DOI: 10.24938/kutfd.1543770 Kırıkkale Üniversitesi Tıp Fakültesi Dergisi 2024;26(3):336-342
Original Article *Özgün Araştırma*

ASSESSING THE PROGNOSTIC VALUE OF THE HEMOGLOBIN-TO-RED CELL DISTRIBUTION WIDTH RATIO IN EMERGENCY DEPARTMENT PATIENTS WITH ACUTE CORONARY SYNDROME

Acil Servisteki Akut Koroner Sendromlu Hastalarda Hemoglobin-Kırmızı Hücre Dağılım Genişliği Oranının Prognostik Değerinin Değerlendirilmesi

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ABSTRACT

Objective: Acute coronary syndrome (ACS) is a critical condition requiring rapid evaluation in the emergency department. The hemoglobin-to-red cell distribution width ratio (HRR) has emerged as a potential prognostic biomarker, reflecting the combined effects of hemoglobin and red cell distribution width. This study aims to evaluate the prognostic value of HRR in patients presenting to the emergency department with ACS.

Material and Methods: A retrospective cohort study was conducted at a single center, involving adult patients who were diagnosed with acute coronary syndrome upon presentation to the emergency department. HRR was calculated as the ratio of hemoglobin to red cell distribution width, and its association with 30-day cardiac mortality (CM), all-cause mortality (ACM), and major adverse cardiovascular events (MACE) was analyzed using Receiver Operating Characteristics (ROC) curve analysis.

Results: The study included 688 patients, with a mean age of 61.9±12.3 years and 57% males. Lower HRR was significantly associated with higher 30-day CM, ACM, and MACE rates. ROC curve analysis showed HRR had acceptable discriminatory power with AUC values of 0.764 for 30-day CM, 0.718 for 30-day ACM, and 0.739 for 30-day MACE. An HRR cut-off value of 0.9 was determined, with sensitivities of 87.8%, 90.2%, and 88.7%, and specificities of 47.6%, 48.4%, and 48.9% for CM, ACM, and MACE, respectively.

Conclusion: HRR is a useful prognostic marker for 30-day outcomes in ACS patients. Its easy accessibility and rapid availability makes it a practical tool for risk stratification in the emergency department.

Keywords: *Acute coronary syndrome, hemoglobin, major adverse cardiac events, mortality*

ÖZ

Amaç: Akut koroner sendrom (AKS) acil serviste hızlı değerlendirme gerektiren kritik bir durumdur. Hemoglobin-kırmızı hücre dağılım genişliği oranı (HRR), hemoglobin ve kırmızı hücre dağılım genişliğinin birleşik etkilerini yansıtan potansiyel bir prognostik biyobelirteç olarak ortaya çıkmıştır. Bu çalışma, acil servise AKS ile başvuran hastalarda HRR'nin prognostik değerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Tek bir merkezde, acil serviste AKS tanısı konulan yetişkin hastaları kapsayan retrospektif bir kohort çalışması yürütülmüştür. HRR, hemoglobinin kırmızı hücre dağılım genişliğine oranı olarak hesaplanmış ve 30 günlük kardiyak ölüm (KÖ), tüm nedenlere bağlı ölüm (TNBÖ) ve majör istenmeyen kardiyovasküler olaylar (MİKO) ile ilişkisi *Receiver Operating Characteristics* (ROC) eğrisi analizi kullanılarak analiz edilmiştir.

Bulgular: Çalışmaya 688 hasta dahil edilmiştir. Hastaların ortalama yaşı 61.9±12.3 yıl ve hastaların %57'si erkektir. Düşük HRR, daha yüksek 30 günlük KÖ, TNBÖ ve MİKO oranları ile anlamlı olarak ilişkilendirilmiştir. ROC eğrisi analizi, 30 günlük KM için 0,764, 30 günlük TNBM için 0.718 ve 30 günlük MİKO için 0.739 eğrinin altında kalan alan değerleri ile HRR'nin kabul edilebilir ayırt edici güce sahip olduğunu göstermiştir. HRR için eşik değer 0,9 olarak belirlenmiştir ve bu değer için KÖ, TNBÖ ve MİKO için sırasıyla %87.8, %90.2 ve %88.7 duyarlılık ve %47.6, %48.4 ve %48.9 özgüllüğe sahiptir.

Sonuç: HRR, AKS hastalarında 30 günlük sonuçlar için faydalı bir prognostik belirteçtir. Kolay erişilebilir olması ve hızlı sonuç vermesi, acil serviste risk sınıflandırması için pratik bir araç olmasını sağlamaktadır.

Anahtar Kelimeler: *Akut koroner sendrom, hemoglobin, major istenmeyen kardiyak olay, mortalite*

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Received / Geliş Tarihi: 05.09.2024 **Accepted** / Kabul Tarihi: 19.09.2024

KÜ Tıp Fak Derg 2024;26(3):336-342
Doi: 10.24938/kutfd.1543770

INTRODUCTION

Chest pain is among the most prevalent presenting complaints in emergency department (ED) settings, constituting approximately 5-10% of ED visits (1,2). The causes of this pain may be non-life-threatening, such as musculoskeletal pain, or fatal, such as acute coronary syndrome (ACS), esophageal rupture, pulmonary embolism, and aortic dissection. Therefore, examining patients presenting with chest pain requires a multimodal approach (3).

Acute coronary syndrome (ACS) is a critical condition encompassing a range of cardiac events resulting from reduced blood flow to the heart. ACS is diagnosed in 8.4-22% of patients presenting with chest pain, and this high rate and high mortality/morbidity risk make ACS one of the most important diagnoses to consider in patients presenting with chest pain (3-5). To aid clinicians in the timely and accurate diagnosis of ACS, various algorithms have been developed by the European Society of Cardiology (ESC), the American Heart Association (AHA), and other cardiology societies. These guidelines underscore the importance of recognizing and treating ACS promptly to improve patient outcomes (6,7).

In recent years, numerous studies have explored various biomarkers and clinical parameters to refine the prognosis and management of ACS in the ED (8). One emerging biomarker is the hemoglobin-to-red cell distribution width ratio (HRR), which combines two easily accessible hematologic indices: hemoglobin (Hb) concentration and red cell distribution width (RDW) (9). Hb reflects the blood's oxygen-carrying capacity, while RDW indicates the variability in red blood cell (RBC) size. The HRR integrates these parameters, potentially providing a more comprehensive insight into the patient's hematologic and inflammatory status.

HRR has shown promise as a biomarker for various cardiovascular and inflammatory conditions. A lower HRR has been associated with poor outcomes, likely reflecting underlying inflammation, anemia, or other pathological conditions that impair oxygen delivery and increase RBC size variability (9-13). Despite its potential, the clinical significance of HRR remains under investigation, and it is not yet a standard diagnostic tool. Existing literature has established the prognostic value of Hb and RDW separately in ACS, but the combined HRR metric could offer a novel approach to risk stratification in these patients (14,15). So, in this study, we aimed to investigate the prognostic value of HRR in patients evaluated in the ED with ACS.

MATERIALS AND METHODS

Study design and settings

A single-center retrospective cohort study was carried out at a tertiary university hospital serving approximately 80,000 adult patients annually. Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (Clinical Research Ethics Committee) approved the study protocol (protocol number: 2023/159; May 23, 2023), and the Declaration of Helsinki was complied with throughout the study. The study report was composed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (16).

Study participants

We retrospectively analyzed all adult patients (>18 years of age) who presented to the ED with acute chest discomfort or an equivalent symptom and were diagnosed with ACS on evaluation with the cardiology department between April 1, 2022, and March 31, 2023. Patients with end-stage diseases (malignancy, stage-4 heart failure, end-stage renal failure, etc.) or pregnant patients were not included. Patients with incomplete data and discharged against medical advice (DAMA) before completion of investigations and treatment were excluded.

Definitions and variables

Acute chest discomfort was defined as pain, pressure, tightness, heaviness, or burning in the chest, as delineated by the ESC guidelines. Similarly, dyspnea, epigastric pain, pain in the left/right arm, and pain in the jaw or neck were defined as equivalent symptoms (6,17).

Patients with ACS are classified into two primary diagnostic categories: acute myocardial infarction (AMI) and unstable angina (UA). The diagnosis of myocardial infarction (MI) is confirmed based on evidence of cardiomyocyte injury, indicated by elevated cardiac biomarkers, and adheres to the 4th universal definition of myocardial infarction (18). AMI is further subdivided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), with STEMI identified by ST-segment elevation on a 12-lead ECG and NSTEMI by its absence. Conversely, the diagnosis of UA is made in the absence of cardiomyocyte injury or necrosis in patients with symptoms of myocardial ischemia at rest or with minimal exertion (6).

ST-segment elevation defined as new ST-segment elevation at the J point in at least two adjacent leads is defined as follows: ≥2.5 mm in men under 40 years old, ≥2 mm in men aged 40 years or older, or ≥1.5 mm in women in leads V2-V3, or ≥1 mm in other leads (17). Major adverse cardiovascular events (MACE) were defined as cardiac death, heart failure, rehospitalization for cardiac causes, reinfarction, or target vessel revascularization.

Outcomes

The primary outcome of the study was 30-day all-cause mortality (ACM) and cardiac mortality (CM). The secondary outcome was MACE within 30 days.

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Data sources/measurement

Data were gathered from the hospital's electronic information management system, as well as from medical records and patient files. Demographic data, comorbid diseases (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, dysrhythmia), smoking status, and laboratory values (Hb, RDW, high sensitive troponin I) were recorded. HRR calculation was recorded as Hb value divided by RDW. ACM, CM, and MACE occurrences within 30 days of hospital presentation were assessed through the hospital's electronic information operating system and the national electronic health database.

Statistical analysis

The SPSS (IBM Statistical Package for Social Sciences) for Windows 23.0 was used for statistical analysis. Histograms and Q-Q plot graphs were used to evaluate the distribution of data. Categorical variables were presented as numbers with percentages. Normally distributed variables were presented as mean and standard deviation, while non-normally distributed variables were presented as medians with interquartile ranges. Independent group comparisons were performed with the Student T-test, while multiple group analyses were performed with Kruskal-Wallis and Pearson-Chi Square. Statistical significance was set at $p < 0.05$. To evaluate the predictive power of the HRR, we employed Receiver Operating Characteristics (ROC) analysis to compute the area under the curve (AUC). The optimal threshold value was identified using the Youden index. The diagnostic accuracy of HRR levels was calculated in terms of sensitivity, specificity, positive predictive value, and negative predictive value using 95% confidence intervals.

RESULTS

During the study period, 73,562 patients presented to the ED. Of these patients, 9,230 presented with acute chest discomfort and equivalent symptoms, and 741 of them were diagnosed with ACS. Patients who were pregnant (n=2), who had end-stage diseases (n=7), who signed DAMA before completion of investigations and treatment (n=14), and who had missing data (n=30) were excluded from the study. As a result, 688 patients were included. Among those included 48 (6.9%) were diagnosed with UA, 385 (56.0%) with NSTEMI and 255 (37.1%) with STEMI (Figure 1).

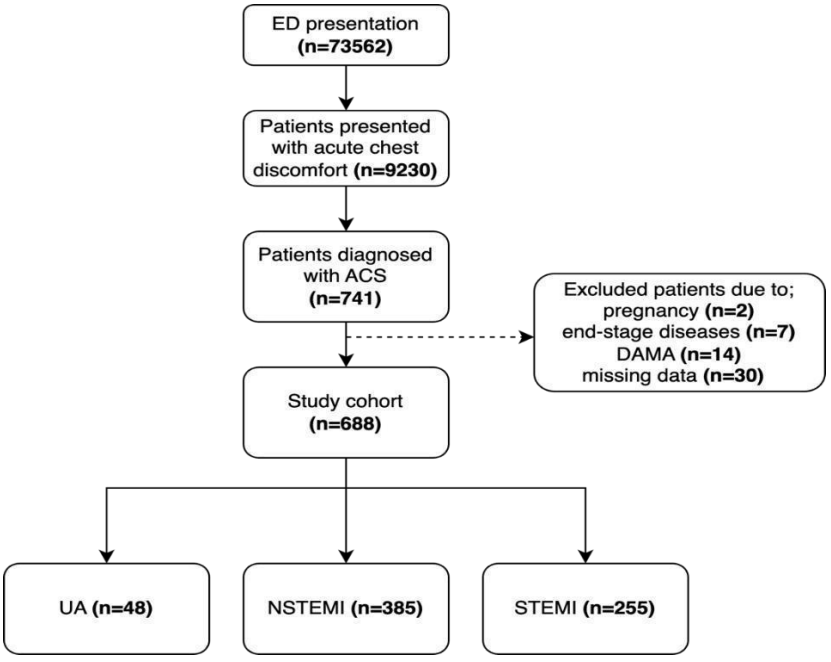

Figure 1: Flow diagram of the study

ACS: Acute coronary syndrome, DAMA: Discharge against medical advice, ED: Emergency department, NSTEMI: Non-ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, UA: Unstable angina

Main Characteristics

The patients' mean (SD) age was 61.9±12.3 years, and 57.0% (n=392) were male. The main characteristics of the patients according to their diagnoses are detailed in Table 1. In subgroup analyses STEMI patients were significantly younger than NSTEMI patients ($p = 0.008$, Kruskal Wallis). The diagnosis of hypertension did not differ between patients with NSTEMI and STEMI ($p=0.167$, Pearson Chi-Square) but was more frequent in patients with UA ($p=0.005$, Pearson Chi-Square). The diagnosis of HL was most common in UA patients, followed by NSTEMI patients, and least common in STEMI patients ($p<0.001$, Pearson-Chi Square).

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Table 1: Characteristics and outcomes of acute coronary syndrome patients by diagnoses (n=688)

Characteristics, n (%)	UA (n=48)	NSTEMI (n=385)	STEMI (n=255)	All patients (n=688)	p
Age, mean±SD	58.9±13.6	63.4±12.0	60.2±12.4	61.9±12.3	0.003 &
Male gender	32 (66.7)	212 (55.1)	148 (58.0)	392 (57.0)	0.282 ^
HT	38 (79.2)	223 (57.9)	137 (53.7)	398 (57.8)	0.005 ^
DM	23 (47.9)	143 (37.1)	83 (32.5)	249 (36.2)	0.107 ^
HL	33 (68.8)	173 (44.9)	68 (26.7)	274 (39.8)	<0.001 ^
Dysrhytmia	8 (16.7)	53 (13.8)	50 (19.6)	111 (16.1)	0.144 ^
CAD	28 (58.3)	175 (45.5)	105 (41.2)	308 (44.8)	0.083 ^
Smoking	29 (60.4)	258 (67.0)	159 (62.4)	446 (64.8)	0.387 ^
Hemoglobin, mean ± SD	12.9±2.5	12.4±2.5	12.3±2.3	12.4±2.4	0.240 &
RDW, median (Q1-Q3)	13.9 (13.0-15.7)	14.1 (13.1-15.8)	14.2 (13.2-15.6)	14.1 (13.1-15.8)	0.586 &
HRR,mean ± SD	0.92±0.26	0.87±0.24	0.86±0.22	0.87±0.23	0.169 &
hs-cTn-I, median (Q1-Q3)	6.1 (3.4-7.9)	243.6 (94.6-813.0)	158.6 (74.9-592.3)	170.9 (73.6-617.4)	<0.001 &
30-Day cardiac mortality	1 (2.1)	23 (6.0)	17 (6.7)	41 (6.0)	0.469 ^
30-Day all causes mortality	1 (2.1)	29 (7.5)	21 (8.2)	51 (7.4)	0.325 ^
30-Day MACE	3 (6.3)	35 (9.1)	24 (9.4)	62 (9.0)	0.779 ^

SD: Standart deviation, CAD: Coronary artery disease, DM: Diabetes mellitus, HL: Hyperlipidemia, HRR: Hemoglobin to red cell distribution width ratio, hs cTn-I: High-sensitivity cardiac troponin I, HT: Hypertension, MACE: Major adverse cardiac event, NSTEMI: Non-ST-segment elevation myocardial infarction, RDW: Red cell distribution width STEMI: ST-segment elevation myocardial infarction, UA: Unstable angina
&: Kruskal Wallis, ^: Pearson Chi-Square Tests

Relationship Between HRR and Outcomes

When the patients included in the study were investigated for 30 days, CM was seen in 6.0% (n=41) of the patients, while ACM was seen in 7.4% (n=51) patients. MACE was seen in 9.0% (n=62) of the patients. Their distribution according to ACS diagnoses is shown in Table 1. The relationship between HRR and patient outcomes is shown in Table 2.

Table 2: Association of patients' outcomes with HRR

Outcome	HRR, mean (95% CI)	p
30-Day Cardiac mortality		
Yes	0.71 (0.66-0.77)	<0.001*
No	0.88 (0.86-0.90)	
30-Day All cause mortality		
Yes	0.66 (0.62-0.72)	<0.001*
No	0.88 (0.87-0.90)	
30-Day MACE		
Yes	0.70 (0.67-0.74)	<0.001*
No	0.88 (0.87-0.90)	

CI: Confidence interval, HRR: Hemoglobin to red cell distribution width ratio, MACE: Major adverse cardiac event,
*: Student T test

Since the HRR levels of patients with poor outcomes were found to be significantly lower, ROC curve analysis was performed. In the ROC analysis, the AUC of HRR for predicting 30-day CM, ACM, and MACE were 0.764 (95% CI 0.705-0.823), 0.718 (95% CI 0.651-0.783) and 0.739 (95% CI 0.685-0.792), respectively (Figure 2). All AUC values are considered acceptable (19). According to the Youden analysis, the best discriminating cut-off point was 0.9. The sensitivity of the identified cut-off point for predicting 30-day CM, ACM, and MACE was 87.8% (95% CI, 73.80–95.92), 90.2% (95% CI, 78.59–96.74), and 87.1% (95% CI, 78.11–95.34), respectively. The specificity for 30-day CM, ACM, and MACE was 47.6% (95% CI, 43.70–51.53), 48.35% (95% CI, 44.41–52.31), and 48.88% (95% CI, 44.90–52.88), respectively. Additional diagnostic parameters, including positive predictive value, negative predictive value, and likelihood ratios, were detailed in Table 3.

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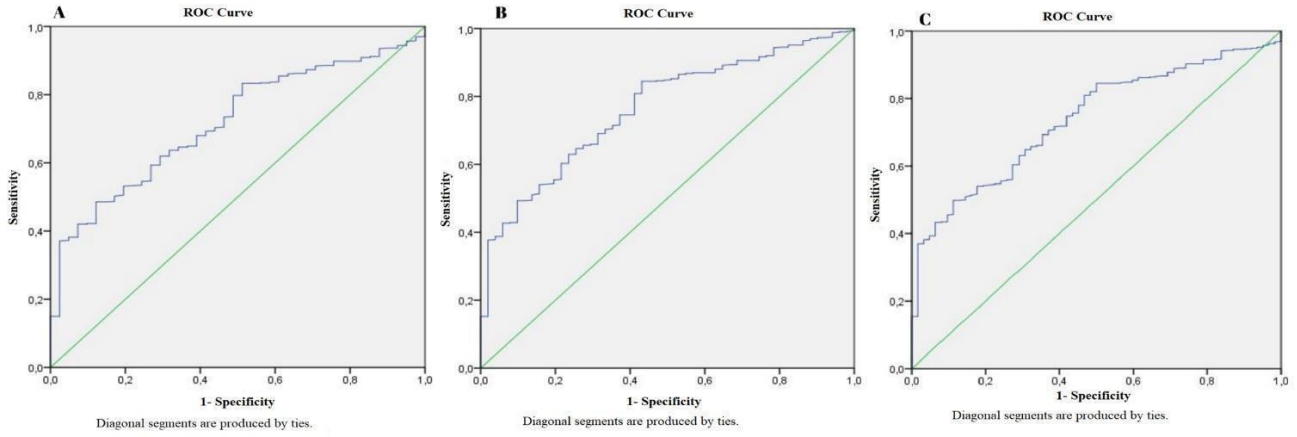

Figure 2: In ACS patients the performance of HRR values in predicting 30-day cardiac mortality (A), all cause mortality (B), and MACE (C)
ACS: Acute coronary syndrome, HRR: Hemoglobin to red cell distribution width ratio MACE: Major adverse cardiac event

Table 3: Diagnostic value of HRR with a cut off of 0.9 to predict poor outcomes

Outcome	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	(+) LR (95% CI)	(-) LR (95% CI)
30-Day Cardiac cause mortality	0.764 (0.705-0.823)	87.80 (73.80-95.92)	47.60 (43.70-51.53)	9.60 (8.49-10.84)	98.40 (96.43-99.29)	1.68 (1.47-1.92)	0.26 (0.11-0.59)
30-Day All cause mortality	0.718 (0.651-0.783)	90.2 (78.59-96.74)	48.35 (44.41-52.31)	12.27 (11.06-13.59)	98.4 (96.39-99.30)	1.75 (1.56-1.97)	0.20 (0.09-0.46)
30-Day MACE	0.739 (0.685-0.792)	88.71 (78.11-95.34)	48.88 (44.90-52.88)	14.67 (13.26-16.20)	97.76 (95.59-98.88)	1.74 (1.55-1.96)	0.23 (0.11-0.46)

AUC: Area under curve, HRR: Hemoglobin to red cell distribution width ratio, MACE: Major adverse cardiac event, (+) LR: positive likelihood ratio, (-) LR: negative likelihood ratio, NPV: Negative predictive value, PPV: Positive predictive value

DISCUSSION

In this study, we investigated the prognostic value of HRR in patients presenting to the ED with ACS. Our findings indicate that a lower HRR is significantly associated with poor outcomes, including 30-day CM, ACM, and MACE. These results underscore the potential utility of HRR as a prognostic marker in ACS, complementing existing diagnostic algorithms and enhancing risk stratification.

Acute chest discomfort is one of the most common reasons for emergency department visits (1). In our hospital, 12.5% of admissions were with this complaint, and 8% of these patients were diagnosed with ACS. The 30-day mortality of these patients ranged from 2 to 8.2%, and the 30-day MACE risk ranged from 6.3 to 9.4, depending on the subgroup diagnosis. Therefore, it is important to comprehensively approach these diseases, which have high morbidity and mortality even in a short period of time, in the ED. The mean age of the cohort was 61.9±12.3 years, with a predominance of males (57.0%). These demographic and clinical characteristics align with prior studies on ACS, which typically report higher prevalence rates among older adults and males (20). In our study, risk factors such as hypertension and hyperlipidemia were seen more frequently in the diagnosis of the UA subgroup. Recent studies have suggested that this may be related to the fact that these patients are receiving medical treatment for their existing diseases, possibly altering the pathophysiology of ACS (21). However, in our study, the patient's comorbidities were examined, and it is impossible to comment on this issue since their medication use or compliance was not evaluated.

The prognostic relevance of HRR is likely attributable to its reflection of underlying pathophysiological mechanisms. Hb concentration indicates the oxygen-carrying capacity of the blood, while RDW reflects the heterogeneity in red blood cell size, which is influenced by various factors, including inflammation, nutritional deficiencies, and bone marrow dysfunction (22). The increase in RDW reflects abnormal erythrocyte homeostasis and deformed red blood cells, resulting to impaired blood flow in the microcirculation (23). Low Hb levels represent decreased oxygen transport capacity and are associated with tissue hypoxia (22). Therefore, low HRR levels encompass both conditions and potentially indicate worsening cardiovascular disease. Since HRR is a rapid and easily accessible test that can be obtained by simple tests (CBC), it has been used in prognosis assessment in many diseases (9). In the study by Xiu et al., patients who underwent angiography were analyzed and divided into two groups according to HRR levels. Patients with HRR levels below 1.02 had a mortality rate of 7.1%, while patients with HRR levels

above 1.02 had a mortality rate of 3.9% (24). In the study by Kilic et al., the cut-of value was found to be 0.947, and it was observed that it might be useful for predicting in long-term mortality (25). Our findings are consistent with recent studies that have identified HRR as a predictor of outcomes in various clinical settings, including cardiovascular diseases and critical illnesses. HRR was significantly lower in patients who experienced adverse outcomes. Specifically, the mean HRR was 0.71 in patients with 30-day cardiac mortality compared to 0.88 in those without. This pattern was consistent for 30-day all-cause mortality and MACE. Also, the ROC curve analysis demonstrated that HRR had acceptable discriminatory power (19), with AUC values of 0.764 for 30-day CM, 0.718 for 30-day ACM, and 0.739 for 30-day MACE, suggesting that HRR can effectively predict these outcomes. Given its high sensitivity and negative predictive value (NPV) across all three outcomes, HRR could serve as a valuable tool in helping clinicians identify non-critical patients in the ED, and support decision-making when combined with other markers.

Despite the promising results, several limitations of this study should be noted. The retrospective design and single-center setting may limit the generalizability of the findings. Additionally, while we adjusted for several confounders, residual confounding cannot be entirely excluded. Future prospective, multicenter studies are warranted to validate these findings and explore the mechanisms underlying the association between HRR and adverse outcomes in ACS.

In conclusion, our study suggests that HRR is a valuable prognostic marker for 30-day poor outcomes in patients presenting with ACS. The easy accessibility and rapid availability of Hb and RDW measurements make HRR a practical tool for risk stratification in the ED.

Conflict of Interest: The authors declare no conflict of interest regarding this study.

Researchers' Contribution Rate Statement: Concept/Design: EK, FD; Analysis/Interpretation: EK, FD; Data Collection: FD; Writing: EK, FD Critical Review: EK, FD; Approver: EK, FD

Support and Acknowledgment: The authors received no specific funding for this work.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee (protocol number: 2023/159; May 23, 2023).

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