

A new hematologic predictor of major adverse events after cardiac surgery: red cell distribution width to lymphocyte ratio

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Background: The perioperative risk factors that cause severe morbidity and prolongation of postoperative hospital stay after cardiac surgery should be determined. Various scores have been used to predict morbidity and mortality. Preoperative blood counts are considered potential biomarkers of inflammation and oxidative stress. Inflammatory and immune imbalances may have a significant impact on postoperative adverse events. The present study aimed to investigate the association and potential predictive properties of red cell distribution width/ lymphocyte ratio (RLR) for major adverse events in adult patients who underwent coronary surgery with cardiopulmonary bypass.

Methods: After approval from the ethics committee, pre- and post-operative data of 700 patients were obtained from the electronic database of the hospital, intra- and post-operative anesthesia, and intensive care unit follow-up charts. We performed a stepwise multiple logistic regression analysis to investigate the association of RLR with major adverse events in adult patients who underwent coronary surgery with cardiopulmonary bypass.

Results: Among 700 patients, 47 (6.7%) had major adverse events after surgery. Multivariate logistic regression analysis showed that age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03–1.12; $P < 0.001$), mean platelet volume (OR, 1.49; 95% CI, 1.07–2.06; $P = 0.017$), and RLR (OR, 1.21; 95% CI, 1.02–1.43; $P = 0.026$) were significantly associated with major adverse events.

Conclusions: RLR indicates the balance between inflammatory and immune responses. Therefore, it can be used to predict adverse events following coronary surgery.

Keywords: Blood cell count; Cardiac surgical procedures; Erythrocyte indices; Inflammatory and immune imbalances; Preoperative blood counts.

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INTRODUCTION

Over the last few decades, the field of cardiac surgery has shown remarkable improvement with advances in surgical techniques and perioperative care. Complex surgeries in pa-

tients with multiple comorbidities have become routine procedures. However, the 30-day mortality rate after cardiac surgery still ranges from 1 to 4% [1]. Cardiac, pulmonary, or neurologic dysfunctions; bleeding; thrombosis; and acute kidney injuries are the major causes of in-hospital mortality

after cardiac surgery.

Recent studies have made notable efforts to predict post-operative adverse events and mortality after cardiac surgery [2]. Many preoperative predictors or algorithms are still being investigated to identify patients with an increased risk of adverse events. Current research suggests that inflammatory and immune imbalances may significantly impact postoperative adverse events. Inflammatory processes are responsible for the progression of vascular wall damage. Immune cells migrate to the endothelium after vessel damage and facilitate platelet activation. The degree of immune cell activation may enable the prediction of morbidity and mortality [3]. Several markers, including red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio (PLR), have been suggested, which are easily accessible from complete blood counts [4,5].

A new marker, RDW-to-lymphocyte ratio (RLR), a combination of two parameters, is an easily acquired parameter using a routine complete blood count and has received attention in oncological research as a predictor of worse prognosis since both RDW and lymphocytes are included in inflammatory reactions [6-8]. However, it has not yet been investigated as a predictor of adverse events in cardiac surgery patients.

The present study investigated the association between and potential predictive properties of RLR for major adverse events in adult patients who underwent coronary surgery with cardiopulmonary bypass. The identification of new predictive markers may allow for determining patients at high risk.

MATERIALS AND METHODS

This was a retrospective, longitudinal observational study comprising adult patients who underwent elective coronary surgery with cardiopulmonary bypass (CPB) between January 2017 and January 2022. This study complied with the Declaration of Helsinki, and ethical approval was granted by the local institutional ethical board (E1-22-2658, 15.06.22). Trial Registration number: NCT05341037

The exclusion criteria were patients aged < 18 years; those with ejection fraction below 30%, preoperative kidney injuries and liver diseases, malignancies, and infections; those who underwent ventricular assist device placement, heart transplantation, emergency and repeated surgeries; or those who lacked clinical data. The pre- and post-operative data of

the patients were obtained from the electronic database of the hospital, intra- and post-operative anesthesia, and intensive care unit (ICU) follow-up charts. All data were collected between June and July 2022.

Preoperative complete blood count parameters, including the number of neutrophils, number of lymphocytes, hemoglobin, RDW, number of platelets, mean platelet volume (MPV), NLR, PLR, and RLR were determined on the first day of hospital admission before surgery as baseline values. NLR was calculated as the neutrophil number divided by the number of lymphocytes, PLR as the number of platelets divided by the number of lymphocytes, and RLR as the RDW value divided by the number of lymphocytes.

Major adverse events (MAE) were determined as follows: (1) all-cause mortality; (2) major adverse cardiac events such as stroke, acute myocardial infarction, and acute heart failure [9]; (3) acute renal failure; (4) prolonged mechanical ventilation (> 24 h); (5) sternal wound infection; (6) the need for additional surgery for any reason within 30 days after surgery.

Statistical analysis

The SPSS for Windows 20.0 (IBM Co.) was used for statistical assessments. The Kolmogorov-Smirnov test was used to determine the distribution of data. Continuous variables with normal distribution are expressed as mean \pm standard deviation, and variables without a normal distribution are given as median (interquartile range). Categorical variables are presented as numbers and percentages. Continuous variables were compared with independent two-sample *t*-tests or Mann-Whitney *U* tests where appropriate. Categorical variables were compared using chi-squared tests. Univariate and multivariate logistic regression analyses were used to calculate the odds ratio (OR) and 95% confidence interval (CI) to identify independent predictors of MAE. A stepwise multiple logistic regression analysis was fitted for the main covariates, which were determined based on their univariate associations ($P < 0.100$) or included based on knowledge of their strong association with MAE. The multivariate model was adjusted for variables such as age, sex, body mass index, diabetes mellitus, hypertension, and laboratory data. Multicollinearity was examined in the model, and the Box-Tidwell test was used to check the logit linearity for the continuous independent variables in the logistic regression analysis. Model fit was analyzed using the Hosmer-Lemeshow test. Potential interactions between MAE and

other covariates were examined by including an interaction term in the model, and their significance was determined. With the RLR and MPV scores as the test variables and MAE as the status variable, the receiver operating characteristic (ROC) curve was formulated, and the diagnostic value of the RLR score was determined according to the area under the curve (AUC). In statistical analysis, $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 700 adult patients who underwent coronary surgery participated in our study. Among them, 47 (6.7%) patients had MAE after surgery. The mean age was 58.4 ± 11.9 years, and 74.9% of patients were men. Approximately 2.5% ($n = 18$), 4.0% ($n = 28$), 3.1% ($n = 22$), 0.4% ($n = 3$), 2.7% ($n = 19$), and 3.4% ($n = 24$) had acute renal failure, major adverse cardiac events, prolonged mechanical ventilation, sternal wound infection, need for additional surgery, and mortality, respectively.

Table 1 compares the patients' demographics and baseline laboratory values according to MAE occurrence. Patients in the MAE (+) group were older and had a higher percentage of hypertension ($P < 0.001$). The MAE (+) group also had lower lymphocyte count and higher NLR and PLR ($P = 0.002$, 0.002 , and 0.002 , respectively).

Multivariate logistic regression analysis using the MAE as the dependent variable showed that age (OR, 1.08; 95% CI, 1.03–1.12; $P < 0.001$); MPV (OR, 1.49; 95% CI, 1.07–2.06; $P = 0.017$); and RLR (OR, 1.21; 95% CI, 1.02–1.43; $P = 0.026$) were significantly associated with MAE (Table 2). The model explained 23.5% (Nagelkerke R^2) of the variance in MAE (Table 2). No significant violations of the linearity of the logit assumption were found in the multivariate model.

The ability of RLR and MPV to predict the presence of MAE was evaluated using ROC curve analysis. The AUC values of RLR and MPV were 0.606 (95% CI, 0.522–0.691; $P = 0.015$) and 0.552 (95% CI, 0.470–0.633; $P = 0.234$) for MAE postoperatively, respectively. The RLR predicted the MAE by a statistically significant margin (Fig. 1).

DISCUSSION

In the current study, the overall incidence of major adverse events was 6.7%, and at an advanced age, higher levels of preoperative RLR and MPV were associated with higher rates of adverse events within 30 days of cardiac surgery. Additionally, the relationship between RLR and major adverse events in these patients remained significant even after adjusting for possible confounding factors. Accordingly, this finding provides evidence of the evaluated risk of major adverse events among individuals undergoing cardiac surgery

Table 1. Baseline Characteristics and Laboratory Data of Participants

Variable	Total (n = 700)	Major adverse events		P value
		Negative (n = 653)	Positive (n = 47)	
Demographics				
Age (yr)	58.4 ± 11.9	57.8 ± 11.6	66.6 ± 10.1	0.001
Sex (M)	524 (74.9)	488 (74.7)	36 (76.6)	0.776
Body mass index	28.0 ± 4.8	28.1 ± 4.8	27.2 ± 5.2	0.254
Hypertension	328 (47.2)	298 (45.9)	30 (65.2)	0.011
Diabetes mellitus	215 (30.7)	200 (30.6)	15 (31.9)	0.853
Baseline laboratory values				
Neutrophil (× 10 ⁹ /L)	5.5 ± 2.2	5.5 ± 2.2	5.9 ± 2.8	0.113
Lymphocyte (× 10 ⁹ /L)	2.2 ± 1.1	2.2 ± 1.1	1.9 ± 0.8	0.018
Hemoglobin (g/dl)	13.8 ± 1.8	13.9 ± 1.8	13.1 ± 2.7	0.076
RDW (%)	14.2 ± 1.7	14.2 ± 1.7	14.4 ± 1.5	0.405
Platelet (× 10 ⁹ /L)	231.7 ± 66.7	232.2 ± 66.5	226.1 ± 70.1	0.549
MPV (fl)	9.0 ± 1.1	9.1 ± 1.1	9.2 ± 1.1	0.256
NLR	3.1 ± 0.6	3.0 ± 0.2	3.4 ± 1.6	0.002
RLR	7.7 ± 6.6	7.7 ± 6.5	9.0 ± 6.4	0.002
PLR	108 (84, 137)	107 (83, 136)	120 (98, 146)	0.080

Values are presented as mean \pm SD, number (%), or median (1Q, 3Q). RDW: red cell distribution width, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, PLR: platelet to lymphocyte ratio.

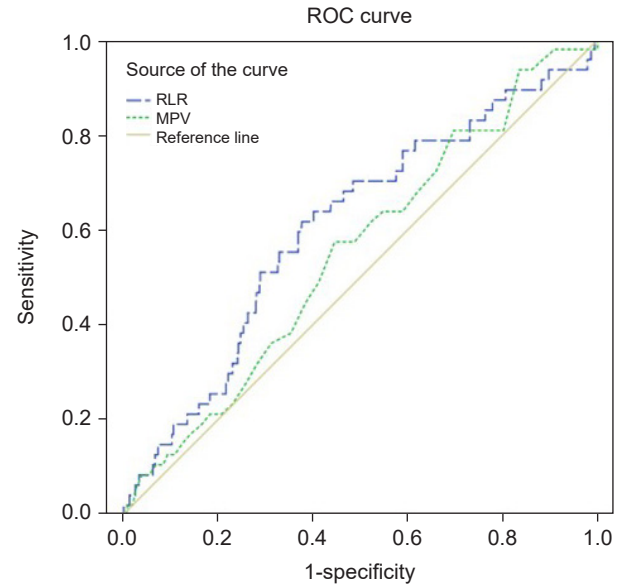
Table 2. Logistic Regression Analysis for the Predictors of 30-day Major Adverse Events after Coronary Artery Surgery

Variable	Major adverse events (+)	
	Odds ratio (95% CI) (multivariate)	P value
Age (yr)	1.07 (1.03–1.12)	0.001
Sex (M)	0.58 (0.24–1.39)	0.228
Body mass index	0.95 (0.87–1.03)	0.203
Hypertension	1.65 (0.77–3.54)	0.202
Diabetes mellitus	0.83 (0.22–3.24)	0.792
Neutrophil	1.12 (0.95–1.45)	0.142
Lymphocyte	0.20 (0.04–1.01)	0.050
Hemoglobin	0.92 (0.76–1.12)	0.400
RDW	0.76 (0.55–1.03)	0.076
Platelet	1.01 (1.0–1.02)	0.131
MPV	1.49 (1.08–2.06)	0.017
NLR	0.86 (0.70–1.06)	0.141
RLR	1.21 (1.02–1.43)	0.026
PLR	0.98 (0.95–1.01)	0.119

CI: confidence interval, RDW: red cell distribution width, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, PLR: platelet to lymphocyte ratio. Multivariate analysis is adjusted for variables, including age, sex, body mass index, diabetes mellitus, hypertension, and laboratory data. $P < 0.05$ is considered to be statistically significant.

with high levels of RLR rather than other inflammatory biomarkers such as RDW, NLR, or PLR. To our knowledge, this is the first such study in the literature.

RDW reflects the size variability of circulating red blood cells (RBC) and is routinely measured in complete blood counts. It is calculated by dividing the standard deviation of the RBC volume by the mean corpuscular volume and multiplying it by 100 to express the result as a percentage [10]. It does not carry additional costs or risks for patients. Higher RDW values indicate greater variation in the distribution of RBC volume in the circulation. The current study suggests that higher RDW values are associated with inflammatory reactions and oxidative stress. The reason for this is that inflammation results in changes in RBC maturation by disturbing the red cell membrane, leading to increased RDW [11]. The correlation between RDW and inflammatory markers has been previously shown [10]. Erythropoiesis in oxidative stress results in large immature erythrocytes in the circulatory system, which can be concluded with elevated RDW [12]. RDW reveals the ability of cells to support the strong hypoxia stress under high-stress circumstances such as surgeries [13]. This can explain the higher rates of morbidities in patients with higher RDW values [11]. Higher val-

**Fig. 1.** Diagonal segments are produced by ties. ROC: receiver operating characteristic, RLR: red cell distribution width to lymphocyte ratio, MPV: mean platelet volume.

ues of RDW have been reported as a strong predictor of morbidity and mortality in studies including patients with coronary disease [14], aortic valve replacement [11], pulmonary hypertension [15], heart failure [16], and those undergoing percutaneous coronary intervention.

Lymphocytes are a significant part of the immune response system and play critical roles in the production of cytokines. A low lymphocyte count is linked to an increased incidence of cardiovascular events [17]. Several studies have shown the association of lymphocyte-based inflammatory markers, such as PLR and NLR, with adverse outcomes in cardiac surgery [3-5].

RLR, a combination of RDW and lymphocytes, may reflect a better balance of inflammation [6]. Higher RDW and fewer lymphocytes are associated with worse outcomes in the oncological group of patients [6-8]. They commonly claim that the level of RLR combines the overall state of the patient's immunity and inflammation [7]. In patients with higher baseline inflammatory status, cardiac surgery may further exacerbate inflammatory mechanisms [18,19]. Consistent with this, a recent study conducted in older cardiac surgery patients suggested that elevated RLR levels are associated with a prolonged length of stay in the ICU [19]. Additionally, researchers have emphasized that preoperative RLR may have predictive value for the risk of long-term ICU stay in this population. However, they could not evaluate MAE as a study outcome. Therefore, this is one of the unique studies

depicting the relationship between RLR and MAE in cardiac surgery patients.

The present study demonstrated another association of an inflammatory predictor, MPV, with adverse events. MPV is an indicator of platelet activity and plays a significant role in the pathogenesis of atherosclerosis. Enlarged and reactive platelets accompany cardiovascular diseases [20]. Previous studies have shown an association between high MPV levels and adverse events after coronary surgeries [21-23].

This study had some limitations. First, it was a retrospective, non-randomized register study on patients undergoing coronary surgery. Studies on MAE after cardiac surgery generally compare surgical techniques, anesthesia, or CPB management techniques. However, this study population had the same coronary surgery technique, anesthesia, fluid, and CPB management and did not focus on intraoperative variables. Second, the authors did not perform long-term follow-up; only 30-day complications were analyzed.

In conclusion, the prediction of adverse events after cardiac surgery is crucial for managing the postoperative period. Moreover, predictors should also guide clinicians in considering the risks versus benefits [2]. RLR is a valuable parameter that can be used to identify high-risk patients, as it is significantly associated with adverse events compared to previously reported immunologic and inflammatory markers based on blood cells.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Methodology: Aslı Demir. Investigation: Eda Balcı. Resources: Hülya Yiğit Özay. Software: Bilal Katipoğlu. Supervision: Hayrettin Levent Mavioğlu. Validation: Seda Kurtbeyoğlu.

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