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ADULT CARDIOLOGY

Association of Red Cell Distribution Width with Thrombus Burden in Patients of ST Elevation Myocardial Infarction Undergoing Primary PCI

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ABSTRACT

Objective: To study the association of Red Cell Distribution Width (RDW) with thrombus burden in patients of ST Elevation Myocardial Infarction (STEMI) undergoing Primary Percutaneous Coronary Intervention (PPCI).

Study Design: Analytical Cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Cardiology/National Institute of Heart Diseases Rawalpindi, Pakistan, from Aug 2022 to Dec 2022.

Methodology: Using non-probability consecutive sampling, three hundred and sixty-nine (n=369) patients were included in the study. RDW values were obtained from complete blood count sent at presentation in emergency department. Thrombolysis in Myocardial Infarction (TIMI) thrombus grading was used to determine the angiographic thrombus burden. For quantitative variables, means and standard deviations were calculated, while frequencies and percentages were calculated for qualitative variables. Receiver Operating Characteristic (ROC) curve for RDW values for predicting thrombus burden was plotted. Correlation between RDW with thrombus burden was established. Eta, Chi-square and independent samples t-test was used to determine *p*-value.

Results: The study included 369 STEMI patients, out of which 287(77.8%) were males and 82(22.2%) were females. 203(55.0%) patients had high thrombus burden while 166(45.0%) patients had low thrombus burden. Patients in the high RDW group more frequently had ventricular arrhythmias, and heart blocks. Mean RDW was 13.57±0.71 in low thrombus burden group while it was 14.67±1.21 in high thrombus burden group. Area under the curve derived from ROC curve for RDW for predicting high thrombus burden was 0.79(CI=0.74-0.83, $p<0.001$)

Conclusion: The study demonstrates that high RDW is a sensitive and specific predictor of high angiographic thrombus burden in patients of STEMI treated with PPCI.

Keywords: Primary PCI, Red cell distribution width, ST elevation myocardial infarction, Thrombus burden.

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INTRODUCTION

ST Elevation Myocardial Infarction (STEMI) is a major cause of mortality and morbidity. Primary Percutaneous Coronary Intervention (PPCI) is the treatment of choice in STEMI if presentation to the hospital is within the therapeutic window. A high angiographic thrombus burden in the Infarct Related Artery (IRA) can increase risk of procedural complications following PPCI and poor clinical outcomes by mechanisms such as increased myocardial necrosis and no reflow phenomenon and hence increased mortality.[1] A recent meta-analysis found that female patients of STEMI with high thrombus burden had poor prognosis and increased one year mortality.[2] Complete blood count (CBC) is a common lab investigation done in all cases of STEMI. Parameters like increased mean platelet volume, mean platelet volume to platelet count ratio,[3] raised C-reactive protein levels and increased troponins have been associated with adverse outcomes. Recent studies have shown that in setting of STEMI, increased monocyte count serves as a predictor of the extent of intracoronary thrombus burden.[4,5] Red Cell Distribution Width (RDW) is a standard parameter, assessed on CBC and has demonstrated its role as an independent predictor of incident MI in general population[6] as well as long-term mortality in patients treated with PPCI.[7] RDW is also correlated with severity and complexity of Coronary Artery Disease.[8] A recent study,[9] found that the incidence of Acute Coronary Syndrome (ACS) amongst the military personnel was higher in patients having higher RDW. Moreover, scientific evidence is now highlighting RDW as an independent marker of high intracoronary thrombus burden, in STEMI treated with PPCI which in turn has been found to be

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associated with low post procedural TIMI flow, raised troponins, greater percentage of distal embolization and no reflow phenomenon.[10] Hence, RDW can serve as a useful prognostic tool in patients undergoing PPCI for STEMI.

CBC is an inexpensive routinely performed test. The study aims to assess the possible association of RDW with thrombus burden in patients of STEMI undergoing PPCI.

METHODOLOGY

This was an Analytical Cross-Sectional study, carried out over a time period of 5 months (August 2022 - December 2022) at Armed Forces Institute of Cardiology/National Institute of Heart Diseases. There were no ethical issues, and had approval of Institutional Ethical Review Board of the hospital vide letter no 9/2/R&D/2022/177.

The sample size was n=369, by taking prevalence of patients with STEMI as 40%,[11] confidence level of 95% and 5% margin of error, using WHO sample size calculator.

Inclusion Criteria: Study participants were males and females aged 18-80 years admitted with STEMI, presenting within therapeutic window (presentation within 12 hours from the onset of symptoms); in case of cardiogenic shock, irrespective of time from the onset of symptoms and who underwent PPCI.

Exclusion Criteria: Patients with STEMI who had undergone thrombolysis or were unwilling for PPCI, with no follow up, preexisting chronic kidney disease, chronic liver disease and malignancies, history of hemorrhage in last 3 months, as well as transfusion of blood products in preceding 3 months, pregnancy and baseline creatinine >1.5mg/dl were excluded.

After taking informed consent, using non-probability consecutive sampling, data was collected from a total of n=369 patients who satisfied the inclusion and exclusion criteria. Angiographic thrombus burden referred to the severity of intracoronary thrombus found on coronary angiography graded by Thrombolysis in Myocardial Infarction (TIMI) grade as shown in Table-I,[12] RDW was defined as a measure of variation in size of red blood cells (anisocytosis), representing the coefficient of variance of Mean Corpuscular Volume (MCV), where RDW= (Standard deviation of MCV/ Mean of MCV) x 100. Reference value of RDW-CV is 11.6-14.0%, as per the reference values used in the AFIC/NIHD Pathology Laboratory, vide Letter No: Path-04/22 dated 10th May 2022.

Patient's name, age, gender, co-morbidities, symptoms, duration of symptoms, ECG findings diagnosis, door to balloon time and list of medications were noted. Red cell distribution width values were obtained from complete blood count sent at the time of presentation in AFIC emergency department using Mandray BC 6200 CBC analyzer available at the hospital's pathology laboratory. Thrombus burden was assessed during the coronary angiograms performed at the time of PPCI, and thrombus grades were established using Thrombus Grade Classification.[13] Patients who had initial TIMI thrombus Grade-5, were reclassified for the final TIMI thrombus grade after passing a wire or small balloon past the lesion in the IRA, depending upon the final TIMI thrombus grades. Patients with TIMI thrombus Grade 0-3 were designated into low thrombus burden group and those having TIMI thrombus Grade-4 & 5 were designated into high thrombus burden group. Based upon RDW values, patients were classified[14] into high RDW (RDW>14) and low RDW groups (≤14)

Table-I: TIMI Thrombus Burden Classification,[12]

Grade-0	No angiographic evidence of thrombus
Grade-1	Angiographic features suggestive of thrombus (decreased contrast density, haziness of contrast: irregular lesion contour, a smooth convex meniscus at the site of a total occlusion suggestive but not firmly diagnostic of thrombus)
Grade-2	Definite thrombus present in multiple angiographic projections (marked irregular lesion contour with a significant filling defect the greatest dimension of thrombus is <1/2 vessel diameter)
Grade-3	Definite thrombus appears in multiple angiographic views (greatest dimension from >1/2. to <2 vessel diameters)
Grade-4	Definite large size thrombus present (greatest dimension >2 vessel diameters)
Grade-5	Definite complete thrombotic occlusion of a vessel (a convex margin that stains with contrast, persisting for several cardiac cycles). Angiographic detection of a grade 5 TIMI thrombus leads to further exploration of the occlusive thrombotic content. Either a PCI guidewire or a small balloon is advanced across the thrombotic total occlusion. Crossing the thrombus results in restoration of antegrade flow in the treated vessel. Consequently, the ensuing angiogram enables re-stratification of the underlying residual thrombus (final TIMI thrombus grade)

TIMI=Thrombolysis in Myocardial Infarction; PPCI=Primary Percutaneous Coronary Intervention

For data analysis, Statistical Package for Social Sciences (SPSS) version 23:00 was used. Mean± Standard Deviations were calculated to present quantitative variables, while frequencies and percentages were calculated for qualitative variables. Chi Square test was used to determine statistical significance of qualitative variables. Association between red cell distribution width with thrombus burden was established using Eta and independent t-test. ROC Curve was drawn to establish optimal RDW cutoff values to predict high thrombus burden.The *p*-value ≤0.05 was considered as significant.

RESULTS

A total of three hundred and sixty nine (n=369) patients participated, out of which 287(77.8%) were males and 82(22.2%) were females. About 203(55.0%) of the patients had high thrombus burden while 166(45.0%) of the patients had low thrombus burden. Chest pain was the most common symptom 248(67.2%). 208(56.4%) patients had hypertension, 187(50.7%) had diabetes, 80(21.7%) had obesity, 4(1.1%) had polycythemia, 74(20.1%) had chronic obstructive pulmonary disease (COPD), 14(3.8%) had hyperthyroidism and 18(4.9%) of the patients had hypothyroidism. Ventricular arrhythmias were observed in 37(10%) patients, 33(8.9%) patients had Atrial fibrillation, sinus tachycardia and sinus bradycardia were reported in 66(17.9%) and 48(13%) patients respectively, while heart blocks were documented in 36(9.8%) of the patients.

Table-II compared the clinical and angiographic findings in the two thrombus burden strata. We found no statistical difference in age between the low and high thrombus burden groups, (59.51±10.42 years vs 61.12±10.16 years respectively, *p*=0.13). Patients in the high thrombus burden group more frequently suffered from hypertension, diabetes, COPD, obesity, hypothyroi-dism and hyperthyroidism. They also had significantly higher frequencies of ventricular arrhythmias (17.7% vs 0.6%, *p*<0.001) and heart blocks (13.3% vs 5.4% respectively, *p*=0.01) . Atrial fibrillation was also more common in the high thrombus burden group but the difference was insignificant (11.3% vs 6.0% respectively, *p*<0.05). In contrast sinus bradycardia was more commonly reported in the low thrombus burden subset in comparison to the high thrombus burden group (16.9 %vs 9.9% respectively, *p*<0.06). Mean symptoms duration and door to balloon times were longer in the high thrombus burden group as opposed to their counterparts in the other group,

Table-II: Baseline clinical and angiographic features according to thrombus burden (n=369)

Variables	Low Thrombus Burden Frequency(%) (Total=166)	High Thrombus Burden Frequency (%) (Total=203)	*p*-value
Gender			
Male	136(81.9)	151(74.4)	0.10
Female	30(18.1)	52(25.6)	
Age (years) (Mean±SD)	59.51±10.42	61.12±10.16	0.13
Comorbid			
Chest pain	101(60.8)	147(72.4)	0.02
Dyspnea	90(54.2)	103(50.7)	0.57
Apprehension	58(34.9)	94(46.3)	0.03
Sweating	84(50.6)	122(60.1)	0.08
Hypertension	84(50.6)	124(61.1)	0.05
Diabetes	82(49.4)	105(51.7)	0.73
Obesity	28(16.9)	52(25.6)	0.05
Polycythemia	2(1.2)	2(1.0)	1.00
COPD	33(19.9)	41(20.2)	1.00
Hyperthyroidism	5(3.0)	9(4.4)	0.66
Hypothyroidism	7(4.2)	11(5.4)	0.77
Complications			
Ventricular Arrhythmias	1(0.6)	36(17.7)	<0.001
Atrial Fibrillation	10(6.0)	23(11.3)	0.11
Sinus Tachycardia	27(16.3)	39(19.2)	0.55
Sinus Bradycardia	28(16.9)	20(9.9)	0.06
Heart Blocks	9(5.4)	27(13.3)	0.01
ACS Medications			
ACS Protocol+tirofiban	9(5.4)	197(97.0)	<0.001
ACS Protocol	157(94.6)	6(3.0)	
Previous Medications			
Insulin	29(17.5)	73(36.0)	<0.001
Oral hypoglycemic	64(38.6)	77(37.9)	0.98
Iron/Vit. Supplements	0(0.0)	1(0.5)	1.00
Diagnosis			
Anterior wall MI	88(53.0)	110(54.2)	0.28
Lateral wall MI	25(15.1)	20(9.9)	
Inferior wall MI	53(31.9)	73(36.0)	
Infarct Related Artery			
LAD	86(51.8)	111(54.7)	0.32
LCX	24(14.5)	18(8.9)	
RCA	53(31.9)	72(35.5)	
Trifurcation	3(1.8)	2(1.0)	
Total Diseased Vessels			
SVCAD	51(30.7)	61(30.0)	0.35
DVCAD	66(39.8)	66(32.5)	
TVCAD	41(24.7)	66(32.5)	
TVCAD plus LMS	8(4.8)	10(4.9)	
Initial TIMI Thrombus Grade			
0	23(13.9)	0(0.0)	<0.001
1	24(14.5)	0(0.0)	
2	31(18.7)	0(0.0)	
3	13(7.8)	0(0.0)	
4	0(0.0)	39(19.2)	
5	75(45.2)	164(80.8)	
Final TIMI Thrombus Grade			
0	23(13.9)	0(0.0)	<0.001
1	38(22.9)	0(0.0)	
2	67(40.4)	0(0.0)	
3	38(22.9)	0(0.0)	
4	0(0.0)	183(90.1)	
5	0(0.0)	20(9.9)	

MI= Myocardial Infarction, LAD= Left Anterior Descending, LCX= Left Circumflex, RCA= Right Coronary, artery SVCAD= Single Vessel Coronary Artery Disease, DVCAD= Double Vessel Coronary Artery Disease, TVCAD= Triple Vessel Coronary Artery Disease, LMS=Left Main Stem, TIMI= Thrombolysis in Myocardial Infarction, COPD= Chronic Obstructive Pulmonary Disease, ACS= Acute Coronary Syndrome

(5.25±2.23 hrs vs 5.04±2.24 hrs respectively; p=0.37) and (47.49±11.78 min vs 42.43±10.45 min respectively; p<0.001) respectively. Patients with high thrombus burden had significantly more frequent administration of tirofiban in comparison to their counterparts (97% vs 5.4%, p<0.001). The mean Hb in the low thrombus burden group was (14.14±1.23g/dl, p=0.83) while the mean Hb was (14.11±1.29g/dl, p=0.83) in their high thrombus burden counterparts. The difference between mean RDW values amongst the low and high thrombus burden groups was statistically significant as the mean RDW in the low thrombus burden group was (13.57±0.71, p<0.001) while the mean RDW value in the high thrombus burden group was (14.67±1.21, p<0.001). There was a significant correlation between RDW and thrombus burden (Eta coefficient=0.56) (Figure-1).

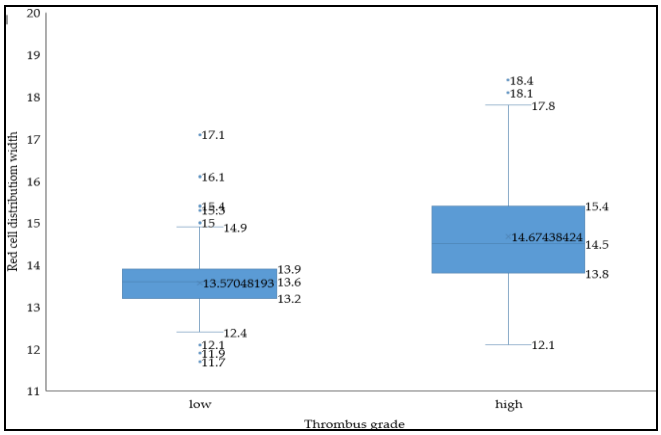

Figure-1: Red Cell Distribution Width (RDW) values according to Thrombolysis In Myocardial Infarction (TIMI) thrombus burden (n=369)

Analysis of the data of High RDW and Low RDW groups presented in Table-III, showed that Ventricular arrhythmias and heart blocks were significantly more common in the High RDW group (18.7% vs. 2.5% p<0.001 and 14.6% vs. 5.6%, p=0.006). Atrial fibrillation was more frequent in the high RDW group, however, the difference was statistically insignificant. Sinus bradycardia was observed more commonly in the low thrombus burden strata and the difference was significant (18.2% vs 7.0%, p=0.002).

ROC Curve of RDW was plotted to predict High TIMI thrombus burden (Figure-2). The Area under ROC curve came out to be 0.79(0.74-0.83, p<0.001). The opti-mal cut off value of RDW predicting high intracoronary TIMI thrombus burden was 14.15 % (86.1% Sensitivity and 66.5% Specificity).

Table-III: ECG and Angiographic Findings in the two RDW Groups (n=369)

Variables	Low RDW Group (≤14) Frequency(%) (Total=198)	High RDW Group (>14) Frequency(%) (Total=171)	p-value
Atrial Fibrillation	13(6.6)	20(11.7)	0.12
Sinus Tachycardia	36(18.2)	30(17.5)	0.98
Sinus Bradycardia	36(18.2)	12(7.0)	0.002
Heart Blocks	11(5.6)	25(14.6)	0.006
Ventricular Arrhythmias	5(2.5)	32(18.7)	<0.001
Infarct Related Artery			
LAD	98(49.5)	99(57.9)	0.26
LCX	27(13.6)	15(8.8)	
RCA	71(35.9)	54(31.6)	
Trifurcation	2(1.0)	3(1.8)	
Total Diseased Vessels			
SVCAD	60(30.3)	52(30.4)	0.98
DVCAD	72(36.4)	60(35.1)	
TVCAD	56(28.3)	51(29.8)	
TVCAD Plus LMS	10(5.1)	8(4.7)	

LAD=Left Artery Disease; LCX=Left Circumference; RCA= Right Coronary Artery

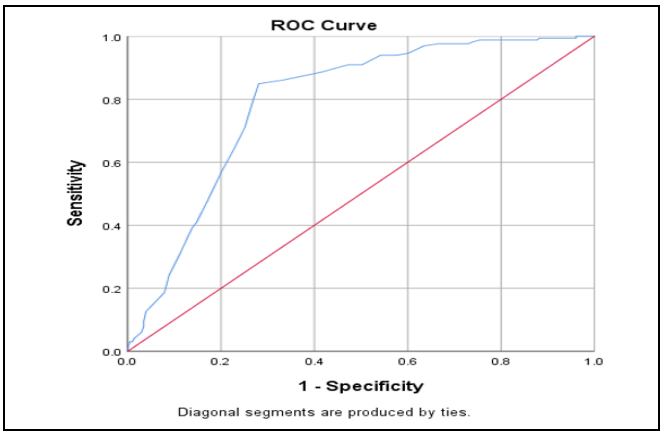

Figure-2: Receiver Operating Characteristics Curve for Red Cell Distribution Width (RDW) Value for predicting high Thrombolysis in Myocardial Infarction (TIMI) Thrombus Burden

DISCUSSION

STEMI is a common, treatable cause of cardiovascular mortality and high intracoronary thrombus burden is linked to poor cardiovascular outcomes. As demonstrated by our study a high intracoronary thrombus burden is associated with significantly more frequent episodes of ventricular arrhythmias and atrial fibrillation. It is also associated with more frequent use of tirofiban. It was also shown that patients with high thrombus burden had higher RDW values. Moreover, RDW can serve as a sensitive and specific marker of high intracoronary thrombus burden.

Age of the study participants was higher in the high thrombus burden group in comparison to the low thrombus burden group (61.12±10.16 years vs. 59.51 ±10.42 years respectively, p=0.13), however the difference wasn't statistically significant, which was consistent with other studies.[13,15] In another study,[16] patients had significantly higher ages in the high thrombus burden group. We found that hypertension and obesity were significantly more common in patients having higher thrombus burden, consistent with another recent study conducted in Pakistan.[17] Percentage of patients having diabetes was similar in both the groups, consistent with other studies.[10,13,15,16] Chest pain was more common in the high thrombus burden group, conforming to the findings of Tanboga *et al*.[10] No statistical difference in the mean Hb between the high and low thrombus burden groups was found similar to other studies.[10,13,18] As expected, use of tirofiban was significantly higher in the high thrombus burden group consistent with other studies.[10,18]

Some studies,[19,20] indicated that patients with high RDW group may be more likely to have arrhythmias, by mechanisms such as enhanced automaticity. In our study, we observed that ventricular arrhythmias and heart blocks were significantly more common in the high thrombus burden group. Atrial fibrillation was also more common in the high RDW group but the difference was statistically insignificant.

Mean RDW values were statistically higher in the high thrombus burden group as compared to the low thrombus burden group, (14.67±1.23% vs 13.57±0.71% respectively, p<0.001). Tanboga et al found that the mean RDW in the high thrombus burden group was 17.3%(15.3–19.3%) and it was 14.5% (12.8–16.5%) in the low thrombus burden group. It can be seen that the mean RDW was higher in the higher thrombus burden group in comparison to the lower thrombus burden in our study as well as the study conducted by Tanboga *et al*.[10] The difference between the comparatively lower mean values of RDW in both the thrombus burden groups in our study in comparison to the study of Tanboga *et al.* could be because of differences in ethnic and racial profile of the patients in the two studies, The area under ROC curve of RDW for predicting high thrombus burden was 0.79(.74-.83, p<0.001). The optimal cut off value of RDW predicting high intracoronary TIMI thrombus burden was 14.15% (86.1% sensitivity and 66.5% specificity) while in comparison to our study the cut off RDW value for predicting high intracoronary thrombus in the study conducted by Tanboga *et al*[10] was 15.2% (75% sensitivity and of 57% specificity).

LIMITATIONS OF STUDY

The study was conducted at a single center. We were to establish that RDW is a sensitive as well as specific predictor of high intracoronary thrombus burden in STEMI, which consequently was associated with higher rates of ventricular arrhythmias, atrial fibrillation and more frequent use of tirofiban, but the mortality outcome was not studied in the research. Further studies are required to establish RDW as a predictor of morbidity and mortality in STEMI.

CONCLUSION

Our study demonstrated a statistically significant difference in RDW values between patients suffering from STEMI having high and low intracoronary thrombus burden at angiography performed during PPCI. The optimal cut off value of RDW for predicting high intracoronary thrombus burden is 14.15% (86.1%-Sensitivity and 66.5%-Specificity). Having a high intracoronary thrombus burden is associated with higher rates of ventricular arrhythmias, atrial fibrillation, and more frequent use of tirofiban.

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Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript:

IAK & SKS: Study design, drafting the manuscript, concept, approval of the final version to be published.

FUR, AAC & ZA: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

AF, SAK & JK: Data acquisition, data analysis, data interpretation, critical review, approval of the 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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