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Red Cell Distribution Width and Neutrophil-Lymphocyte Ratio Predict Thrombus Burden in Acute Myocardial Infarction

Islam Bastawy*[1], Sherif Samir Elzahwy[1], Kerolos Youssef[2], Tamer Mohamed Abu Arab[1]
[1]Departments of Cardiology, Ain Shams University, Cairo, Egypt
[2]Departments of Cardiology, National Heart Institute, Giza, Egypt
***Corresponding author:** Islam Bastawy, **Mobile:** (+20) 01288700196, **E-mail:** islambastawy@hotmail.com

ABSTRACT

Background: In patients with ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) tries to reestablish coronary flow and ensure effective cardiac reperfusion. An independent predictor of no-reflow is a large thrombus load.

Objective: This investigation sought to determine if the red cell distribution width (RDW) and neutrophil-lymphocyte ratio (NLR) were reliable indicators of excessive thrombus load on coronary angiography.

Patients and methods: Two-hundred patients, with STEMI managed by primary PCI within 12 hours from chest pain onset, were divided into group A with high thrombus burden (Thrombolysis in myocardial infarction (TIMI) thrombus grade 4-5) and group B with low thrombus burden (TIMI thrombus grade 1-3).

Results: One-hundred and seventeen patients (58.5%) had a high thrombus burden (group A). They had more mean number of cardiovascular disease (CVD) risk factors (2.4 ±0.99 versus 2.06 ±1.06, p=0.02), longer pain to balloon time (PTB) (151.28 ±42.05 versus116.99 ±43.16 minutes, p<0.001), higher mean Killip class (1.49±0.73 versus 1.28±0.6, p=0.03), higher RDW (18.99±1.55 versus 14.03±1.52, p<0.001), and higher NLR (5.93±1.39 versus 4.08±0.93 p<0.001) compared to group B. Independent predictors of high thrombus burden were RDW (OR: 4.06, p<0.001), NLR (OR: 1.35, p= 0.04), number of CVD risk factors (OR: 1.62, p= 0.01), and PTB time (OR: 1.02, p<0.001). Cut-off values to predict high thrombus burden were 16% for RDW and 4.55 for NLR**.**

Conclusions: Rapid identification of RDW more than 16% or NLR more than 4.55, could predict a high thrombus burden.

Keywords: Neutrophil-lymphocyte ratio, No-reflow, Pain to balloon time, PCI, RDW, TIMI thrombus grade.

INTRODUCTION

Till now, acute myocardial infarction (MI) has been contributing significantly to morbidity and mortality worldwide despite improving management outcomes [(1)].

Acute thrombotic blockage of an epicardial coronary artery brought on by the rupture or surface erosion of an atherosclerotic plaque results in ST-segment elevation myocardial infarction (STEMI) [(2)].

Coronary thrombus consists of platelets, red-blood corpuscles (RBC), and fibrin, which increases with increased ischemic time [(3)].

Primary percutaneous coronary intervention (PCI) is the most effective reperfusion modality if available. It aims to restore coronary flow and achieve successful myocardial reperfusion (myocardial blush grade (MBG) 2/3) [(4)], as no-reflow (Thrombolysis in myocardial infarction (TIMI) < 3 or MBG < 2) is related to worse in-hospital, short-term, and long-term outcomes [(5)].

It is of value to identify the predictors of no-reflow to apply preventive measures that can be more beneficial than its treatment, or to intervene promptly and rapidly if it happens, as its optimal management is still unclear [(6)]. A large thrombus load is an independent predictor of no-reflow, and it should be addressed as soon as possible to limit the incidence of no-reflow [(7)].

This investigation sought to determine if the red cell distribution width (RDW) and neutrophil-lymphocyte ratio (NLR) were reliable indicators of excessive thrombus load on coronary angiography.

PATIENTS AND METHODS

This cross-sectional observational study was carried out in two centers (University Hospitals and National Heart Institute) between October 2019 and May 2021. Two hundred patients were included, who presented with STEMI within 12 hours from the onset of chest pain and were managed by primary PCI. The fourth universal definition of MI defined criteria of STEMI diagnosis [(8)]. The study excluded patients younger than 18 years, patients who refused to sign consent, and patients without coronary angiographic thrombus.

All patients were subjected to a detailed history taking and clinical examination, aiming to identify age, gender, known risk factors of cardiovascular diseases (CVD) (hypertension, diabetes mellitus (DM), dyslipidemia, current smoking, family history of premature CAD) [(9)], previous history of CVD (MI, PCI, coronary artery bypass graft (CABG), transient ischemic attack, cerebrovascular disease, peripheral arterial disease, chronic kidney disease), previous use of antithrombotics (antiplatelets or anticoagulants), pain to balloon (PTB) time, body mass index (BMI), admission heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and Killip class [(10)].

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All patients underwent twelve lead surface ECGs within 10 minutes of first medical contact to diagnose STEMI [4], localize whether it was anterior STEMI or non-anterior STEMI, and calculate the ST-elevation score index [11]. Venous blood samples were taken immediately in the emergency room to measure complete blood count parameters using a fully automated cell counter, cardiac biomarkers (troponin and cardiac enzymes), serum creatinine, and creatinine clearance using a fully automated biochemical analyzer (Advia 1200, Germany).

All patients were preloaded with acetylsalicylic acid 300 mg, clopidogrel 600 mg, and primary PCI was done within 60 minutes from first medical contact (door to balloon less than 60 minutes) by experienced interventional cardiologists through a femoral or radial approach [4]. Coronary angiography and intervention identified culprit vessel (left anterior descending (LAD) artery, left circumflex (LCX) artery, right coronary artery (RCA), left main (LM) trunk, or bypass graft), lesion site (proximal, mid, or distal), number of coronary arteries with more than 50% stenosis, TIMI thrombus grade [12,13], use of thrombus aspiration, percutaneous transluminal coronary angioplasty (PTCA), direct stenting, and post-procedural TIMI flow [14].

TIMI thrombus grading was assessed using Gibson score [15]. Thrombus grading in those with total occlusion (grade 5) was re-evaluated after crossing of a guide wire. Patients were divided into 2 groups. Group A included patients with high thrombus burden (TIMI thrombus grade 4 or 5), while group B included those with low thrombus burden (TIMI thrombus grade 1, 2, or 3) [12].

Ethical approval:

Rules of the Declaration of Helsinki for studies involving human, were followed in this study. The study's design was authorised by the Ethics Committee of Ain Shams University (8/2019). Informed written consent to participate in this study was obtained from the patients.

Statistical analysis

In this study, patients with high and low grades of thrombus load had their clinical, ECG, and laboratory data evaluated. The SPSS Version 25 of was used to analyse the data. While frequency and percentage indicated qualitative data, mean±standard deviation (SD) expressed quantitative data.

To compare two means, the independent-samples t-test was chosen, and Chi-square analysis was employed to investigate the relationship between two variables or to compare two independent groups with reference to the categorised data. Data were associated with thrombus grade using the Spearman's correlation coefficient (rho) test, and then ordinal regression analysis was used to determine the independent predictors of high thrombus grade. To determine cut-off values to forecast a high thrombus load, ROC curve analysis was employed. P-values < 0.05 were deemed significant.

RESULTS

Baseline characteristics

Group A with a high thrombus burden included 117 patients (58.5%), while group B with a low thrombus burden included 83 patients (41.5%). There was no significant difference in comparing age and gender between both groups. Among known risk factors of CAD, a history of hypertension and positive family history of premature CAD were significantly higher in group A.

But, on combining smoking, hypertension, DM, dyslipidemia, and positive family history of premature CAD, group A had a significantly higher mean number of risk factors. There was no significant difference in comparing the previous CVD between both groups. The use of anticoagulants or anticoagulants plus antiplatelet was higher in group B. PTB time was significantly longer in group A, while the door to balloon time was nearly similar in both groups. On clinical examination, group A patients had significantly higher Killip class, higher HR, and lower DBP (Table 1).

Table (1): Comparing baseline characteristics between both groups

		High thrombus burden n= 117	Low thrombus burden (n= 83)	p value
		Mean/frequency (SD/%)	**Mean/frequency (SD/%)**	
Age (years)		61.44 (±4.82)	60.88 (±6.25)	0.49
Males		68 (58.1%)\	48 (57.8%)	0.96
Cardiovascular risk factors				
Smoking		70 (59.8%)	50 (60.2%)	0.95
Hypertension		65 (55.6%)	33 (39.8%)	**0.03**
DM		29 (24.8%)	21 (25.3%)	0.93
Dyslipidemia		59 (50.4%)	42 (50.6%)	0.98
Family history of CAD		58 (49.6%)	25 (30.1%)	**0.006**
Number of CVD risk factors		2.4 (±0.99)	2.06 (±1.06)	**0.02**
Cardiovascular disease				
Chronic kidney disease		6 (5.1%)	3 (3.6%)	0.61
Previous CABG		7 (6%)	3 (3.6%)	0.45
Previous MI		13 (11.1%)	5 (6%)	0.21
Previous PCI		8 (6.8%)	6 (7.2%)	0.91
Pre infarction pain		28 (23.9%)	17 (20.5%)	0.56
Antithrombotics	Antiplatelets	51(43.6%)	38(45.8%)	0.75
	Anticoagulants	2(1.7%)	7(8.4%)	**0.02**
	Both	0 (0.0%)	6 (7.3%)	**0.03**
PTB time (minutes)		151.28 (±42.05)	116.99 (±43.16)	**<0.001**
Door to balloon time (minutes)		34.99 (±3.09)	35 (±3.06)	0.98
Clinical examination				
SBP (mmHg)		133.55 (±27.03)	137.23 (±18.81)	0.25
DBP (mmHg)		80.73 (±9.766)	85.30 (±11.7)	**0.003**
HR (bpm)		90.89 (±13.36)	86.40 (±11.6)	**0.01**
BMI (kg/m2)		33.50 (±6.36)	32.72 (±6.36)	0.39
Killip class	I	75(64.1%)	66(79.5%)	0.13
	II	29(24.8%)	12(14.5%)	
	III	11(9.4%)	4(4.8%)	
	IV	2(1.7%)	1(1.2%)	
	Mean	1.49±0.73	1.28±0.61	**0.03**

BMI: Body mass index, CABG: Coronary artery bypass graft, CAD: Coronary artery disease, CVD: Cardiovascular disease, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HR: Heart rate, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, PTB: Pain to balloon time, SBP: Systolic blood pressure, SD: Standard deviation.

Electrocardiography

There was insignificant difference regarding STEMI localization between both groups. Also, the ST-elevation score index was comparable between both groups (Table 2).

Laboratory tests

Group A patients showed significantly higher red cell distribution width (RDW), total leukocytic count (TLC), neutrophil-lymphocyte ratio (NLR), troponin, creatine kinase (CK)-total and CK-myocardial band (MB) (Table 2).

Table (2): Comparing electrocardiography and laboratory investigations between both groups

		High thrombus burden n= 117	Low thrombus burden n= 83	p value
		Mean/frequency (SD/%)	Mean/frequency (SD/%)	
ECG				
ST elevation score index		3.51±1.26	3.38±1.15	0.42
STEMI localization	Anterior	69(59%)	56(67.5%)	0.22
	Non-anterior	48(41%)	27(32.5%)	
Laboratory investigations				
Platelet count (10*3)		238.75±40.34	239.95±37.44	0.83
Hemoglobin (g/dl)		12.99±1.55	13.32±1.17	0.09
RDW (%)		18.99±1.55	14.03±1.52	**<0.001**
TLC (10*3)		12.50±1.18	11.00±1.52	**<0.001**
Lymphocyte (10*3)		2.61±0.53	2.86±0.18	0.15
Neutrophil (10*3)		9.22±2.21	8.24±1.86	0.07
NLR		5.93±1.39	4.08±0.93	**<0.001**
Troponin (ng/ml)		94.91±22.98	50.06±12.23	**<0.001**
CK-MB (IU/L)		39.89±4.99	29.02±5.26	**<0.001**
CK-total (IU/L)		313.41±43.23	245.18±47.27	**<0.001**
Creatinine (mg/dl)		1.34±0.32	1.29±0.31	0.34
Creatinine clearance (ml/minute)		77.28±9.21	78.22±9.30	0.75

Coronary angiography and intervention

Group A was more associated with proximal segment lesions, especially proximal LAD lesions, while group B was more associated with mid-segment lesions, especially mid LAD lesions. Group A patients significantly underwent more thrombus aspiration, PTCA using larger balloon diameter, moreover they underwent coronary stenting using longer stents. On comparing the post-procedural TIMI flow, group A had significantly lower post-procedural TIMI flow and a higher incidence of TIMI flow less than 3 (Table 3).

Table (3): Comparison of coronary angiographic findings between both groups

		High thrombus burden n= 117	Low thrombus burden n= 83	p value
		Mean/frequency (SD/%)	Mean/frequency (SD/%)	
Coronary angiography				
Thrombus grade		Grade 4 = 42(21%) Grade5=75(37.5%)	Grade 1 = 24(12%) Grade 2 = 20(10%) Grade 3=39(19.5%)	
Culprit lesion vessel	LAD	70(59.8%)	61(73.5%)	0.12
	LCX	11(9.4%)	6(7.2%)	
	RCA	36(30.8%)	16(19.3%)	
Lesion site	Proximal	60(51.3%)	38.6%	**0.006**
	Mid	35(29.9%)	51.8%	
	Distal	22(18.8%)	9.6%	
Thrombus aspiration		19(16.2%)	0(0%)	**<0.001**
PTCA		117(100%)	72(86.7%)	**<0.001**
Balloon diameter		1.9±0.32	1.7±0.73	**0.02**
Stent length		31.34 ± 12.65	27.9 ±11.6	**0.004**
Post-procedural TIMI flow	TIMI 0	2(1.7%)	0(0%)	**<0.001**
	TIMI 1	32(27.4%)	3(3.6%)	
	TIMI 2	31(26.5%)	9(10.8%)	
	TIMI 3	52(44.4%)	71(85.5%)	
	TIMI <3	65(55.6%)	12(14.5%)	**<0.001**
	TIMI =3	52(44.4%)	71(85.5%)	

Correlations and independent predictors of thrombus grading

On studying the correlation of thrombus grading with different variables, it had weak positive correlation with age, hypertension, number of CVD risk factors (Figure 1), Killip class and ST-elevation score index. And it had moderate positive correlation with PTB time (Figure 2), TLC, troponin, CK-total, CK-MB and NLR (Figure 3), while it had a strong positive correlation with RDW (Figure 4). However, it showed a moderate negative correlation with post-procedural TIMI flow (Figure 5). Table 4 shows these data.

Table (4): Correlations of thrombus grading

Variable	rho	p value
Age	0.16	**0.02**
Hypertension	0.14	**0.04**
Number of CVD risk factors	0.25	**<0.001**
PTB time	0.45	**<0.001**
Previous CABG	0.04	0.53
Previous MI	0.07	0.28
Previous PCI	0.02	0.79
Pre infarction pain	0.08	0.25
Killip class	0.21	**0.003**
BMI	0.001	0.98
ST elevation score index	0.18	**0.009**
Platelet count	0.06	0.39
Hemoglobin	-0.06	0.32
RDW	0.87	**<0.001**
TLC	0.44	**<0.001**
NLR	0.56	**<0.001**
Troponin	0.6	**<0.001**
CK-MB	0.66	**<0.001**
CK-total	0.53	**<0.001**
TIMI flow	-0.44	**<0.001**

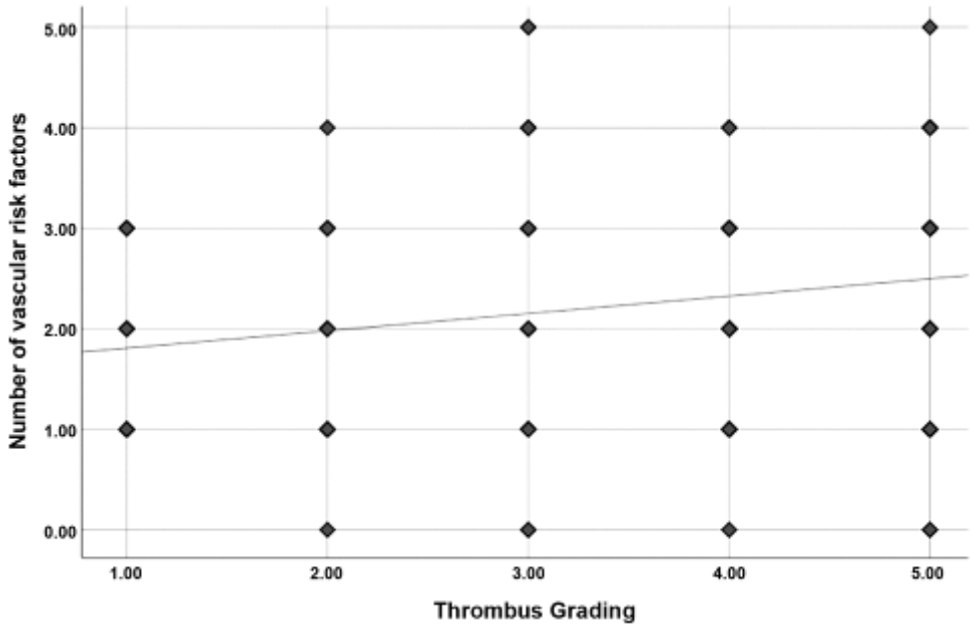

Figure (1): Correlation between number of cardiovascular risk factors with thrombus grading

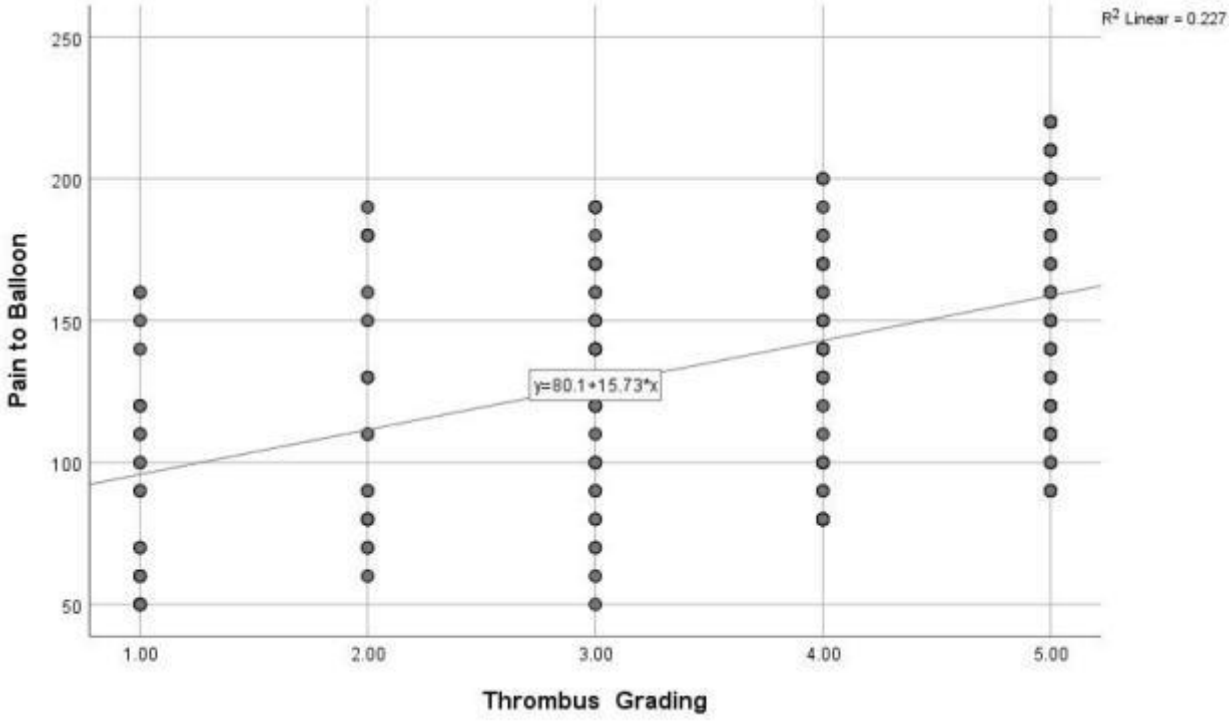

Figure (2): Correlation between pain to balloon time with thrombus grading

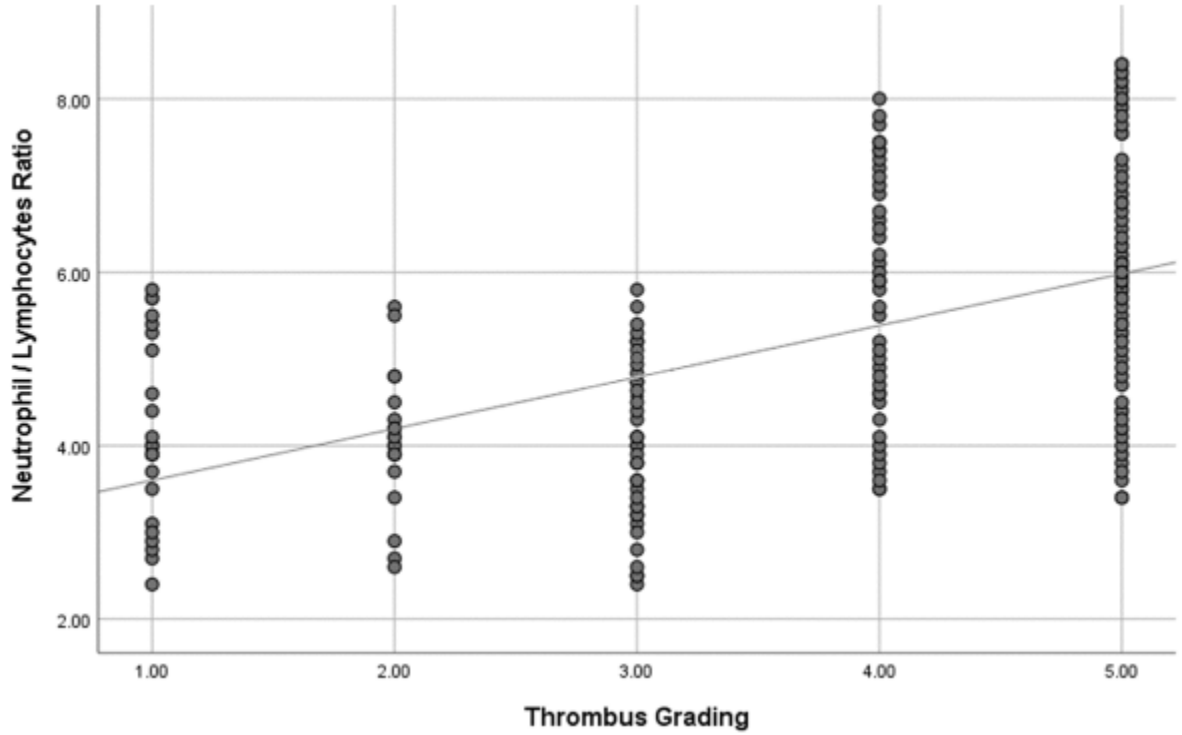

Figure (3): Correlation between neutrophil-lymphocyte ratio with thrombus grading

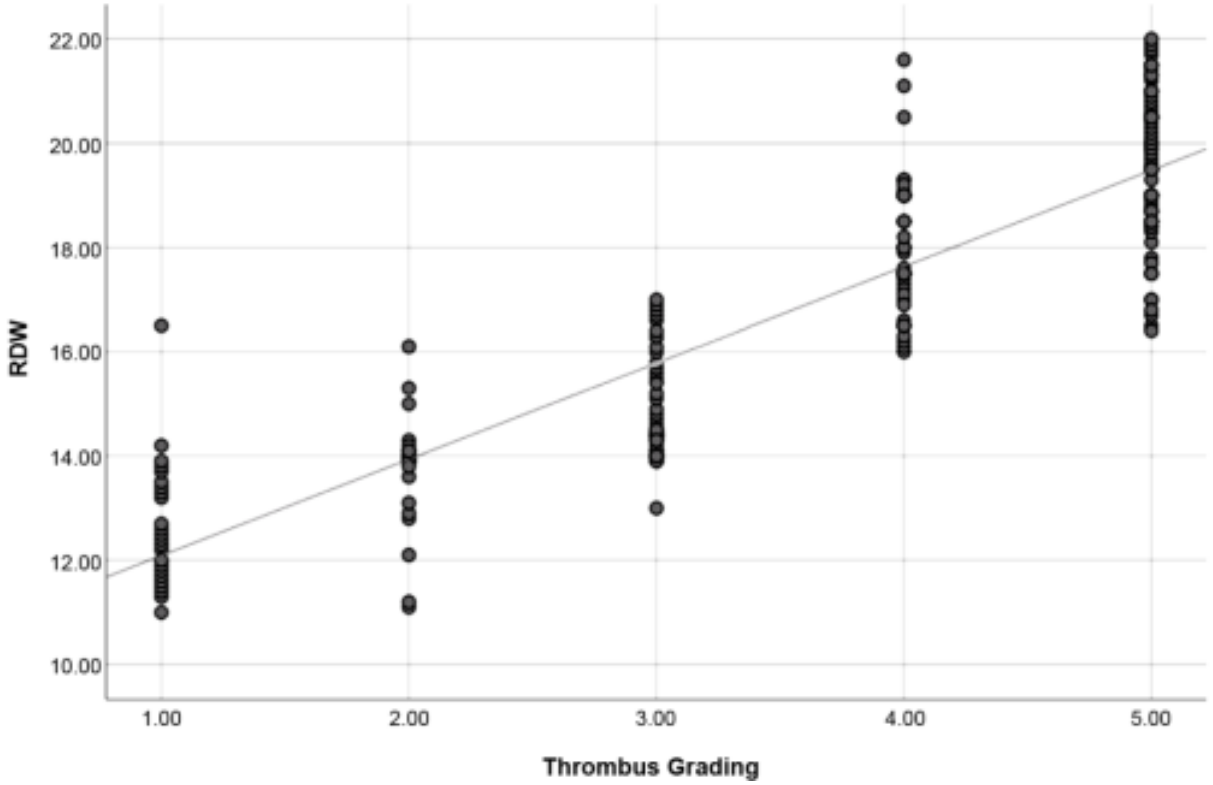

Figure (4): Correlation between red cell distribution width with thrombus grading.

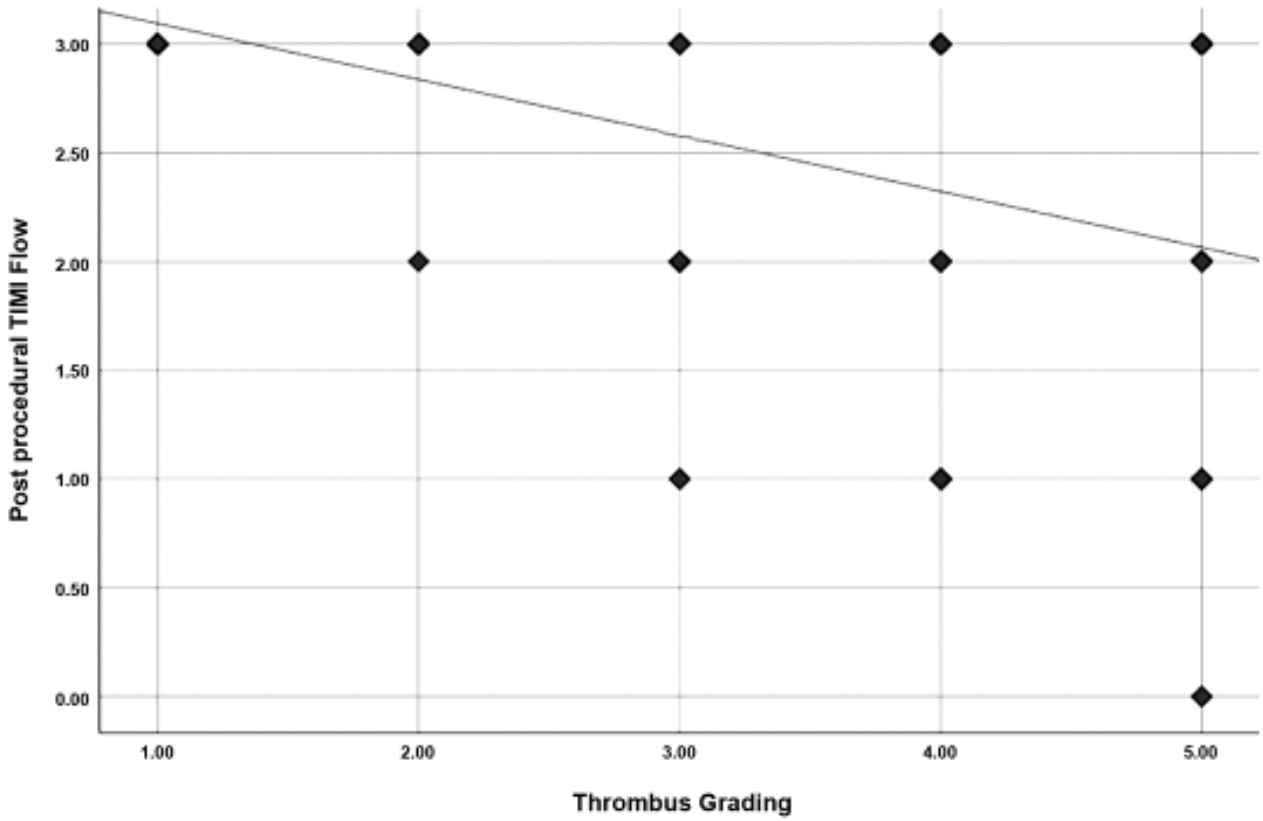

Figure (5): Correlation between post-procedural TIMI flow with thrombus grading

Ordinal regression analysis showed that independent predictors of high thrombus grade are RDW, NLR, number of CVD risk factors, and PTB time (Table 5). ROC curve analysis identified RDW best cut-off value of 16 % to predict high thrombus burden with sensitivity of 99%, specificity of 88%, area under the curve of (0.99), while NLR best cut-off was 4.55 with sensitivity of 80%, specificity of 69%, and area under the curve of (0.85) (Figure 6).

Table (5): Independent predictors of high thrombus grade

Variable	Estimate	Odds ratio	p value
Age	0		0.91
Number of CVD risk factors	0.48	1.62	**0.01**
PTB time	0.02	1.02	**<0.001**
Killip class I	-1.06		0.5
Killip class II	0.01		0.99
Killip class III	-1.19		0.47
Killip class IV	0a		
ST elevation score index	0.27		0.08
RDW	1.40	4.06	**<0.001**
TLC	0.24		0.1
NLR	0.30	1.35	**0.04**
Troponin	0.01		0.3
CK-MB	0.02		0.6
CK-total	0		0.2

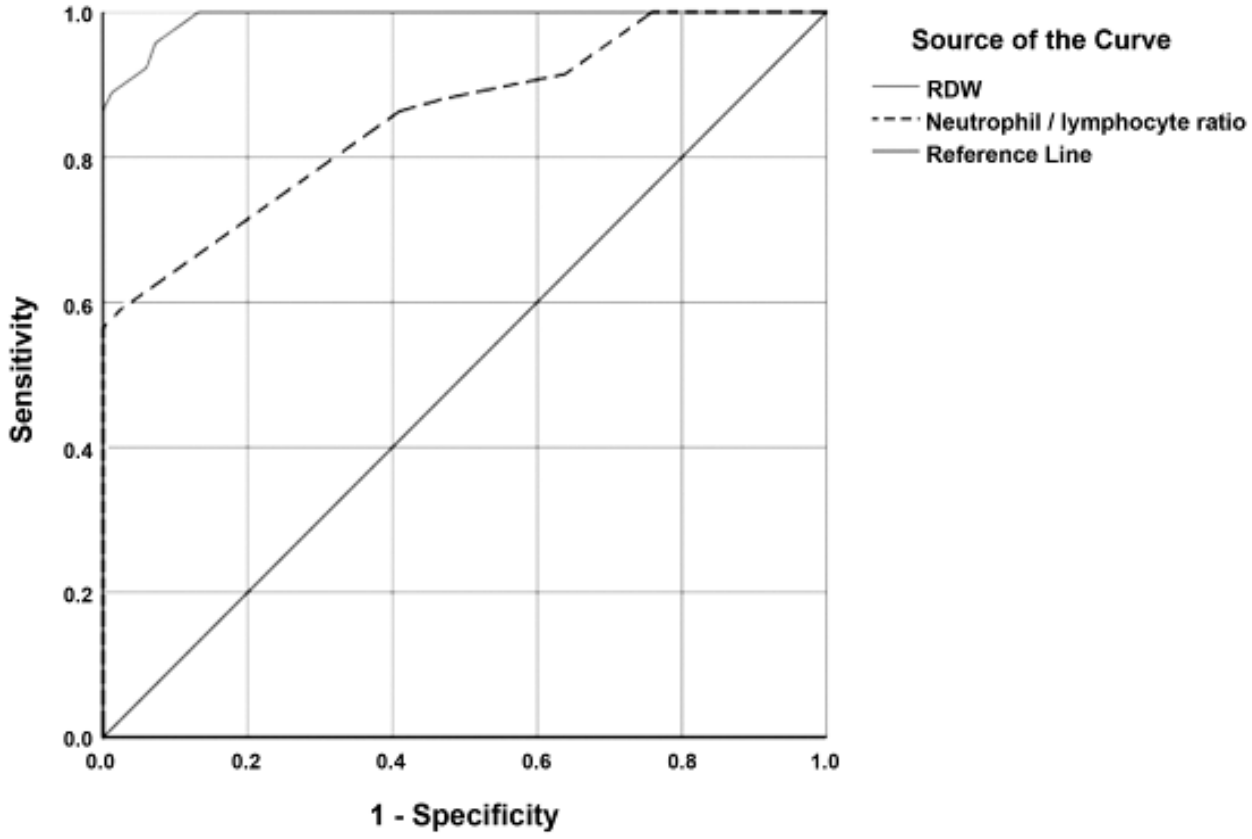

Figure (6): Best cut-off values of red cell distribution width and neutrophil-lymphocyte ratio to predict a high thrombus burden

DISCUSSION

A large thrombus load is an independent predictor of no-reflow, severe adverse cardiac events, and death with initial PCI for STEMI [7,16,17].

The current study showed that RDW and NLR could predict independently high thrombus burden. RDW was surprisingly identified as the most powerful independent predictor of thrombus grade. Previous studies concluded that RDW is an independent predictor of thrombus grade with a cut-off value of 14% [18,19]. While the best cut-off value was 16% in the current study having higher sensitivity and specificity. The relationship between RDW and mean corpuscular volume may explain this finding, as the number of smaller RBCs increases with aging resulting in increased RDW [20].

In the elderly, these smaller RBCs have lower plasticity and a higher risk of adherence to endothelium forming thrombi. Also, RDW is related to some inflammatory markers and enhances angiotensin II 1a receptor activation increasing the risk of unstable plaques [19,21,22].

Also, the NLR independently predicted high thrombus grade, and NLR above 4.55 could predict a high thrombus burden. According to **Yilmaz and his colleagues**[23] study, patients with a significant amount of thrombus likely to have a larger proportion of neutrophils. Leukocyte activation is expected to result in oxygen free radicals and proteolytic enzymes that have an adverse effect on nearby RBCs at thrombus locations [24]. The interaction between neutrophils and erythrocytes causes neutrophils to have an impact on thrombus components and raise thrombus load.

The current study's therapeutic relevance is that RDW and NLR could help in early identification of high-thrombus burden patients that may improve their treatment. As no-reflow has not had optimum management yet, its prevention may be more valuable than its treatment. Many trials have discussed the value of using glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors, thrombus aspiration, and deferred stenting in the presence of a large load of thrombi to lessen no-reflow and thrombotic distal embolisation [4].

The bleeding risk of using routine GP IIb/IIIa inhibitors outweighs their benefit, so they are recommended as a bailout therapy in the presence of a high thrombus burden, either intravenous or intracoronary [4,25]. Also, their use is the most beneficial intervention in case of no-reflow [26]. As for thrombus aspiration, increased risk of stroke in the TOTAL trial led to avoidance of its routine use, and subgroup analysis showed that most of its patients had had a high thrombus burden [27,28]. However, it may be of value in case of a high thrombus burden [29]. Also, despite the decreased incidence of no-reflow with deferred stenting strategy, it was associated with increased revascularization [30].

Based on the evidence of GP IIb/IIIa inhibitors in dealing with a high thrombus burden, the early prediction of a high thrombus burden may give a chance for reconsidering upstream use of GP IIb/IIIa inhibitors.

STUDY LIMITATIONS

This study focused on predictors of high thrombus burden rather than no-reflow, so it did not involve MBG as a measure of no-reflow.

CONCLUSIONS

The current study showed that CVD risk factors number, PTB, NLR, and RDW could independently predict high thrombus grade. Rapid identification of RDW above 16% or NLR above 4.55 in the emergency room in patients with STEMI could predict a high thrombus burden in coronary angiography. Also, it showed that patients with a high thrombus burden had lower post-procedural TIMI flow, less than 3, denoting non-successful epicardial reperfusion.

- **Conflict of Interest:** The authors affirm that they do not have any interests that conflict.
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