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Original Article

Relationship Between Red Blood Cell Distribution Width and No-Reflow In ST-Elevation Myocardial Infarction patients Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

Objective: To find the association between Red Blood Cell Distribution Width (RDW) and the incidence of no-reflow in ST-Elevation Myocardial Infarction patients treated with Primary Percutaneous Coronary Intervention.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: At Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi Pakistan, from Aug 2023 to Feb 2024.

Methodology: Total one hundred and thirty-nine patients who underwent Primary Percutaneous Coronary Intervention within 24 hours of symptoms onset were enrolled via consecutive sampling for study purpose. RDW values were noted from Complete Blood Count conducted upon the patients' arrival at the emergency department. Thrombolysis in Myocardial Infarction grading system was utilized to assess the scale of blood flow during angiography. On the basis of mean RDW value, participants were categorized into two groups: Group-I=RDW<14 and Group-II=RDW≥14. Receiver Operating Characteristics curve was generated to evaluate the predictive capability of RDW values for identifying cases of no-reflow. The association of study variables with RDW was assessed by applying Chi-square test, and significance level was set at $p<0.05$.

Results: Out of 139 participants, 118(84.9%) were males and 21(15.1%) were females. The mean age of study sample was 61.75±10.91 years. 64(46.0%) patients were present in RDW<14 group and 75(53.9%) in RDW≥14 group. Out of 64, the incidence of No Reflow Phenomenon (NRP)/slow flow was 28(43.8%) in Group-I while in Group-II, it was 32(42.7%) out of 75 patients with non-significant association ($p=1.00$). Area under the curve was 0.503, for RDW in predicting NRP, with a sensitivity of 30.4% and specificity of 73.3%.

Conclusion: RDW does not independently predict no-reflow in patients with ST-Elevation Myocardial Infarction undergoing Primary Percutaneous Coronary Intervention.

Keywords: No-reflow phenomenon, Red Cell Distribution Width, ST Segment Elevation Myocardial Infarction

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INTRODUCTION

Myocardial Infarction (MI), commonly recognized as a heart attack, is a prevalent cause of death in developed countries. As per the World Health Organization (WHO), heart attacks remain a primary cause of mortality worldwide, with significant occurrence in both developed and developing nations. In 2016, 17.9 million people succumbed to Cardiovascular Diseases (CVD), representing 31% of the total global mortality rate. In Pakistan, the reported deaths due to CVDs were 29.1% in 2017.[1] ST-Segment Elevation Myocardial Infarction (STEMI) is a severe form of Acute Myocardial Infarction (AMI) characterized by ST-segment elevation on an electrocardiogram (ECG) and the presence of complete occlusion of a coronary artery.[2,3] The preferred treatment approach for STEMI patients is the swift restoration of blood flow in obstructed artery using Primary Percutaneous Coronary Intervention (PPCI), aimed at restoring blood flow to the myocardium and minimizing myocardial damage.[4]

While primary PCI has significantly improved patient outcomes, a phenomenon known as "no-reflow" occasionally occurs even after successful revascularization. No-reflow refers to inadequate myocardial reperfusion despite the restoration of epicardial blood flow, leading to impaired tissue perfusion and subsequent adverse clinical outcomes. It is a complex phenomenon resulting from microvascular dysfunction, inflammation, endothelial injury, and micro-thrombus formation.[5]

Red Blood Cell Distribution Width (RDW) is a routinely measured parameter in complete blood counts (CBC). It reflects the heterogeneity in red blood

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cell size, with higher values indicating greater variation. Elevated RDW levels have been associated with various cardiovascular diseases, including Coronary Artery Disease, Acute Coronary Syndrome, and heart failure.[6] Recent studies have suggested a potential link between RDW and incidence of no-reflow among STEMI patients undergoing primary PCI.[7,8]

The underlying mechanisms linking RDW to no-reflow in STEMI patients are still not entirely elucidated. However, various hypotheses have emerged. One theory suggested that increased RDW may reflect chronic inflammation, endothelial dysfunction, and oxidative stress, all of which can contribute to micro-vascular damage and impaired re-perfusion. Another possibility is that RDW can be a marker of increased red blood cell aggregation and impaired deformability, leading to micro-thrombus formation and subsequent no-reflow.[9]

Understanding the relationship between RDW and no-reflow holds promise for risk stratification, prognostication, and potentially identifying new therapeutic targets. Investigating this association could provide insights into the underlying patho-physiological mechanisms involved in micro-vascular dysfunction, aiding in the development of novel therapeutic strategies to mitigate the incidence of no-reflow and improve clinical outcomes for STEMI patients.[10] Current study aimed to showcase the predictive capacity of RDW in anticipating the occurrence of NRP among STEMI patients who underwent PPCI.

METHODOLOGY

This Analytical Cross-sectional study was conducted at Armed Forces Institute of Cardiology/ National Institute of Heart Diseases Rawalpindi, Pakistan from August 2023 to February 2024. Data was collected through non-probability consecutive sampling technique after obtaining approval from the Institutional Ethical Review Board (IERB) (Ltr# 9/2/R&D/2023/276).

Sample size of n=139 was calculated using WHO sample size calculator with 10.0% prevalence of no-reflow phenomenon in STEMI patients, keeping confidence level of 95% and 5% margin of error.[8]

Inclusion criteria: All STEMI patients aged 25-80 years regardless of gender who underwent PPCI within 24 hours of symptoms onset were eligible to participate in the study.

Exclusion criteria: Patients who were in cardiogenic shock at presentation or came after thrombolysis for rescue PCI, those with previous Coronary Artery Bypass Grafting (CABG) or with history of major surgeries in past 6-months, history of thromboembolic disease, chronic inflammatory, autoimmune, hematologic or rheumatic disorders, pregnant women and patients treated with cancer were excluded.

Diagnosis of STEMI was made as per European Society of Cardiology (ESC) guidelines which involved a chief complaint of continuous typical chest pain lasting at least 30 minutes, accompanied by new, persistent ST- segment elevation of at least 1 mm in 2 contiguous ECG leads. This diagnosis was made within 12-hours of symptom onset or up to 24-hours if there were indications of hemodynamic instability, persistent ischemia, or new left bundle-branch block in the electrocardiogram, coupled with elevations in cardiac biomarkers such as creatine kinase-MB (CK-MB) and troponin I, exceeding the 99th percentile upper reference limit. Blood samples were obtained from venous site at presentation before primary PCI procedure with laboratory tests conducted in emergency laboratory including CBC for RDW, serum total cholesterol, serum creatinine, Troponin-I and CK-MB.

Coronary angiography was performed in all these STEMI patients who fulfilled inclusion criteria. Epicardial blood flow in Infarct Related Artery (IRA) was assessed using the TIMI grading system to determine the extent of coronary blood flow. On the basis of mean RDW value, participants were categorized into two groups: Group-I=RDW<14 and Group-II=RDW≥14.

The blood flow in coronary vessel was categorized into 4 grades: "grade-0 = no perfusion; grade-1 =penetration without perfusion; grade-2 =partial perfusion; grade-3 =complete perfusion".[5-11] Grade 0, 1 and 2 were considered as No/Slow flow and grade 3 was considered as normal flow.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version-23:00. Frequencies & percentages and mean & standard deviations were calculated for categorical and continuous data respectively. Association of variables was analyzed using Chi-square test with RDW grouping, p-value was taken statistically significant at <0.05. Receiver Operating Characteristic (ROC) curve was drawn to delve deeper into the potential of RDW as a biomarker for predicting NRP.

Table-I: Comparison of Baseline/Clinical parameters among RDW Groups (n=139)

Variables		Total Frequency (%)	RDW<14 (Total=64) Frequency (%)	RDW≥14 (Total=75) Frequency (%)	*p*-value
Gender	Male	118(84.9)	60(93.8)	58(77.3)	0.01
	Female	21(15.1)	4(6.3)	17(22.7)	
Age (years) [Mean±SD]		61.75±10.91	60.66±11.14	62.68±10.69	0.27
Comorbid	Hypertension	99(71.2)	45(70.3)	54(72.0)	0.97
	Chronic Kidney Disease	4(2.9)	1(1.6)	3(4.0)	0.62
	Diabetes Mellitus	68(48.9)	32(50.0)	36(48.0)	0.94
No. of diseased Vessel	SVCAD	51(36.7)	21(32.8)	30(40.0)	0.66
	DVCAD	42(30.2)	20(31.3)	22(29.3)	
	TVCAD	46(33.1)	23(35.9)	23(30.7)	
Initial TIMI Flow	TIMI 1	10(7.2)	5(7.8)	5(6.7)	0.96
	TIMI 2	15(36.0)	23(35.9)	27(36.0)	
	TIMI 3	79(56.8)	36(56.3)	43(57.3)	

RDW=Red Cell Distribution Width, "SVCAD=Single Vessel Coronary Artery Disease, DVCAD= Double Vessel Coronary Artery Disease TVCAD= Triple Vessel Coronary Artery Disease LAD=Left Anterior Descending Artery, LCx=Left Circumflex Artery, RCA=Right Coronary Artery, PDA=Posterior Descending Artery, TIMI=Thrombolysis In Myocardial Infarction"

RESULTS

One hundred and thirty nine patients were included in our research with the mean age of 61.75±10.91 years. Among them, 118(84.9%) were males and 21(15.1%) were females. 64(46.0%) patients were present in RDW<14 group (Group-I) and 75(53.9%) in RDW≥14 (Group-II). Clinical characteristics showed that patients who had hypertension were 99(71.2%), diabetics were 68(48.9%), 4(2.9%) had renal impairment, and majority 51(36.7%) had single vessel coronary artery disease (SVCAD) as shown in Table-I.

Table-II Association of No-Reflow Phenomenon and Culprit artery with RDW (n=139)

Variables		Total Frequency (%)	RDW <14 (Total=64) Frequency (%)	RDW ≥14 (Total=75) Frequency (%)	*p*-value
TIMI Flow	No/Slow Flow	60(43.2)	28(43.8)	32(42.7)	1.00
	Normal Flow	79(56.8)	36(56.3)	43(57.3)	
Culprit artery	LAD	68(48.9)	33(51.6)	35(46.7)	0.91
	LCx	19(13.7)	9(14.1)	10(13.3)	
	RCA	50(36.0)	21(32.8)	29(38.7)	
	PDA	2(1.4)	1(1.6)	1(1.3)	

RDW=Red Cell Distribution Width, LAD=Left Anterior Descending Artery, LCx=Left Circumflex Artery, RCA=Right Coronary Artery, PDA=Posterior Descending Artery, TIMI=Thrombolysis In Myocardial Infarction

The incidence of NRP/slow flow was 43.2% (60 of 139 patients) in the whole subjects, 28(43.8%) out of 64 in RDW<14 group and 32(42.7%) out of 75 in RDW≥14 group (p>0.05). The results indicated that the rate of no-reflow was marginally higher in the high-RDW group compared to the low-RDW group, although the difference was not statistically significant. Most common culprit vessel involved was LAD 68(48.9%), followed by RCA 50(36.0%). (Table-II)

The Receiver Operating Characteristic (ROC) curve for Red Cell Distribution Width (RDW) in predicting the NRP is displayed in Figure-1. The findings revealed value for area under the curve (AUC) as 0.503, for RDW in predicting NRP across all subjects, with a sensitivity of 30.4% and specificity of 73.3%.

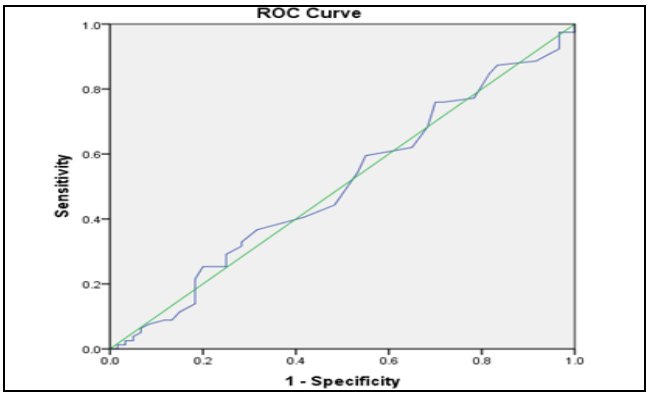

Figure-1 ROC Curve to illustrate the Predictive Capacity of RDW for NRP

DISCUSSION

Our investigation was a step to find a link between RDW levels and NRP. The incidence of NRP/slow flow was 43.2% (60 of 139 patients) in the whole subjects, 28(43.8%) in RDW<14 group and 32(42.7%) in RDW≥14 group (p=1.00) with 30.4% of sensitivity and 73.3% of specificity. However, the findings did not reach statistical significance.

Historically, RDW has served as a diagnostic marker for anemia, especially in identifying iron-deficiency anemia.[12] The recent focus has shifted towards exploring the RDW impact on CAD. Various studies have demonstrated a connection between RDW levels and the prognosis of patients with stable angina.[6] Acute Myocardial Infarction.[13] heart failure.[14,15] and those undergoing primary PCI.[16] Another study conducted by Celık T *et al*..[7] unveiled a link between elevated RDW and slow flow in normal coronary arteries. Moreover one-unit increase in RDW level raises the likelihood of developing no-reflow by 23.48 times.[17] A prospective examination with one hundred STEMI patients uncovered that elevated RDW levels independently predict NRP after primary PCI.[18] Though, a meta-analysis[(16)] contradicted these findings, revealing no substantial link between the risk of no-reflow and RDW. However, in line to this, our research involving n=139 STEMI patients also found non-significant association (p>0.05) and RDW was not an independent predictor to NRP. Consequently, further investigations are necessary to substantiate the correlation between RDW and NRP particularly in CAD patients, undergoing primary PCI.

While the pathological and physiological mechanisms of NRP remain incompletely understood, its etiology appears multifactorial.[19] Several theories attempt to explain fundamental mechanisms behind impaired myocardial reperfusion. One hypothesis revolved around distal micro-vascular embolism obstruction triggered by the active adhesion and aggregation of platelets during plaque rupture.[18] Additionally, balloon expansion and stent placement can induce endothelial damage, leading to increased endothelin release, a potent vasoconstrictor, causing micro-vascular spasms and heightened resistance to blood flow.[20] Another study suggested that prolonged ischemia leads to endothelial dysfunction.[13] Inflammation has been identified as a significant player in the pathophysiological process of NRP.

Sun Y *et al*.,[(8)] in his study reported 15.0% incidence of NRP in the whole subjects with 45.1% of specificity and 65.8% of sensitivity (p= 0.092). The area under the curve value of RDW for predicting NRP in all subjects was reported as 0.503 in our study, with 30.4% of sensitivity and 73.3% of specificity. Comparative to the findings, prevalence of NRP/slow flow was 43.2% in current study.

Studies done by Hu Y *et al*.[21] and Salvagno *et al*.[22] proposed that RDW is an indicator of numerous processes, such as; oxidative stress and inflammation. Given the extensively documented involvement of inflammation in the AMI development, it is postulated that inflammation could serve as a link between higher RDW and an increased incidence of NRP.

LIMITATIONS OF STUDY

Our research has various limitations. First, all the data of our research was derived from single center with limited sample size. Hence, it is essential to interpret these results with great care. Future investigations may require multi-center approaches with larger sample sizes and extended durations to validate these findings. Secondly, RDW measurements were obtained only upon admission. Consequently, further research incorporating dynamic observation is required to fully grasp the mechanism underlying the association between RDW and NRP in patients with AMI undergoing PPCI.

CONCLUSION

In conclusion, our study was a trial to identify the association between RDW and the no-reflow phenomenon in acute STEMI patients, although the statistical significance was not observed. The results suggested that RDW does not independently predict no-reflow in patients with STEMI undergoing primary PCI.

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Conflict of Interest: None

Authors' Contribution

Following authors have made substantial contributions to the manuscript:

ZI & IA: Concept, drafting the manuscript, data acquisition and analysis, approval of final version to be published

AN & NA: Study design, data interpretation, critical review, approval of final version to be published

MM & JK: Data analysis, critical review, approval of final version to be published

MSM & TA: Data interpretation, critical review, approval of final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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