before the addition of ECG and cTnI results by some studies. One study showed that even at the lowest probability level, not only is the risk of a missed diagnosis only about 5%, but also only a small fraction (4.4%) of patients were included in these strata (20). Other studies considered the addition of ECG and cTnI results to the clinical judgment; one study showed acceptable MACE rate (0.3%) (21), but in a large cohort, other investigators stated that they had reached the target of 100% sensitivity and 100% NPV but were only able to label 4.1% of patients as low risk which made it imprac-

tical for clinical application (20). In our study, clinical judgment deemed 64 patients (42.21%) to be low risk for ACS with no misdiagnosis, and only 1 (1.56%) incident of MACE in 6 weeks.

5. Limitations

ACS presentation after the COVID-19 outbreak was dramatically decreased all over the world (22,23). Although this study did not reach its predetermined sample size due to premature termination, post hoc power analysis showed a nearly acceptable power for the included patients. In addition, although the patients were recruited during different shift times due to convenience sampling, there still remains a risk of sampling bias. Furthermore, while no laboratory studies are ordered in STEMI patients and this subgroup was not included in the first place, the presence of a STEMI protocol in one of the study sites decreased the heterogeneity of patients included in this study. Finally, although we hoped the presence of a PGY-2 emergency medicine resident would create similar conditions to that of an attendant emergency physician, and help with generalizability of the results, the performance of the rules may still vary when used by less experienced physicians.

6. Conclusion

In conclusion, our study showed that while the CARE rule and HEART score cannot be used reliably for the discharge of patients with non-traumatic chest pain, physicians' gestalt showed promising results.

7. Declarations

7.1. Acknowledgement

We would like to express our commitment and appreciation to the Prehospital and Hospital Emergency Research Center affiliated with Tehran University of Medical Sciences.

7.2. Authors' contribution

The conception and design of the work by HM and AA; Data acquisition by MC, AA, TM, and HM; Analysis and interpretation of data by ADI and HM; Drafting the work by MC, LF, TM, and HM; Revising it critically for important intellectual content by AA, LF, and HM; All the authors approved the final version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

7.3. Conflict of interest

The authors declared that there is no conflict of interest to declare.

7.4. Funding

The study was conducted without any found.

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