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Preoperative red cell distribution width and its relation with in-hospital morbidities including atrial fibrillation after coronary artery bypass

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Abstract

Background and Aims: Atrial fibrillation (AF) and other adverse events are significant concerns following coronary artery bypass grafting (CABG). In recent years, Red Cell Distribution Width (RDW) has been identified as a potential biomarker for predicting these adverse outcomes. This study aims to assess early in-hospital adverse events in patients undergoing isolated off-pump CABG (OPCAB) and to analyze the relationship between these events and preoperative RDW levels.

Methods: This study prospectively included 150 patients who underwent elective isolated OPCAB procedures. Patients were categorized into an "event group" (those experiencing adverse events) and a "no-event group" (those who did not). Additionally, they were stratified according to preoperative RDW levels into three groups: Group A (RDW ≤14%), Group B (RDW 14-16%), and Group C (RDW ≥16%). A receiver operating characteristic (ROC) curve, followed by both univariate and multivariate regression analyses were utilized to evaluate the predictive value of RDW for in-hospital morbidity.

Results: The in-hospital mortality rate was 2.7%, and AF occurred in 20.7% of the patient population. The ROC analysis for early adverse events yielded an Area Under the Curve (AUC) of 0.681 with a p-value <0.001, indicating moderate predictive capability; the sensitivity was 73% and specificity was 64% for RDW ≥14.05%. Multivariate regression analysis demonstrated that RDW independently predicts in-hospital morbidity after OPCAB, with an odds ratio of 0.713 (95% CI 0.566-0.899, p=0.004).

Conclusion: Elevated preoperative RDW levels serve as a simple and cost-effective independent predictor of early adverse events following isolated OPCAB.

Keywords: morbidity; off-pump coronary artery bypass; predictors; red cell distribution width; risk factors

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INTRODUCTION

Red cell distribution width (RDW) has emerged as a valuable, yet often underestimated, biomarker in clinical practice. As a measure of the variability in erythrocyte volume, RDW can provide insights into various pathological conditions, including hematological disorders, cardiovascular diseases, and beyond[1]. Despite its availability as part of the complete blood count (CBC), RDW is frequently overlooked[2].

Research indicates that RDW can change significantly in response to both acute and chronic diseases[3,4]. Its elevation has been linked to negative clinical outcomes during hospitalization, particularly after events like acute myocardial infarction. RDW is considered a marker of oxidative stress, chronic inflammation, and cardiovascular disease risk, though the exact mechanisms are unclear[3-5]. Studies have shown that higher RDW levels correlate with increased risks of heart failure, coronary artery disease, and peripheral artery disease[6]. Additionally, a rise in RDW is associated with various serious conditions, including new-onset atrial fibrillation (AF), sepsis, and ischemic stroke[7].

Existing tools for assessing cardiac morbidity and mortality have limitations, particularly regarding their ability to effectively monitor patients at risk for cardiovascular events post-surgery. Thus, there is a compelling need for improved models that can incorporate additional risk factors. RDW could serve as a pragmatic solution, providing a cost-effective and straightforward approach to enhance existing risk assessment frameworks[2,8].

The study's objective was to evaluate the predictive value of preoperative RDW levels for in-hospital morbidity following off-pump coronary artery bypass grafting (OPCAB). It is important to note that while this research does not seek to establish causality regarding the increased RDW levels and early morbidity post-OPCAB. The underlying mechanisms that link elevated RDW to adverse outcomes remain poorly understood, necessitating further investigation[9].

MATERIALS AND METHODS

This prospective study, conducted from July 2017 to August 2019, included 185 elective OPCAB patients, with 150 meeting eligibility criteria. Informed consent and ethical clearance were obtained (Institutional Review Board reference no. 2018/8107). Extensive exclusion includes[2]:

- Previous treatment for anemia or preoperative blood transfusion within 3 months before surgery
- Clinical evidence of active infection within 7 days before surgery
- Concomitant valve surgery
- Congestive cardiac failure, AF, thyroid disorder, chronic renal or hepatic disease, or overt/active hematologic proliferative diseases at the time of preoperative evaluation
- Preoperative need for respiratory support, inotropic drug support, or intra-aortic balloon pump.
- Emergency operations

The study population was grouped in two ways:

1. Event Group (n=56) and No Event Group (n=94), based on the presence or absence of in-hospital adverse events/morbidities following OPCAB.
2. According to preoperative RDW levels:
    - Group A: RDW ≤14% (n=75)
    - Group B: RDW 14-16% (n=36)
    - Group C: RDW ≥16% (n=39)

In-hospital adverse events/morbidity: The primary endpoint was early adverse events, including in-hospital mortality before discharge, development of AF, ventricular tachycardia, infection, stroke, acute kidney injury, excessive bleeding, reoperation for hemodynamic instability, prolonged mechanical ventilation (>24 hours), and hospital stay (>10 days)[6].

Infections: Included sternal wound infection and/or harvest site infection, confirmed by clinical signs (fever, redness) and wound site culture.

Acute Kidney Injury: Defined as a postoperative creatinine level increase by two or more-fold compared to the preoperative level or the need for hemodialysis[5].

Postoperative Bleeding: Defined as blood loss of more than 1.5 ml/kg/hour for six consecutive hours within the first 24 hours or reoperation for hemostasis within the first 12 postoperative hours, regardless of transfusion volume[10].

Laboratory

Preoperative blood samples were collected, and RDW levels were estimated using the Hematology Autoanalyzer Sysmex XN-2000. The normal reference range for RDW in our laboratory was 11.6% - 14.0%. Only RDW-CV was used for analysis, referred to as "RDW".

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0. Continuous data were presented as mean ± standard deviation, and categorical data as frequency and percentage. The Chi-Square test and Fisher's exact test were used for categorical data analysis. One-Way ANOVA and Kruskal-Wallis test were used for continuous parametric and non-parametric data, respectively. A receiver operating characteristic (ROC) curve was constructed to assess the effect of threshold RDW identified by the study on AF and overall in-hospital morbidity. Univariate and multivariate regression analyses were conducted addressing potential confounders to identify the independent association of preoperative RDW levels with in-hospital adverse events. A p-value ≤0.05 was considered statistically significant.

RESULTS

Early adverse events

Baseline clinical characteristics and perioperative data, categorized by early adverse events and RDW levels, are presented in Table 1 and Table 2. The data indicate that male patients experienced more adverse events compared to female patients. The body mass index (BMI) was generally lower in the event group, with the lowest BMI observed in Group B (RDW 14-16%) among the three RDW groups. Risk factors for coronary heart disease did not show statistical significance across the groups. However, EuroSCORE II was statistically significant among the groups based on RDW levels (p=0.001).

Table 1: Baseline clinical characteristics and perioperative data according to early adverse events

Variables	No-event (n=94)	Event (n=56)	p value
Age (years)	54.63 ± 9.16	55.30 ± 8.68	0.657
Gender (female)	11 (11.7)	7 (12.5)	1.000
Body mass index (kg/m^2)	23.78 ± 3.11	23.71 ± 3.10	0.894
Risk factors			
Smoker	69 (73.4)	36 (64.3)	0.271
IHD/MI	75 (79.8)	42 (75.0)	0.544
Peripheral vessel disease	2 (2.1)	2 (3.6)	0.629
Hypertension	59 (62.8)	35 (62.5)	1.000

Diabetes mellitus	42 (44.7)	28 (50.0)	0.612
EuroSCORE II	1.00 ± 0.47	1.16 ± 0.59	0.076
Preoperative diagnoses			
SVD	1 (1.1)	1 (1.8)	
DVD	13 (13.8)	6 (10.7)	
TVD	51 (54.3)	35 (62.5)	0.899
SVD with LMD	2 (2.1)	1 (1.8)	
DVD with LMD	7 (7.4)	2 (3.6)	
TVD with LMD	20 (21.3)	11 (19.6)	
Operative data			
Number of distal anastomoses	2.86 ± 0.58	3.07 ± 0.65	0.043
Postoperative period			
Intensive care unit (ICU) stay (hours)	77.72 ± 20.74	98.76 ± 29.49	< 0.001
Mechanical ventilation (hours)	7.51 ± 2.72	13.18 ± 15.71	0.001
Duration of inotropes used (hours)	74.30 ± 20.94	94.73 ± 29.98	< 0.001
Duration of hospital stay (>10 days)	6 (6.4)	20 (35.7)	< 0.001

Data are shown as Mean ± SD. Figure within parenthesis indicates percentage. p-value < 0.05 is considered statistically significant.

IHD: Ischemic heart disease, MI: Myocardial Infarction, EuroSCORE: European System for Cardiac Operative Risk Evaluation, SVD: Single vessel disease, DVD: Double vessel disease, TVD: Triple vessel disease, LMD: Left main vessel disease.

Table 2: Baseline clinical characteristics and perioperative data stratified by RDW values

Variables	Group A (RDW ≤14%)	Group B (RDW 14-16%)	Group C (RDW ≥16%)	p value
Age (years)	54.51 ± 9.33	53.75 ± 7.67	56.64 ± 9.30	0.334
Gender (female)	10 (13.3)	4 (11.1)	4 (10.3)	0.947
Body mass index (kg/m^2)	24.02 ± 3.32	23.13 ± 2.30	23.84 ± 3.28	0.359
Risk factors				
Smoker	49 (65.3)	27 (75.0)	29 (74.4)	0.481
IHD/MI	57 (76.0)	29 (80.6)	31 (79.5)	0.872
Peripheral vessel disease	1 (1.3)	0 (0.0)	3 (7.7)	0.120
Hypertension	53 (70.7)	22 (61.1)	19 (48.7)	0.070
Diabetes mellitus	32 (42.7)	18 (50.0)	20 (51.3)	0.650
EuroSCORE II	0.94 ± 0.33	1.05 ± 0.44	1.32 ± 0.75	0.001
Operative data				
Number of distal anastomoses	2.79 ± 0.58	3.00 ± 0.63	3.18 ± 0.60	0.004
Postoperative events				
In-hospital mortality	0 (0.0)	1 (2.8)	3 (7.7)	0.037
Atrial fibrillation	8 (10.7)	12 (33.3)	11 (28.2)	0.009
Ventricular tachycardia	1 (1..3)	3 (8.3)	5 (12.8)	0.021
Acute kidney injury	0 (0.0)	2 (5.6)	3 (7.7)	0.037
Stroke	0 (0.0)	0 (0.0)	1 (2.6)	0.500
Infection	4 (5.3)	1 (2.8)	4 (10.3)	0.437
Bleeding requiring re-exploration	1 (1.3)	2 (5.6)	3 (7.7)	0.146
Intensive care unit (ICU) stay (hours)	76.04 ± 20.47	93.09 ± 22.72	96.85 ± 32.46	< 0.001
Mechanical ventilation (hours)	8.17 ± 4.15	9.99 ± 8.07	12.00 ± 17.22	0.154
Duration of inotropes used (hours)	72.47 ± 20.92	88.94 ± 23.39	93.49 ± 32.11	< 0.001
Duration of hospital stay (>10 days)	8 (10.7)	6 (16.7)	12 (30.8)	0.024

Data are shown as Mean ± SD. Figure within parenthesis indicates percentage. p-value < 0.05 is considered statistically significant.

IHD: Ischemic heart disease, MI: Myocardial Infarction, EuroSCORE: European System for Cardiac

Operative Risk Evaluation.

Operative data revealed that patients who experienced adverse events following OPCAB had a higher number of distal grafts placed (p=0.043), as did those with an RDW level of ≥16% (p=0.004). The in-hospital mortality rate was 2.7% (N=150). Patients in the event group had longer stays in the intensive care unit, extended durations of mechanical ventilation, and hospital stays exceeding 10 days, with the shortest durations observed in the RDW ≤14% group. However, the duration of mechanical ventilation did not show statistical significance based on RDW levels. Among the 150 patients studied, 56 (37.3%) experienced one or more adverse events, as detailed in Table 3. Atrial fibrillation (AF) was the most common adverse event, occurring in 31 patients (20.7%).

Table 3: Early adverse events following coronary artery bypass grafting

Variables	Numbers of patients (%)
In-hospital mortality	4 (2.7)
Atrial fibrillation	31 (20.7)
Ventricular tachycardia	9 (6.0)
Acute kidney injury	5 (3.3)
Stroke	1 (0.7)
Infection	9 (6.0)
Bleeding requiring re-exploration	6 (4.0)
Prolonged mechanical ventilation over 24 hours	6 (4.0)

Figure within parenthesis indicates percentage.

Laboratory data

Perioperative investigation data (Table 4) indicated that the RDW level (%) was significantly higher in the event group (15.33 ± 1.98) compared to the non-event group (14.22 ± 1.66) ($p<0.001$). Additionally, platelet counts and left ventricular ejection fraction (LVEF) were lower in the event group, while the neutrophil/lymphocyte (N/L) ratio was higher ($p<0.05$). Postoperative investigations revealed that only serum creatinine levels and serum glutamic-pyruvic transaminase (SGPT) levels were statistically significant between the event and non-event groups.

Table 4: Perioperative investigations data of two groups (the No-event and Event)

Variables	No-event (n=94)	Event (n=56)	p value
Preoperative Investigations:			
RDW (%)	14.22 ± 1.66	15.33 ± 1.98	< 0.001
Hemoglobin (gm/dL)	12.72± 1.45	12.39 ± 1.44	0.178
ESR (mm in 1st hour)	29.06 ± 18.54	28.25 ± 17.63	0.792
Platelet count (x10^{12}/L)	274.52 ± 78.42	247.45 ± 69.64	0.035
Total WBC count (x10^9/L)	8.50 ± 2.06	8.37 ± 2.13	0.694
Neutrophil/Lymphocyte Ratio	1.97 ± 0.78	2.29 ± 0.94	0.027
Serum Total Bilirubin (mg/dL)	0.60 ± 0.24	0.52 ± 0.27	0.089
SGPT (U/L)	35.69 ± 23.64	36.10 ± 34.10	0.932
Serum Albumin (gm/L)	41.90 ± 6.43	40.58 ± 4.40	0.180
Total Cholesterol (mg/dL)	160.81 ± 45.33	150.43 ± 45.51	0.280
Low Density Lipoprotein (mg/dL)	88.15 ± 38.79	80.19 ± 30.78	0.308
High Density Lipoprotein (mg/dL)	35.44 ± 7.78	39.67 ± 18.50	0.136
Triglyceride (mg/dL)	182.30 ± 96.91	184.00 ± 110.68	0.938
C-Reactive Protein (mg/L)	3.82 ± 4.57	3.67 ± 4.44	0.850
Random Blood Sugar (mmol/L)	7.84 ± 3.80	7.93 ± 2.86	0.890
Thyroid-stimulating hormone (mlU/L)	1.99 ± 1.24	1.77 ± 1.02	0.274
Serum Creatinine (mg/dL)	1.08 ± 0.20	1.11 ± 0.27	0.504
Echocardiography			
LVEF (%)	55.63 ± 10.45	52.16 ± 9.76	0.046
RWMA	78 (83.0)	45 (80.4)	0.826
Left Atrial size (mm)	33.64 ± 4.06	33.64 ± 4.65	0.998
Postoperative investigations:			
Hemoglobin (gm/dL)	11.65 ± 1.11	11.61 ± 1.30	0.826
ESR (mm in 1st hour)	31.71 ± 19.03	30.45 ± 15.82	0.680
Total WBC count (x10^9/L)	15.13 ± 5.86	15.88 ± 5.67	0.447
Serum Creatinine (mg/dL)	1.31 ± 0.34	1.53 ± 0.58	0.004
Serum Total Bilirubin (mg/dL)	0.89 ± 0.41	0.97 ± 0.80	0.449
SGPT (U/L)	41.30 ± 18.65	58.05 ± 48.91	0.003

Data are shown as Mean ± SD. p-value < 0.05 is considered statistically significant.

RDW: Red cell distribution width, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, SGPT: Serum glutamic-pyruvic transaminase, LVEF: Left ventricular ejection fraction, RWMA: Regional wall motion abnormality.

Receiver Operating Curve (ROC)

The ROC curve (Figure 1) was used to assess the predictive value of preoperative RDW levels for postoperative AF and overall, in-hospital morbidity. For AF, the area under the curve (AUC) was 0.685, with a sensitivity of 74% and specificity of 56.3% at an RDW threshold of ≥14.05% (95% CI 0.591-0.778, p=0.002). For overall in-hospital morbidity, the AUC was 0.698, with a sensitivity of 73% and specificity of 64% at the same RDW threshold (95% CI 0.614-0.783, p<0.001).

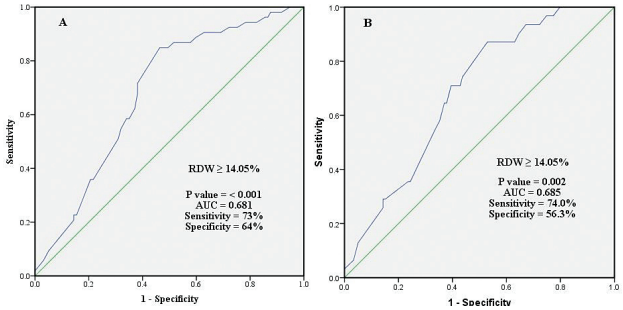

Figure 1: ROC (Receiver Operating Characteristic) Curve of RDW for the prediction of (A) early adverse events and (B) atrial fibrillation after off-pump coronary artery bypass grafting. RDW: Red cell distribution width, AUC: Area under curve. p-value < 0.05 is considered statistically significant.

Predictive factors of in-hospital morbidity

The predictive value of variables for early adverse events was assessed using univariable and multivariable logistic regression analyses (Table 5). Statistically significant variables and well-known predictors of morbidity after OPCAB, such as age, female gender, history of smoking, hypertension, diabetes mellitus, WBC count, N/L ratio, C-reactive protein (CRP), platelet count, and LVEF, were included in the analysis.

The univariable analysis revealed that several factors were associated with early adverse events, including RDW (p=0.001), platelet count (p=0.038), LVEF (p=0.048), number of distal anastomoses (p=0.046), duration of mechanical ventilation (p=0.001), duration of inotropes used (p<0.001), ICU stay (p<0.001), and duration of hospital stay (p<0.001).

Table 5: Analysis of predictive factors of early adverse events by logistic regression test

Variables	Univariable			Multivariable		
	OR	95.0% CI (OR)	p value	OR	95.0% CI (OR)	p value
RDW	0.709	0.579-0.868	0.001	0.713	0.566-0.899	0.004
Gender	0.928	0.337-2.550	0.884	0.765	0.257-2.276	0.630
Platelet count	1.005	1.000-1.010	0.038	1.004	1.000-1.009	0.075
N/L ratio	0.643	0.431-0.959	0.030	0.587	0.382-0.902	0.015
LVEF	1.034	1.000-1.068	0.048	1.041	1.003-1.081	0.035
Euro-SCORE II	0.562	0.291-1.083	0.085	0.879	0.424-1.823	0.729
Number of distal anastomoses	0.562	0.319-0.990	0.046	-	-	-
Mechanical ventilation	0.781	0.677-0.902	0.001	-	-	-
Duration of inotropes used	0.965	0.948-0.981	< 0.001	-	-	-
Intensive care unit (ICU) stay	0.962	0.945-0.980	< 0.001	-	-	-
Duration of hospital stay	0.123	0.046-0.331	< 0.001	-	-	-

RDW: Red cell distribution width, N/L: Neutrophil/Lymphocyte, LVEF: Left ventricular ejection fraction, EuroSCORE II: European System for Cardiac Operative Risk Evaluation, CI: Confidence Interval, SGPT: Serum glutamic-pyruvic transaminase, OR: Odds Ratio. p-value < 0.05 is considered statistically significant.

A stepwise multivariable analysis was conducted on preoperative variables that were significantly different in the univariable analysis, along with well-known predictors of adverse events. The results indicated that RDW (OR 0.713, 95% CI 0.566-0.899, p=0.004), N/L ratio (OR 0.587, 95% CI 0.382-0.902, p=0.015), and LVEF (OR 1.041, 95% CI 1.003-1.081, p=0.035) were independent predictors of early adverse events following OPCAB.

DISCUSSION

In this study, we examined the relationship between preoperative RDW levels and the occurrence of early postoperative complications after cardiac surgery. All patients included in this study were subjected to comprehensive inclusion and exclusion criteria and underwent isolated OPCAB to minimize biases associated with different types of cardiac surgery. Our findings indicated that RDW levels in the event group were significantly higher than those in the no-event group. When we classified all 150 subjects by RDW levels, we observed a marked increase in the incidence of overall early adverse events, including AKI, infection, arrhythmia, and postoperative bleeding, in the higher RDW group. Importantly, we discovered that RDW independently predicted early adverse events following isolated OPCAB, alongside LVEF and the N/L ratio.

Over the last decade, several studies have shown that RDW is a predictor of clinical outcomes in cardiovascular disease[11-13]. Similarly, preoperative RDW has been strongly linked to surgical outcomes after cardiac procedures[5]. Recent research suggests that elevated RDW may have potential utility in preoperative risk stratification to identify patients at risk for postoperative mortality and morbidity, yet this area requires further investigation[14]. Additional detailed studies are needed to explore the relationship between preoperative RDW, acute inflammation, and oxidative stress following cardiac surgery[5].

Although the mechanisms behind elevated RDW remain unclear, a study has indicated a correlation between chronic inflammation and increased RDW, with RDW levels aligning with both CRP and ESR[1]. While WBC count and CRP are established inflammatory markers, neither demonstrated an association with early adverse events in our study. This discrepancy suggests that inflammation alone does not account for the variations in inflammatory marker results, indicating that elevated RDW is likely due to a multifactorial phenomenon. Large-scale studies are necessary to identify the factors contributing to the increase in RDW[5].

Increased RDW levels are linked to higher risks of new-onset atrial fibrillation (AF), sepsis, and ischemic stroke[7]. Güngör et al. found RDW >13% predicts non-valvular AF with 73.5% sensitivity and 68.3% specificity[15]. Our study had similar findings, but inconsistent ECG monitoring after patients were transferred from the ICU to the general ward may have underestimated AF incidence.

Low LVEF and enlarged left atrial (LA) size are prognostic factors for adverse outcomes post-cardiac surgery[15]. Our study found lower LVEF in the event group, highlighting the importance of normal LVEF for favorable outcomes post-OPCAB. Although larger LA size and high RDW may lead to atrial stretch, resulting in the release of NT-proBNP, thus increasing the risk of lasting adverse outcomes[16], our patients had normal LA sizes. We didn't investigate long-term outcomes, as this was outside the study's scope.

In summary, our study identified that elevated RDW can independently predict early complications, alongside LVEF and the N/L ratio. Moreover, ROC analysis indicated that a higher RDW cut-off of 14.05% correlates with increased rates of early adverse events. Factors such as the duration of ICU stay, mechanical ventilation, and hospital stay were extended in the event group as well as among those with higher RDW levels, aligning with in-hospital morbidities following OPCAB. Thus, the easy availability of RDW through standard automated CBC reports could be integrated into current preoperative screening protocols and could provide valuable insights, prompting surgeons to maintain vigilance for patients with

elevated preoperative RDW levels to potentially avoid preventable adverse events after OPCAB.

STUDY LIMITATIONS

Stringent inclusion and exclusion criteria limited the study population, excluding many OPCAB patients from a single center. This may introduce potential biases. The study focused on early postoperative morbidities and the predictive value of RDW levels for in-hospital adverse events, without establishing a causal link between elevated RDW and OPCAB complications.

CONCLUSION

An inexpensive and readily available RDW level independently predicts early adverse events following OPCAB. Cardiac surgeons should be vigilant for patients with a preoperative raised RDW level to prevent avoidable in-hospital adverse events following OPCAB.

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