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Red cell distribution width as a novel prognosticator for in-hospital mortality in patients with acute myocardial infarction

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Abstract

Aim: To investigate the association between red blood cell distribution width (RDW) and in-hospital mortality; to develop a clinical risk model of in-hospital mortality in patients with acute myocardial infarction (AMI). **Materials and methods.** The prospective observational study included 577 AMI patients undergoing coronary angiography (CAG) < 24 h after symptom onset and was divided according RDW median. The association between RDW, clinical parameters and in-hospital mortality was evaluated using logistic regression and receiver operating characteristic (ROC) curve analysis. A prognostic model was developed by using Bayesian approach and logistic regression analysis with identifying predictors for mortality. **Results.** The median age of patients was 65 (interquartile range [IQR]: 56–74) years. 60.7% were male, 47.1% with ST-elevation. The in-hospital mortality rate was 5.4% (n = 31). Median RDW was 14.2% (IQR 13.5–15.0%). In univariate analysis, RDW was a significant risk predictor of in-hospital mortality (odds ratio [OR] 1.27, 95% confidence intervals [CI] 1.07–1.50, p = 0.005). The area under the ROC curve [AUC] was 0.649 (95% CI: 0.540–0.758, cut-off value 15.11%). In Bayesian multivariate logistic model, age (OR 1.10, 95% CI 1.06–1.14, p < 0.001), ST-elevation (OR 3.22, 95% CI 1.41–7.35, p = 0.006) RDW (OR 1.26, 95% CI 1.04–1.53, p = 0.021), were identified as risk factors for in-hospital mortality. Overall, the model showed excellent discrimination in predicting in-hospital mortality (AUC = 0.832, 95% CI: 0.779–0.885, p < 0.001, sensitivity: 87.1%, specificity: 72.2%) and with good calibration (Hosmer-Lemeshow test, p = 0.632). **Conclusions.** Elevated RDW value was independently associated with an increased risk of in-hospital mortality in AMI patients undergoing CAG. The model, including age, ST-elevation and RDW for prediction of in-hospital mortality demonstrated high prognostic potential, enabling the identification of patients at high-risk of adverse outcome.

Keywords:	acute myocardial infarction; in-hospital mortality; model; red blood cell distribution width.
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Ширина распределения эритроцитов как новый прогностический фактор госпитальной летальности у пациентов с острым инфарктом миокарда

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Аннотация

Цель: исследовать ассоциацию между шириной распределения эритроцитов (Red cell Distribution Width, RDW) и госпитальной летальностью, разработать клиническую модель риска госпитальной летальности у пациентов с острым инфарктом миокарда (ОИМ).
Материал и методы. Проспективное наблюдательное исследование включило 577 пациентов с ОИМ, которым проводили коронарографию (КАГ) в течение 24 ч с момента заболевания, и было разделено в соответствии с медианным значением RDW. Ассоциация между RDW, клиническими параметрами и госпитальной летальностью оценивалась с использованием логистической регрессии и анализа рабочей характеристики приемника (ROC-кривая). Прогностическая модель была разработана с использованием байесовского подхода и логистического анализа с выявлением предикторов смертности.
Результаты. Медиана возраста пациентов составила 65 (межквартильный размах (МКР): 56–74) лет, 60,7% были мужчинами, 47,1% с подъемом сегмента ST. Госпитальная летальность составила 5,4% (n = 31). Медиана RDW составила 14,2% (МКР 13,5–15,0%). Однофакторный анализ показал, что RDW был значимым предиктором госпитальной летальности (Отношение шансов (ОШ) 1,27; 95% доверительный интервал (ДИ): 1,07–1,50; p = 0,005). Площадь под ROC-кривой составила 0,649 (95% ДИ: 0,540–0,758; пороговое значение – 15,11%). Байесовский многофакторный логистический анализ показал, что возраст (ОШ 1,10; 95% ДИ: 1,06–1,14; p < 0,001), подъем сегмента ST (ОШ 3,22; 95% ДИ: 1,41–7,35; p = 0,006), RDW (ОШ 1,26; 95% ДИ: 1,04–1,53; p = 0,021), являлись независимыми предикторами неблагоприятного исхода. В целом модель показала отличную дискриминацию при прогнозировании госпитальной летальности (площадь под ROC-кривой – 0,832; 95% ДИ: 0,779–0,885; p < 0,001; чувствительность 87,1%, специфичность 72,2%) и хорошую калибровку (тест Хосмера – Лемешоу, p = 0,93).
Заключение. Повышенное значение RDW независимо ассоциировано с увеличенным риском госпитальной летальности у пациентов с ОИМ, проходящих КАГ. Модель, включающая возраст, подъем сегмента ST и RDW для прогнозирования госпитальной летальности, продемонстрировала высокий прогностический потенциал, позволяя выявить пациентов с высоким риском неблагоприятного исхода.

Ключевые слова:	байесовский многофакторный логистический анализ; госпитальная летальность; модель; острый инфаркт миокарда; ширина распределения эритроцитов.
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Introduction

Acute myocardial infarction (AMI) remains a leading cause of cardiovascular mortality globally with far-reaching health implications [1]. Despite advancements in prevention, diagnosis, and treatment, millions of individuals continue to succumb to AMI each year. While in-hospital mortality rates have shown a significant decrease over time, mortality remains substantial [2]. This underscores the critical necessity of identifying high-risk patients with AMI.

Red blood cell distribution width (RDW) is a hematological parameter that reflects the size variability among red blood cells (RBCs) [3] and traditionally utilized for the differential diagnosis of anemia and hematological disorders. Several studies showed that high RDW values associate with poor prognosis in patients with cardiovascular disease (CVD) [3, 4]. In two large-scale, population-based studies, RDW was correlated with an increased risk of future incident myocardial infarction [5, 6] and ischemic stroke [3]. However, the precise biological mechanisms underpinning these associations are not yet fully understood.

In the context of AMI, inflammation assumes a key role during both the acute phase and the subsequent healing process [7]. Previous studies have shown the association of inflammatory markers and prognosis of AMI [3, 8]. Inflammation can affect the lifespan of RBCs and modulate the impact of erythropoietin on erythropoiesis, thereby influencing RDW [3, 8]. Studies have also reported associations between RDW and inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and interleukin-6 [7–9]. Given that chronic inflammation is concerned with a higher risk of CVD and RDW is associated with various markers of chronic inflammation, it is suggested that the observed correlation between RDW and CVD risk may be related to chronic inflammation.

Although there is growing evidence to suggest that high RDW value predicts adverse cardiovascular outcomes patients with AMI [3, 10, 11], data on the association between RDW and in-hospital mortality has been limited. The aim of the present study was to investigate the association between RDW on admission and in-hospital mortality and develop a clinical risk model for in-hospital mortality in patients with AMI.

Methods

Population study

The study was designed as a single-center prospective observational cohort investigation, conducted at the Vinogradov municipal clinical hospital (Moscow, Russia). All patients aged > 18 years admitting with AMI and undergoing coronary angiography (CAG) < 24 hours after symptom onset from January 1, 2017, to December 31, 2017, were included. We excluded men or women who were with type 3, 4 and type 5 MI as well as those who developed MI during hospitalization. MI was diagnosed by using the Third universal definition of MI.

The baseline demographic and clinical characteristics, cardiovascular risk factors and comorbidities, data on physical examination, blood tests and imaging methods (electrocardiography, echocardiography, CAG), and medications during hospitalization were collected. Access 2 Immunoassay System (Beckman Coulter. USA) was used for the measurement of cardiac Troponin I with 99th percentile upper reference limit (URL) being 0.02 ng/L. Patients with incomplete medical history were not originally included in the dataset. The CBCs, thus including the measurement of RDW and hemoglobin, was performed in all patients within 1 hour of admission using a Siemens ADVIA 2120i hematology analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). Anemia was defined according to the World Health Organization's definition as a hemoglobin concentration of less than 120 g/L for women or less than 130 g/L for men. Microcytosis and macrocytosis were defined as mean corpuscular volume (MCV) <80 fl and > 100 fl, respectively, as per our laboratory values. Renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. eGFR was estimated using the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines. The Global Registry of Acute Coronary Events (GRACE) 2.0 score and the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) score were used to assess risk stratification of AMI patients.

The population study was divided into high and low RDW groups based on the median value. A high RDW (n = 283) was defined as an RDW value ≥ 14.2%, and a low RDW (n = 294) was defined as an RDW value < 14.2%.

The primary outcome was in-hospital mortality. The study complies with the guidelines of the Declaration of Helsinki and was independently approved by the local Ethics Committee of the Institute of Medicine, Peoples' Friendship University of Russia. All patients provided written informed consent.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, IL, USA) and R software (version 3.6.3). Categorical variables were described as frequencies and percentages, while continuous variables were presented as mean, median (Me), and interquartile range (IQR) values when appropriate. Categorical variables were compared using Chi-square test or Fisher's exact test, while Student's t test and the Kruskal–Wallis test were used for continuous variables. To evaluate the association of RDW with in-hospital mortality, receiver operating characteristic (ROC) curve analysis was performed, generating the area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity and the cut-off value of RDW. Stratified analysis was used to determine whether the impact of RDW was different in different subgroups. All variables were analyzed for their relationship with in-hospital mortality using the aforementioned test for both categorical and continuous variables. Logistic regression analysis was performed to identify factors associating with mortality, calculating odds ratios (OR) and 95% confidence intervals (CI). Bayesian model average (BMA) was performed to find series of parsimonious models predicting mortality ("BMA" package in R). The most parsimonious model was selected by using the Bayesian information criterion (BIC) with lowest BIC value, indicating overall better fit. Based on the estimated factors from the most parsimonious model, a nomogram was constructed to assess risk of in-hospital death ("rms" package in R). Performance of nomogram was assessed by AUC. The calibration was assessed by Hosmer-Lemeshow chi-square statistics for goodness of fit. All analyses with P values < 0.05 were considered statistically significant, and all reported P values were 2-sided.

Results

Baseline characteristics of the study patients

We identified 577 patients with AMI undergoing CAG. The median age of patients was 65 (IQR: 56–74) years, 60.7% were male (n = 350). In-hospital mortality rate was 5.4% (n = 31). Median time to fatal outcome was 3 (IQR: 2–8) days. The immediate causes of death in the cohort of patients with AMI were acute heart failure in 15 cases, progression of multiple organ failure in 10 cases, cardiogenic shock in 4 cases, myocardial rupture in 1 case, and gastrointestinal bleeding in 1 case.

The median RDW were 14.2% (IQR: 13.5–15.0%). The baseline characteristics and laboratory findings of the patients are shown in Table 1.

Age, proportion of arterial hypertension, previous cerebrovascular accident (CVA), atrial fibrillation, peripheral arterial disease (PAD), anemia, dyspnea, GRACE and CRUSADE score were significantly higher in high-RDW group (all p < 0.05). Patients with higher RDW had significantly lower levels of admission hemoglobin (p < 0.001), left ventricular ejection fraction (LVEF) (p < 0.001), lower

1-vessel coronary artery disease (CAD) and percutaneous coronary intervention (PCI) rates (p = 0.023). Other clinical and laboratory characteristics of the 2 groups were similar.

Table 1. Clinical and demographic characteristics of patients

Таблица 1. Клинико-демографическая характеристика пациентов

Variables	Population, n = 577	Low RDW Group, n = 294	High RDW Group, n = 283	p value
Age, years, *Me (IQR)*	65 (56; 74)	64 (55; 73)	67 (56; 76)	0.021
Females, *n* (%)	227 (39.3)	108 (36.7)	119 (42)	0.202
ST-elevation, *n* (%)	272 (47.1)	143 (48.6)	129 (45.6)	0.505
Arterial hypertension, *n* (%)	516 (89.4)	253 (86.1)	263 (92.9)	0.01
Previous MI, n (%)	124 (21.5)	46 (15.6)	78 (27.6)	0.001
Previous revascularization, n (%)	72 (12.5)	30 (10.2)	42 (14.8)	0.102
Previous HF, *n* (%)	40 (6.9)	17 (5.8)	23 (8.1)	0.326
Diabetes mellitus, *n* (%)	126 (21.8)	58 (19.7)	68 (24)	0.227
Previous CVA, *n* (%)	41 (7.1)	13 (4.4)	28 (9.9)	0.014
Atrial fibrillation, *n* (%)	62 (10.7)	17 (5.8)	45 (15.9)	< 0.001
PAD, *n* (%)	18 (3.1%)	2 (0.7)	16 (5.7)	< 0.001
Chronic lung disease, *n* (%)	83 (14.4%)	34 (11.6)	49 (17.3)	0.057
Peptic ulcer disease, *n* (%)	55 (9.5%)	28 (9.5)	27 (9.5)	1.0
Anemia, *n* (%)	156 (27.0)	46 (15.6)	110 (38.9)	< 0.001
Clinical findings:				
Chest pain, n (%)	529 (91.7)	277 (94.2)	252 (89)	0.034
Dyspnea, n (%)	107 (18.5)	41 (13.9)	66 (23.3)	0.004
Troponin I, ng/mL, Me (IQR)	0.39 (0.09; 2.85)	0.38 (0.08; 2.88)	0.36 (0.10; 2.81)	0.819
Hemoglobin, g/L, Me (IQR)	136 (123; 147)	140 (128.7; 149)	132 (115; 44)	< 0.001
MCV, fl, Me (IQR)	90 (86.05; 94)	91.05 (88; 94.42)	88.1 (84.4; 93)	< 0.001
Creatinine, μmol/L, Me (IQR)	94 (80; 107)	92 (80.5; 107)	93 (79; 113)	0.393
eGFR, ml/min/1.73 m^2, *Me (IQR)*	67 (52; 83)	68 (55; 83)	64 (48; 81)	0.053
LVEF, %, Me (IQR)	45 (40; 54)	46 (42; 55)	43 (38; 51)	< 0.001
Coronary stenosis, n (%):	–	–	–	–
No lesions/Stenosis < 50%, n (%)	64 (11.1)	32 (10.9)	32 (11.3)	0.895
1-vessel CAD, n (%)	86 (14.9)	53 (18)	33 (11.7)	0.035
2-vessel CAD, n (%)	124 (24.5)	61 (20.7)	63 (22.3)	0.686
3-vessel CAD, n (%)	301 (52.2)	147 (50)	154 (54.4)	0.317
PCI, n (%)	459 (79.5)	245 (83.3)	214 (75.6)	0.023
GRACE score, points, Me (IQR)	117 (98; 141)	114 (95.7; 136)	124 (100; 148)	< 0.001
CRUSADE score, points, Me (IQR)	21.5 (32; 43)	21 (29; 40)	35 (22; 47)	< 0.001

Note: CAD – coronary artery disease; CRUSADE – Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines; CVA – cerebrovascular accident; eGFR – estimated glomerular filtration rate; GRACE – Global Registry of Acute Coronary Events; HF – heart failure; IQR – interquartile range; LVEF – left ventricular ejection fraction; Me – median; MI – myocardial infarction; PAD – peripheral vascular disease; PCI – percutaneous Coronary Intervention.

Patients with higher RDW had significantly higher rate of in-hospital mortality (7.4% vs. 3.4%, p = 0.041). The ROC curve showed the optimal cut-off value of RDW for prediction of in-hospital mortality was 15.11% (AUC = 0.649, 95% CI 0.540–0.758, p = 0.005, sensitivity 48.4%, specificity 80.4%, OR = 3.85, 95% CI 1.84–8.02, p < 0.001) (Fig. 1).

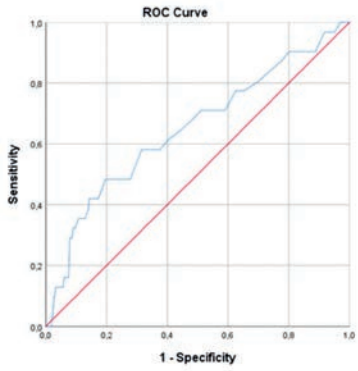

Fig. 1. The receiver-operating characteristic (ROC) curve of red blood cell distribution width (RDW) for predicting in-hospital mortality
Рис. 1. Кривая рабочих характеристик приемника (ROC) для ширины распределения эритроцитов (RDW) при прогнозировании госпитальной летальности

Subgroup assessment was performed to explore the relationship between RDW and in-hospital mortality rate depending on anemia status, MCV level and renal function (Table 2). There were no interactions in anemia status and RDW related to outcome. In contrast, in normocytic MCV subgroup, for every 1% increase in RDW values, the OR for in-hospital increased by 1.58. In both low and high MCV subgroups, no remarkable interaction was observed (p = 0.471 and 0.462, respectively). The same result was observed for renal dysfunction subgroup (p = 0.402).

Table 2. Logistic regression analysis for in-hospital mortality according to RDW in different clinical subgroups

Таблица 2. Логистический регрессионный анализ госпитальной летальности в зависимости от RDW в различных клинических подгруппах

Variables	Odds ratio (95% confidence interval)	p value
Anemia		
Present	1.07 (0.86–1.32)	0.547
Absent	1.27 (0.88–1.83)	0.205
MCV level		
Microcytic	0.81 (0.46–1.43)	0.471
Normocytic	1.58 (1.24–2.02)	< 0.001
Macrocytic	0.66 (0.22–1.99)	0.462
Renal dysfunction		
Present	1.11 (0.87–1.42)	0.402
Absent	1.50 (1.17–1.94)	0.002

Note: CAD – coronary artery disease; CI – confidence interval.

Univariate logistic analysis revealed that RDW, age, female sex, ST elevation, diabetes mellitus, atrial fibrillation, anemia, LVEF, three-vessel coronary artery disease (CAD) were associated with in-hospital mortality (Table 3).

Table 3. Univariate logistic regression analysis of the predictor of in-hospital mortality in acute myocardial infarction

Таблица 3. Однофакторный логистический регрессионный анализ предикторов госпитальной летальности при остром инфаркте миокарда

Variables	Odds ratio (95% CI)	*p value*
RDW, %	1.27 (1.07–1.50)	0.005
Age, years	1.10 (1.07–1.15)	< 0.001
Sex, female	2.23 (1.07–4.65)	0.032
ST elevation	2.47 (1.14–5.34)	0.022
Diabetes mellitus	2.39 (1.13–5.07)	0.023
Atrial fibrillation	3.17 (1.35–7.43)	0.008
Anemia	5.48 (2.56–11.73)	< 0.001
LVEF ≤ 40%	7.82 (3.04–20.09)	< 0.001
Three-vessel CAD	4.08 (1.65–10.09)	0.002

Note: CAD – coronary artery disease; CI – confidence interval; LVEF – left ventricular ejection fraction; RDW – red blood cell distribution width.

Based on BMA method, we identified 3 most parsimonious models for predicting the risk of in-hospital mortality with appropriate posterior probability, BIC, and values of area under the ROC curves (Table 4, Fig. 2). The three models included following factors: RDW at admission, presence of ST elevation on ECG, anemia, and age. The AUC of three models were comparable with the average AUC ranging from 0.812 (Model I, II) to 0.832 (Model III). Based on the BIC as a metric of model selection, it appeared that the model III was the most parsimonious with the lowest values of BIC.

Table 4. Association of risk factors of selected models and in-hospital mortality: results from multivariate analysis and Bayesian Model Averaging

Таблица 4. Связь факторов риска выбранных моделей и госпитальной летальности: результаты многофакторного анализа и байесовского моделирования

Models	Unit	Odds ratio (95% CI)	*p value*
Model I (BIC = –29.01), post prob = 0.743, AUC = 0.812 (95% CI 0.749–0.875, *p* < 0.001)			
Age (years)	+1	1.08 (1.04–1.13)	< 0.001
Presence of ST elevation	Yes	3.08 (1.37–6.92)	0.007
Presence of anemia	Yes	3.29 (1.40–7.34)	0.006
Model II (BIC = –26.43), post prob = 0.204, AUC = 0.812 (95% CI 0.750–0.875, *p* < 0.001)			
Age (years)	+1	1.08 (1.04–1.13)	< 0.001
Presence of anemia	Yes	2.92 (1.29–6.59)	0.01
Model III (BIC = –23.72), post prob = 0.053, AUC = 0.832 (95% CI 0.779–0.885, *p* < 0.001)			
Age (years)	+1	1.10 (1.06–1.14)	< 0.001
Presence of ST elevation	Yes	3.22 (1.41–7.35)	0.006
RDW (%)	+1	1.26 (1.04–1.53)	0.021

Note: AUC – area under the curve; BIC – Bayesian information criteria; CI – confidence interval; post prob – posterior probability; RDW – red blood cell distribution width.

Using the estimated variables of the Model III, a nomogram was established for predicting the risk of in-hospital death in AMI patients. The risk of in-hospital death in AMI patients was assessed according to the following equation:

$$Risk = 1 / ((1 + e^{(-Z)}));$$

where Z = –13.525 + 0.093 × Age + 1.168 × presence of ST elevation + 0.229 × RDW at admission.

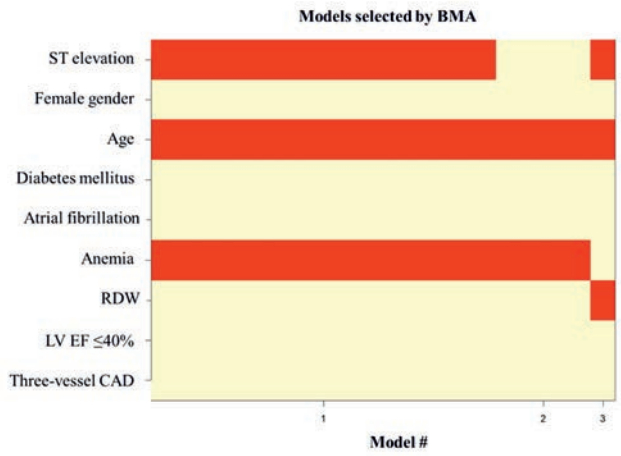

Fig. 2. Bayesian Model Average analysis to identify most optimal models for prediction of in-hospital mortality in acute myocardial infarction
Note: CAD – coronary artery disease; LVEF – left ventricular ejection fraction; RDW – red blood cell distribution width.
Рис. 2. Анализ байесовской средней модели для выявления наиболее оптимальных моделей для прогнозирования госпитальной летальности при остром инфаркте миокарда
Примечание: ИБС – ишемическая болезнь сердца, ФВ ЛЖ – фракция выброса левого желудочка, RDW – ширина распределения эритроцитов.

In ROC curves analysis of a developed nomogram for predicting in-hospital mortality, the AUC was 0.832 (95% CI: 0.779–0.885, p < 0.001). The sensitivity and specificity were 87.1% and 72.2%, respectively (Fig. 3). A nomogram showed good calibration (chi-square 6.132, p for Hosmer-Lemeshow test 0.632).

Discussion

Our study found that RDW was an independent predictor of in-hospital mortality among patients with AMI. Using Bayesian approach, the prognostic value of RDW was confirmed in the predictive model for in-hospital mortality that included age, presence of ST elevation and RDW, demonstrating excellent discriminatory ability in this population. These results advocate the use of admission RDW in risk stratifying AMI patients since it is easier and more valuable to be included in the initial clinical evaluation and risk scoring.

Previous studies have consistently demonstrated an association between RDW and an unfavorable prognosis in patients with acute coronary syndrome (ACS). Uyarel et al. [10] conducted a study involving 2,506 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI. Their findings revealed that patients presenting with elevated RDW (16.1%) at admission exhibited a higher in-hospital mortality rate compared to those with normal RDW (7.6% vs. 3.6%; $p < 0.001$). In a cross-sectional study including 3,101 patients with AMI, RDW was found to be as a significant predictor of in-hospital mortality, even after adjusting for age, sex, and various clinical and laboratory variables. Specifically, the hazard ratio for in-hospital mortality in the highest RDW tertile (≥ 14.2%) versus the lowest tertile (≤ 13.2%) was 2.3 (95% CI 1.39–4.01; *p* for trend < 0.05) [11]. Additionally, S. Khaki et al. [12] conducted a longitudinal study involving 649 patients with AMI over a 6-month follow-up period. Their results indicated a significantly higher 6-month mortality rate in patients with elevated RDW (≥ 14.6%) compared to those with lower RDW (< 14.6%) (24.3% vs. 7.9%; $p < 0.001$). These findings underscore the consistent

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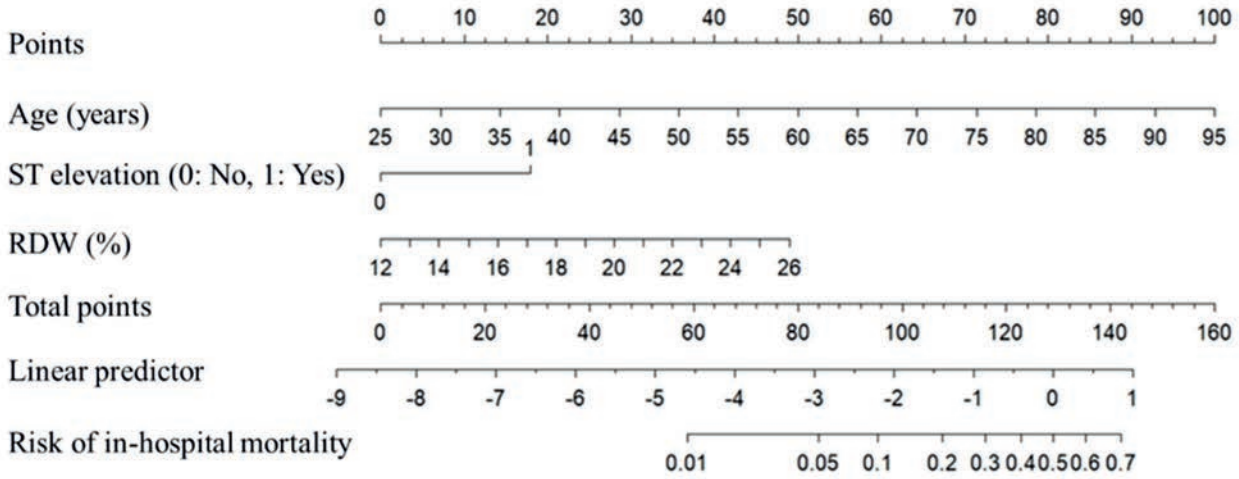

Fig. 3. Nomogram for prediction of in-hospital mortality in acute myocardial infarction. The nomogram included three variables, including age, presence of ST elevation and red cell distribution with at admission
Note: RDW – red blood cell distribution width. Instruction for usage: A total score was generated by using the number of the points of each factor on the corresponding axis with drawing a vertical line to "Points" axis. Summary the points of all the factors and drawing a vertical line to the "Risk of in-hospital mortality" line to determine the individual's probability of death during hospitalization.
Рис. 3. Номограмма для прогнозирования госпитальной летальности при остром инфаркте миокарда. Номограмма включает три переменные: возраст, наличие подъема сегмента ST и ширину распределения эритроцитов при поступлении
Примечание: RDW – ширина распределения эритроцитов. Инструкция по применению: Общая оценка была получена с использованием количества баллов каждого фактора на соответствующей оси с проведением вертикальной линии к оси «Баллы». Суммируйте баллы всех факторов и проведите вертикальную линию к линии «Риск внутрибольничной смертности», чтобы определить вероятность смерти человека во время госпитализации.

association between elevated RDW levels and adverse outcomes in patients with ACS, reinforcing the potential prognostic value of RDW in this clinical context.

Although RDW has traditionally served as a diagnostic indicator for hematological disorders, such as chronic anemia resulting from vitamin deficiencies, liver dysfunction, or kidney failure, recent investigations have explored the involvement of RDW in the etiology of non-hematological disorders. Previous studies has identified a significant association between elevated RDW levels and an increased risk of hypertension, atrial fibrillation, AMI, heart failure, stroke, and mortality [3, 4]. Consistent with findings from other studies, our results indicate that heightened RDW is associated with a higher prevalence of additional risk factors, such as advanced age, arterial hypertension, prior CVA, atrial fibrillation, and PAD. Furthermore, our findings reveal a correlation between elevated RDW, low level of hemoglobin, reduced LVEF, and higher GRACE score, aligning with previous studies [3, 12, 13]. S. Huang et al. [11] studied the association between RDW and in-hospital mortality among 3101 patients with AMI found that, compared to patients in first tertile (RDW ≤ 13.2%), patients in third tertile (RDW ≥ 14,2%) had a lower of hemoglobin on admission (10.9 vs. 12.8 g/dL, $p < 0.001$) and a higher PCI rate (29.73% vs. 20%, $p < 0.001$). However, data on angiographic characteristics were not shown in this study. In our study, the lower level of PCI among high RDW group may be explained by lower 1-vessel CAD among these patients. There was no observed difference in the severity of CAD (2- or 3-vessel) between groups, although RDW has been shown to be positively correlated with the severity of CAD among AMI patients [14]. The association between RDW and left ventricular dysfunction may be explained by the trend toward higher arterial hypertension, atrial fibrillation and prior myocardial infarction rates in patients with high RDW in our cohort and in previous studies [4, 10, 13].

Anemia has been identified as a robust prognostic indicator for unfavorable outcomes in patients with AMI, demonstrating its predictive efficacy in both short-term and long-term outcomes [15]. This observation implies that the prognostic utility of RDW in CAD may be contingent upon the presence of anemia. Nevertheless, it would be inaccurate to assert that the predictive capacity of RDW for major adverse events in ACS patients is solely attributable to anemia. S. Dabbah et al. [16] demonstrated that the prognostic significance of RDW in ACS patients remains independent of anemia, and an increase in RDW during hospitalization was associated with an unfavorable prognosis, indicating a dynamic nature of RDW. This finding aligns with a study by E. Cavusoglu et al. [17], wherein the predictive value of elevated RDW was evident in both anemic and non-anemic patients, consistent with our own results.

RDW may serve as a marker of renal insufficiency, a well-established risk factor for CAD. Elevated RDW has been associated with declining kidney function [3, 4]. However, in our study, no significant association was observed between higher serum creatinine levels and elevated RDW. Moreover, no discernible interaction between renal insufficiency and RDW concerning in-hospital mortality was identified. Consequently, the association between RDW and in-hospital mortality in AMI patients may be attributed to alternative mechanisms.

Previous studies have established an association between RDW with various inflammatory markers [7, 9, 18]. In the context of atherosclerosis, inflammatory factors influence RBCs, prompting the production of numerous immature RBCs from the bone marrow, resulting in elevated RDW levels and ineffective hematopoiesis [3]. The rupture of an unstable fibrous cap induces thrombosis, diminishing the deformability of RBCs entrapped within a fibrin clot, thereby elevating RDW. Furthermore, several pathophysiological mechanisms linking RDW to cardiovascular diseases, such as microvascular disorders, inflammatory cytokines, oxidative stress, free cholesterol, thrombosis, and involvement of neurohumoral and adrenergic systems, have been postulated

in the context of AMI [3, 4].

The GRACE risk score has demonstrated clear prognostic significance for in-hospital death stratification in patients with AMI, earning endorsement in current guidelines [15], with an AUC of 0.84 for predicting in-hospital mortality in the validation cohort. In our study, we identified age, ST elevation, and RDW as significant predictors of in-hospital death, yielding an AUC of 0.832. Consequently, our model's prognostic performance is comparable to that of the GRACE score with more risk variables. This underscores the potential role of RDW as a valuable risk factor for risk stratification in this patient population.

Numerous studies have investigated the additive value of RDW in the context of AMI. For instance, N. Zhao et al. [19] conducted a study involving 480 ACS patients over a median follow-up period of 37.2 months. The inclusion of RDW alongside the GRACE score resulted in a heightened AUC of 0.805 compared to the GRACE score alone (AUC = 0.749, p = 0.034) for predicting major adverse cardiac events, defined as all-cause death or non-fatal AMI. Similar findings were reported by Chang et al. [20] in a study involving 390 STEMI patients, with a combined AUC of 0.775 for RDW and the GRACE risk score in predicting Major Adverse Cardiac Events (MACEs) during a mean follow-up of 33.5 months These findings suggest that RDW, as a biomarker, holds potential for assessing short-term outcomes in AMI.

Our study has several limitations. This single-center investigation, with a relatively small sample size and lacking nomogram validation, may restrict the generalizability and clinical application of our findings. The absence of data on essential variables such as folic acid, vitamin B12, iron levels, and detailed liver function tests poses a limitation, as subclinical deficiencies in these factors cannot be fully excluded. Despite subgroup analysis having shown no interaction, the cross-sectional design hinders the establishment of causal mechanisms underlying the observed association between RDW and mortality. Addressing these limitations in future research is crucial for a more nuanced understanding of RDW's predictive role in AMI.

Conclusions

RDW on admission was independently associated with in-hospital mortality in AMI patients. A nomogram, integrating age, ST elevation, and RDW, demonstrates excellent predictive performance for in-hospital death, facilitating the identification of patients at a heightened risk of adverse outcome.

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Merai I.A. – literature review, analysis, and interpretation of the results.

Kobalava Z.D. – research concept, study protocol.

All authors have made significant contributions to the development concepts, research, and manuscript preparation, read, and approved final version before publication.

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