

Diagnostic Impact of Hs-CRP and IL-6 for Acute Coronary Syndrome in Patients Admitted to the ED with Chest Pain: Added Value to the HEART Score?

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Objective: To investigate whether hs-CRP and IL-6 provide additional diagnostic value beyond that achieved by the HEART score in patients with chest pain suggestive of acute coronary syndrome (ACS) admitted to the emergency department (ED).

Methods: This was a post hoc analysis using data from the RACING-MI study. Baseline data, including hs-CRP and IL-6 levels, were analyzed using the plasma from the biobank. A total of 818 patients with chest pain suggestive of ACS were included in this analysis. Of these, 98 were diagnosed with ACS (12%). Logistic regression was used to identify the independent predictors of ACS development in patients with chest pain.

Results: hs-CRP levels >2 mg/L were observed in 50% of all ACS cases. IL-6 levels >1.3 pg/mL were observed in 71% of all ACS cases. hs-CRP had a sensitivity of 50% and specificity of 51% for the diagnosis of ACS, whereas IL-6 had a sensitivity of 71% and specificity of 29%. The diagnostic likelihood ratios for ACS was 1.0 for hs-CRP>2 mg/L and IL-6 > 1.3 pg/mL, respectively. Logistic regression analysis revealed that age, male gender, and ongoing smoking were associated with ACS in patients with acute chest pain. No association was found between IL-6 or hs-CRP level and ACS. This was observed for both IL-6 and hs-CRP, whether assessed on a continuous scale or using prespecified cut-off values.

Conclusion: Among the 818 patients admitted to the ED with chest pain suggestive of ACS, neither hs-CRP nor IL-6 provided an independent added diagnostic value. Our results suggest that inflammatory markers have limited diagnostic value in detecting patients with ACS in the ED.

Keywords: admission hs-CRP and IL-6 values, HEART-score, acute coronary syndrome, diagnosis

Introduction

Chest pain is one of the most common reasons for emergency department (ED) visits. In the United States alone, more than six million patients with chest pain are evaluated in EDs each year.¹ The potential etiologies vary from harmless to life-threatening manifestations of acute coronary syndrome (ACS). Any delay in the diagnosis and treatment of ACS can have a negative impact on the prognosis.^{2,3} Risk stratification to safely identify patients at low risk of ACS has the potential to reduce the length of stay in the ED, thereby reducing the patient burden, frequency of hospitalization, and costs.^{4,5}

The Global Registry of Acute Coronary Events (GRACE) score⁶ and Thrombolysis in Myocardial Infarction (TIMI) score⁷ are widely used risk evaluation scores that were initially developed for a large number of patients with confirmed

Table 1 HEART Score

Projects	Score
History	
High suspicion	2
Moderate suspicion	1
Mild suspicion or exclusion	0
ECG	
Significant STEMI or N-STEMI	2
Nonspecific repolarization abnormalities	1
Bundle branch conduction block	1
Left ventricular hypertrophy	1
Normal	0
Age	
>65	2
45~65	1
<45	0
Risk factors (including diabetes, smoking, hypertension, hyperlipidemia, obesity, family history of coronary artery disease)	
>3 coronary heart disease risk factors or history of atherosclerosis treatment	2
1 or 2	1
0	0
Troponin	
>2 times the upper limit of the normal value	2
1~2 times the upper limit of the normal value	1
≤Upper limit of the normal value	0

ACS and have later been validated for use in patients admitted to the ED with suspected ACS.^{8–10} The HEART score is another validated risk score that consists of five elements: History, ECG, Age, Risk factors, and Troponin (Table 1). It can stratify patients with chest pain into low-, moderate-, and high-risk groups based on the development of major adverse cardiac events.¹¹ Comparisons among the three risk scores demonstrated that the HEART score outperformed both GRACE and TIMI in safely identifying low-risk patients admitted to the ED with suspected ACS.^{11–14} However, other important biochemical parameters such as inflammatory biomarkers were not incorporated into the HEART score. Inflammation is thought to be an important factor in ACS through its role in the initiation and progression of coronary plaque disruption and is reflected by an increase in multiple inflammatory markers such as C-reactive protein (CRP) and Interleukin-6 (IL-6).^{15–20} As an example, the CANTOS study found that Canakinumab, a specific human monoclonal anti-human IL-1 β antibody, significantly reduced IL-6, fibrinogen, CRP, and led to a significantly lower rate of recurrent cardiovascular events than placebo.²¹

The present study aimed to investigate whether the ACS-related inflammatory markers hs-CRP and IL-6 add diagnostic value to the HEART score in patients with chest pain suggestive of ACS admitted to the ED.

Methods

Study Design

This study was a post-hoc analysis based on a single-center clinical cohort study, the Rapid Use of High-Sensitive Cardiac Troponin I for Ruling-in and Ruling-out of Acute Myocardial Infarction: the RACING-MI cohort study.^{22,23} The RACING-MI cohort study was conducted between November 2016 and February 2019 and included patients with chest pain indicative of ACS who were admitted to the ED at a Danish regional hospital. The study design and methods have been previously described and published.²² The RACING-MI protocol was approved by The Regional Committee on Health Research Ethics (no.1-10-72-213-16). The investigation conforms with the principles outlined in the Declaration of Helsinki and the Danish Health Act. Written and oral informed consent was obtained from all subjects, including

permission to store and use blood in a biobank for future research (no. 1-16-02-530-16). Approval to perform post-hoc analysis of hs-CRP and IL-6 for this specific study was also obtained (no.1-10-72-206-22).

Patients

All patients admitted to the ED with chest pain suggestive of ACS were eligible for inclusion in the study, see Figure 1. As part of the standard procedure, a prehospital examination was performed on all patients, including ECG and point-of-care cardiac Troponin T in the ambulance. Patients with ST-segment elevation myocardial infarction (STEMI) or significant troponin elevation were transferred directly to a University Hospital with an invasive heart center.²⁴ Patients with non-STEMI or unstable angina pectoris were transferred to regional hospitals (ie Randers Regional Hospital) for further diagnostic investigation and clarification.²⁴

Excluded from the study were patients with STEMI at admission, age ≤ 18 , pregnancy, kidney failure requiring dialysis, prior MI, treatment with percutaneous coronary intervention (PCI), and/or coronary artery bypass graft. Due to potentially high levels of inflammatory biomarkers, patients with signs of infectious disease, cerebral hemorrhage or

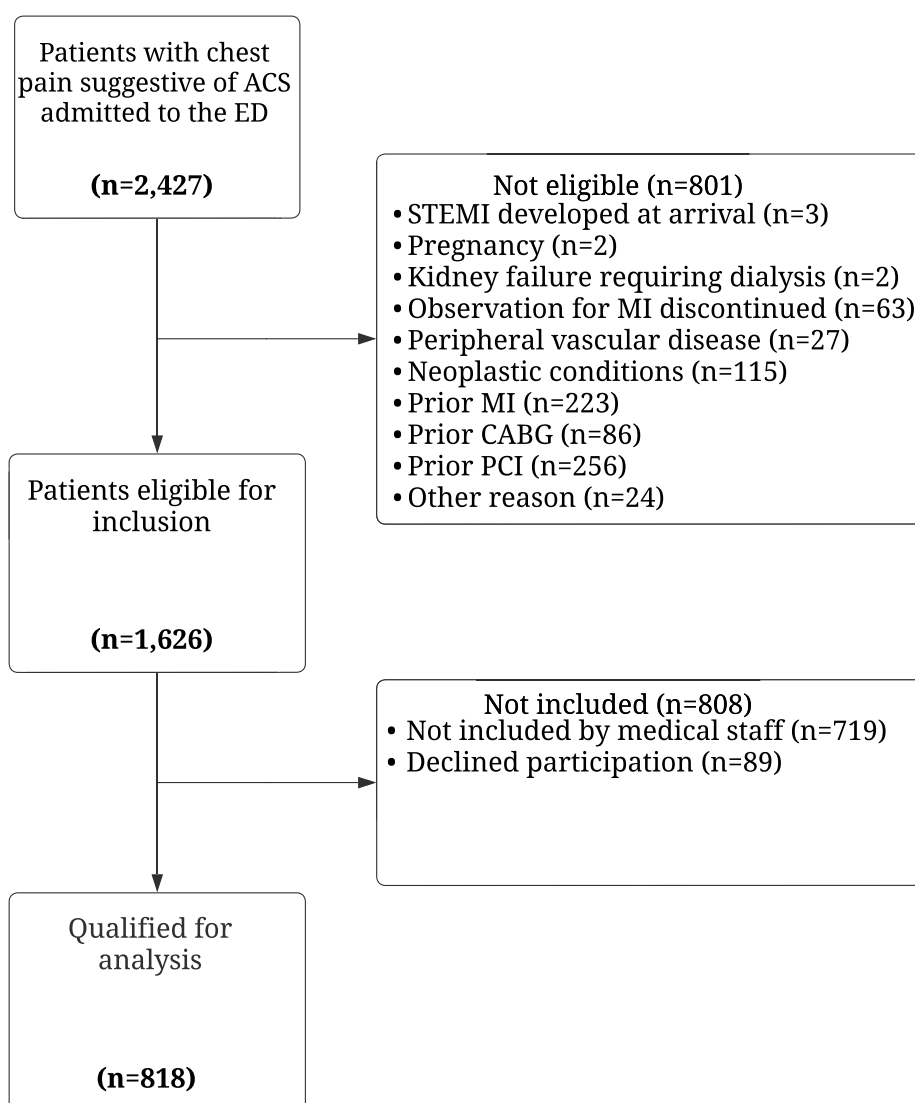


Figure 1 Patient flow-chart.

Abbreviations: ACS, Acute Coronary syndrome; ED, Emergency department; STEMI, ST-elevation myocardial infarction; MI, Acute myocardial infarction; CABG, Coronary artery bypass graft; PCI, percutaneous coronary intervention.

stroke, peripheral vascular disease, neoplastic conditions, known thrombotic disorders, dilated cardiomyopathy, surgery, or major trauma in the last month were also excluded.²⁵

Study Procedures

All patients underwent standard protocol care for chest pain suggestive of ACS. After oral and written consent were obtained, a research assistant registered all baseline parameters, including vital parameters, admission blood samples, serial troponin measurements, concomitant disease, medication upon admission to the ED, and patient demographics. In addition, all patients completed a 19-item questionnaire focusing on chest pain characteristics and cardiovascular risk profiles. Additional blood from each patient was stored in a biobank for future research, and hs-CRP and IL-6 levels were analyzed in the frozen plasma samples.

Determination of Hs-CRP and IL-6 Assays and HEART Score

Measurements of hs-CRP and IL-6 levels were performed using the plasma from the biobank. Siemens ADVIA Chemistry CardioPhase™ High Sensitivity C-Reactive Protein Reagents (Siemens Healthcare GmbH, Erlangen, Germany) were used to analyze hs-CRP levels. IL-6 levels were analyzed using Siemens Advia Centaur® IL-6 (Siemens Healthcare GmbH, Erlangen, Germany). The methods were accredited according to Danish, European and International standards for medical laboratories (DS/EN ISO 15189). The Limit of Detection (LoD) was provided by the manufacturer to be 0.1 mg/L for the hs-CRP assay and 2.7 pg/mL for the IL-6 assay. The 97.5th percentile cut-off point for both sexes were 7.6 mg/L for the hs-CRP assay and 4.4 pg/mL for the IL-6 assay. The cut-off point for hs-CRP \geq 2 mg/L has been used in large clinical trials²⁶ while the mean value of IL-6 in healthy individuals has previously been found to be 1.3 pg/mL.²⁷

Variables included in the HEART score were readily available after patients underwent examination in the ED. The total score was 10 points and was calculated using the software affiliated with the database. The patients were stratified into low group (0–3 points), moderate group (4–6 points), and high-risk groups (7–10 points) groups. The HEART scoring system is presented in Table 1.

Endpoints

The primary endpoint was whether hs-CRP and IL-6 levels provided additional diagnostic value when combined with the HEART score in patients with chest pain who were admitted to the ED with a low risk of ACS.

Adjudication of Final Diagnosis

The 4th universal definition of MI, which includes relative troponin changes, was used to diagnose patients with ACS.²⁸ All patients underwent a 30-day follow-up for major adverse cardiac events after discharge from the hospital. Adjudication was made independently by two physicians and was based on available clinical data from admission to the ED until 30 days after discharge. In the event of a discrepancy, consensus was achieved by consulting a senior attending Cardiologist.²³

Statistical Analysis

Quantile–quantile plots and histograms were used to analyze data with a normal distribution. Continuous variables are presented as mean \pm standard deviation (SD) and categorical variables are presented as counts and percentages. Variables with non-normal distributions are displayed as medians (lower quartile (Q1)] to upper quartile (Q3)). In accordance with the Wilson score method, endpoint measures were calculated using 95% confidence intervals (CI). Logistic regression was used to calculate the odds ratios (ORs) and 95% CIs for development ACS. The models were adjusted for age, sex, smoking status, and diabetes status. Two logistic regression models were constructed: one with Hs-CRP and IL-6 as continuous variables and another with Hs-CRP and IL-6 with the chosen cut-off points (Hs-CRP $>$ 2 mg/L and IL-6 $>$ 1.3 pg/mL). Statistical analyses were performed using the R version 6.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

During the original study period, 2427 consecutive patients were admitted to the ED with chest pain suggestive of ACS. A total of 818 patients were included in the current analysis according to the exclusion criteria. The patient flowchart is shown in Figure 1 and patient characteristics are listed in Table 2. The baseline values of the inflammatory and lipid markers stratified by ACS as the final diagnosis are presented in Table 3.

Occurrence of ACS

Of the 818 patients included in this study, 98 patients were diagnosed with ACS (12%). Of the 98 patients, 58 (59%) were diagnosed with non-STEMI, and 40 (41%) with unstable angina pectoris. Of the 98 patients diagnosed with ACS, 14 (14.3%) had type 2 diabetes (T2D). Other cardiovascular diseases (eg, heart failure, aortic dissection, and arrhythmia) accounted for 10% of the study group. Patients diagnosed with a non-cardiovascular disease (eg, infection, dyspepsia, gastric ulcers) constituted of 238 (29%) patients, and in total 432 (53%) were discharged after evaluation in the ED without any diagnosis requiring treatment (eg, musculoskeletal pain). During the 30-day adjudication period, none of the 720 patients who were not diagnosed with ACS at admission experienced major adverse cardiac events.

Table 2 Baseline Characteristics of Patients Without (-ACS) and with (+ACS)

Variables	-ACS	+ACS	p
	N=720 (88%)	N=98 (12%)	
Age (median [IQR])	58.0 [48.0, 70.0]	62.0 [53.3, 72.0]	0.003
Female gender (%)	378 (52.5)	39 (39.8)	0.02
Medication			
Lipid lowering medication (%)	194 (26.9)	34 (34.7)	0.14
Antihypertensive (%)	293 (40.3)	62 (68.1)	<0.001
Nitrates (%)	82 (11.4)	14 (14.3)	0.50
Other antianginal medication (%)	2 (0.3)	3 (3.1)	0.01
Anticoagulants (%)	62 (8.6)	9 (9.2)	1.000
Platelet inhibitors (%)	144 (20.0)	19 (19.4)	0.99
Diuretics (%)	129 (17.9)	21 (21.4)	0.48
Antiarrhythmics (%)	10 (1.4)	1 (1.0)	1.00
PPI (%)	157 (21.8)	17 (17.3)	0.38
NSAID (%)	51 (7.1)	9 (9.2)	0.59
Antidiabetics (%)	62 (8.6)	10 (10.2)	0.74
Cardiovascular risk factors			
Hypertension (%)	258 (35.8)	43 (43.9)	0.15
Hypercholesterolemia (%)	187 (26.0)	31 (31.6)	0.27
T2D (%)	77 (10.7)	14 (14.3)	0.37
Current smoking (%)			0.28
No	274 (38.2)	39 (39.8)	
Yes	163 (22.7)	29 (29.6)	
Family history of CAD before the age of 50 years (%)			0.69
Yes, more than one	31 (4.3)	4 (4.1)	
Yes, one	55 (7.7)	11 (11.2)	
Final diagnosis			
Non-STEMI (%)	—	58 (59.2)	
Unstable angina pectoris (%)	—	40 (40.8)	

Abbreviations: PPI, Proton pump inhibitors; NSAID, Non-steroidal anti-inflammatory drugs; T2D, type 2 diabetes; CAD, Coronary artery disease; non-STEMI, non-ST-elevation myocardial infarction.

Table 3 Baseline Values Based on Patients with and without ACS

Variables	-ACS	+ACS	p
	N=720 (88%)	N=98 (12%)	
TnI ng/mL (median [IQR])	3.6 [1.8, 7.2]	22.6 [4.6, 101.7]	<0.001
IL-6 pg/mL (median [IQR])	2.2 [1.1, 4.2]	2.1 [0.9, 5.3]	0.81
Hs-CRP mg/L (median [IQR])	2.0 [0.8, 4.7]	2.0 [0.8, 5.0]	0.99
P-Cholesterol mmol/L (median [IQR])	4.9 [4.1, 5.6]	5.0 [4.2, 5.6]	0.81
P-LDL mmol/L (median [IQR])	2.9 [2.2, 3.6]	2.8 [2.4, 3.5]	0.62
P-HDL mmol/L (median [IQR])	1.3 [1.0, 1.6]	1.2 [1.0, 1.5]	1
BMI kg/m ² (median [IQR])	27.5 [24.4, 31.6]	26.8 [24.5, 30.4]	0.50

Abbreviations: TnI, Troponin I; IL-6, Interleukin-6; Hs-CRP, high sensitive-CRP; P-LDL, plasma- low density lipoprotein; BMI, body mass index.

Diagnostic Value of Admission Hs-CRP and IL-6 for ACS

In total, 403 patients had hs-CRP levels >2 mg/L, which amounted to 50% (49 patients) of all the patients. Similarly, IL-6 levels > 1.3 pg/mL were found in 574 patients, and they constituting 71.4% (70 patients) of all ACS patients. Diagnostic value of hs-CRP and IL-6 for the diagnosis of ACS is presented in Table 4 and was 1.0 for hs-CRP>2 mg/L and IL-6 > 1.3 pg/mL, respectively.

Independent Association Between Inflammatory Markers and ACS in Patients with Acute Chest Pain

Table 5 and Table 6 summarize the results of the logistic regression analyses of the factors associated with ACS in patients with acute chest pain. The logistic regression analyses were adjusted for age, sex, smoking status, and diabetes. Age, male sex, and ongoing smoking are associated with ACS in patients with acute chest pain. In contrast, there was no

Table 4 Diagnostic Value of Hs-CRP > 2mg/L and IL-6 >1.3 Pg/L for the Diagnosis of ACS

	Sensitivity	Specificity	+LR	-LR
Hs-CRP >2mg/L N = 818	50.0% (39.7–60.3%)	50.8% (47.1–54.5%)	1.0 (0.8–1.3)	1.0 (0.8–1.2)
IL-6 >1.3pg/L N = 818	71.4% (61.4–80.1%)	28.5% (24.2–32.0%)	1.0 (0.9–1.1)	1.0 (0.7–1.4)

Abbreviations: Hs-CRP, High sensitive C-reactive protein; ACS, acute coronary syndrome; +LR, Positive Likelihood Ratio; -LR, Negative Likelihood Ratio.

Table 5 Logistic Regression Analysis with Continuous Values of IL-6 and Hs-CRP, Outcome: ACS (n=98)

Variables	OR [95% CI]	Standard Error	p
Intercept			
Age (years)	1.0 [1.0, 1.0]	0.008	<0.001
Sex (Female gender)	0.6 [0.4, 0.9]	0.1	0.014
Current smoking			
No	1.1 [0.7, 1.8]	0.3	0.729
Yes	1.9 [1.1, 3.3]	0.6	0.032
T2D (yes vs no)	1.3 [0.7, 2.5]	0.4	0.361
IL-6 continuous	1.0 [0.9, 1.0]	0.00	0.157
Hs-CRP continuous	0.9 [0.9, 1.0]	0.2	0.85

Abbreviations: T2D, type 2 diabetes; IL-6, Interleukin-6; Hs-CRP, high sensitive-CRP.

Table 6 Logistic Regression Analysis with Prespecified Cut-off Values of IL-6 and Hs-CRP, Outcome: ACS (n=98)

Variables	OR [95% CI]	Standard Error	p
Intercept			
Age (years)	1.0 [1.0, 1.1]	0.008	0.000
Sex (Female gender)	0.6 [0.4, 0.9]	0.1	0.022
Current smoking			
No	1.1 [0.7, 1.9]	0.7	0.629
Yes	1.9 [1.1, 3.4]	0.6	0.029
T2D (yes vs no)	1.3 [0.7, 2.4]	0.4	0.426
IL-6 > 1.3 pg/mL	0.9 [0.6, 1.4]	0.2	0.663
Hs-CRP > 2mg/L	0.9 [0.6, 1.5]	0.2	0.977

Abbreviations: T2D, type 2 diabetes; IL-6, Interleukin-6; Hs-CRP, high sensitive-CRP.

association between IL-6 or hs-CRP level and ACS. This was true for IL-6 and hs-CRP at both continuous and prespecified cut-off values.

Discussion

Summary

The present study investigated whether the cardiovascular inflammatory risk markers hs-CRP and IL-6 provide additional diagnostic value for ACS beyond that achieved using the HEART score. Among 818 patients admitted to the ED with chest pain suggestive of ACS, our results showed that neither hs-CRP nor IL-6 provided independent diagnostic value, as demonstrated by 1) similar levels of hs-CRP and IL-6 in patients with versus without ACS, 2) diagnostic likelihood ratios of 1.0 for both inflammatory markers, and 3) that hs-CRP and IL-6 are not independently associated with a higher risk of ACS.

Taken together, the present study adds to the available literature by demonstrating that inflammatory markers do not provide diagnostic value in the workup of patients with chest pain who are being evaluated for ACS.

Previous Literature

A diagnostic threshold of 25 mg/L for CRP showed sensitivity for the diagnosis of ACS of 93%, specificity of 65%, and negative predictive value of 96% in a setting with an invasive heart center [20]. In Another study using a population-based threshold for CRP level ≥ 3.16 mg/L showed sensitivity for the diagnosis of ACS of 70%) and specificity of 74%).^{20,29} These studies reported significantly higher levels of sensitivity and specificity than those in the present study.

However, previous studies have used conventional CRP measurements, whereas hs-CRP levels were measured in this study. This study is consistent with a previous study on low-risk chest pain patients by Diercks et al, which used a diagnostic threshold of hs-CRP ≥ 2 mg/L. The study reported a sensitivity for and diagnosis of ACS of 53.1% and specificity of 50.3%.³⁰ In another study in which 1028 patients developed STEMI, the mean levels of IL-6 were found to be 18.7 pg/mL and mean CRP levels of 13.0 mg/L, and a significant correlation between peak troponins and IL-6 and CRP was also found.³¹ The levels of the inflammatory markers were significantly lower in the present study. As patients with STEMI were not included in the study, the results may underestimate the true values of hs-CRP and IL-6 in patients with ACS.

In this study, cut-off values of 2 mg/L for hs-CRP and 1.3 pg/mL for IL-6 were used, as these values have been used in large-scale clinical trials to define the increased risk of cardiovascular events.^{26,32} Nevertheless, uniform cutoff points for inflammatory markers eg, such as hs-CRP and IL-6, may be challenging because BMI, diabetes mellitus, hypertension, physical activity, alcohol consumption, smoking, and other factors cause baseline variation.^{25,27}

Clinical Perspective

Patients admitted to the ED with acute chest pain suggestive of ACS may find it challenging to obtain a quick and accurate diagnosis. It is necessary to quickly and safely stratify patients to offer optimal treatment for cardiovascular events. The HEART score has been found to be an effective tool for identifying patients with low risk of cardiac ischemia who can be safely discharged early after hospitalization.^{13,33,34}

This study investigated whether hs-CRP and IL-6 levels could provide diagnostic value in combination with the HEART score. Prior studies have used TIMI and GRACE scores in combination with hs-CRP and other serum biomarkers to investigate whether they provide improved risk stratification for patients with ACS.^{35,36} Klingenberg et al found that combinations of biomarkers, including hsTnT, NT-proBNP, and hs-CRP, with GRACE scores enhanced risk discrimination in patients with ACS.³⁵ The current HEART score includes only the laboratory-based biomarker troponin. Variables that reflect the other pathophysiological characteristics of ACS may provide additional diagnostic information. Despite the important role of inflammation in the pathogenesis of atherothrombosis, including myocardial infarction, our findings do not support the notion that inflammatory markers such as hs-CRP and IL-6 provide diagnostic value for detecting ACS among patients with chest pain in combination with the HEART score.

One major strength of the HEART score is that it is a readily available diagnostic tool that requires only information available shortly after admission, together with the troponin level, and can be used in both large hospitals with a coronary catheterization facility and in smaller hospitals with no invasive capabilities. The HEART score summarizes the descriptions and reflections of patients with chest pain. This could have major effects on minimizing unnecessary and expensive bed allocation, which could further increase patient safety as overcrowded ED's have been linked to increased mortality.³⁷ Furthermore, faster diagnosis of patients with cardiovascular events may reduce the time to thrombolysis and/or revascularization, although its effect on morbidity and mortality is still unknown. IL-6 and hs-CRP levels have limited diagnostic value as independent markers in patients with chest pain admitted to the ED with a low risk of ACS. Therefore, we do not recommend that IL-6 and hs-CRP be implemented in clinical practice in the ED because they will most likely not help with a faster diagnosis of patients with cardiovascular events. Larger prospective studies are necessary to confirm the findings of the present study.

Limitations

This study was based on data obtained from a single center. The study relied on the medical staff for patient inclusion and blood sampling. Therefore, not all patients admitted to the ED with chest pain were included in the study, and blood samples were unavailable for IL-6 and hs-CRP measurements. This could have increased the risk of unintended lack of inclusion, resulting in selection bias. However, there is no reason to suspect that patients who were not included in the study by the medical staff were different from the included patients. This was a post hoc analysis of blood samples from a biobank, which means that we did not have multiple blood test samples from each patient. The concentration of inflammatory markers may peak later, which may have impeded the hs-CRP and IL-6 results.³⁸ However, in patients with chest pain, the focus is on myocardial necrosis markers; therefore, it is difficult to take serial hs-CRP and IL-6 measurements.

Conclusion

Among the 818 patients admitted to the ED with chest pain suggestive of ACS, neither hs-CRP nor IL-6 provided an independent added diagnostic value. Our results suggest that inflammatory markers have limited diagnostic value in detecting patients with ACS in the ED.

Abbreviations

ACS, Acute coronary syndrome; ECG, Electrocardiogram; ED, Emergency Department; GRACE, The Global Registry of Acute Coronary Events; HEART-score, History, ECG, Age, Risk factors, Troponin-score; Hs-CRP, High sensitive C-reactive protein; IL-6, Interleukin-6; MI, Myocardial Infarction; PCI, Percutaneous coronary intervention; RACING-MRACING-MI, Rapid Use of High-Sensitive Cardiac Troponin I for Ruling-in and Ruling- out of myocardial infarction;

STEMI, ST-segment elevation MI; SD, Standard deviation; TIMI, Thrombolysis in Myocardial Infarction score; T2D, Type 2 diabetes.

Disclosure

The authors report no conflicts of interest in this work.

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