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D-dimer level estimation for prediction of in hospital adverse outcome after primary percutaneous coronary intervention for St-segment elevation myocardial infarction

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Abstract
Background: D-dimer is a fibrin degradation product that is commonly used as a biomarker to assess the presence of thrombotic activity in various clinical settings. While D-dimer is primarily associated with the diagnosis of venous thromboembolism, aortic dissection and peripheral artery diseases. This trial aimed to evaluate whether the level of D-dimer can predict in-hospital adverse outcome following primary PCI for STEMI.
Patients and Methods: This was a prospective work was performed at Cardiology department on Two hundred participants who assigned into two groups. Group 1: involved 150 participants with normal level D-dimer <0.5 mg/l and Group 2: involved 50 participants with increased D-dimer level >0.5 mg/ l
Results: A substantially more participants presented with reduced LVEF in group (2) in comparison with group (1). D-dimer and peak troponin were substantially greater in group (2) in comparison with group (1). There were substantially more patients presented with No-reflow in group (2) in comparison with group (1) 36% vs 18% respectively. There was long hospital stay in group (2) contrasted to group (1). D-dimer level was substantially higher among individuals with MACE as contrasted to individuals without MACE 1.46 vs 0.5 respectively.
Conclusion: An elevated D-dimer levels had been shown to be an independent factor of risk for MACE during hospitalization among individuals with STEMI who received primary PCI, this includes cases with no-reflow and angiographically evident thrombus (AET). The cutoff value was 0.6 mg/l.

Keywords: Coronary intervention, D-dimer, St-segment elevation myocardial infarction

Introduction
D-dimer soluble fragments, which are produced from fibrin, offer guidance about the level of coagulation, the occurrence of fibrinolysis, and the presence of thrombosis in conditions including venous thromboembolism (VTE), aortic dissection (AD), or peripheral artery disease (PAD) [1, 2].
While the levels of plasma D-dimer may be elevated in individuals with acute myocardial infarction (AMI), its value as a biomarker of diagnosis for AMI is still a subject of debate [3]. This is in part due to the fact that the degree of rupture of plaque and thrombosis in the coronary arteries in AMI is relatively smaller contrasted to that seen in AD and VTE [4].
The correlation between elevated plasma D-dimer levels in those suffering from AMI and the occurrence of post-interventional coronary no-reflow phenomenon has been established [5], This phenomenon is recognized to be correlated with a poor prognosis following STEMI [6], However, studies investigating the correlation between levels of D-dimer and prognosis in individuals with STEMI have produced conflicting results [7].
Throughout primary percutaneous coronary intervention (PPCI), certain patients with STEMI exhibit angiographically evident thrombus (AET) and experience no-reflow phenomenon. However, the potential of elevated D-dimer levels for predicting bad outcomes in this specific subgroup hasn't been studied [8]. This study assessed the potential correlation between elevated levels of D-dimer and prognosis in individuals with STEMI.

The purpose of this work is to assess whether levels of D-dimer can anticipate in-hospital adverse outcome following primary PCI for those suffering from STEMI.

Patients and Methods

200 participants that meet the criteria for eligibility had been enrolled from the Cardiology department in Tanta University and Shebin El Koum Teaching Hospital. Come with acute STEMI, the participants had been assigned into two groups based on D-dimer level.

Group 1: involved 150 participants with normal level of D-dimer <0.5 mg/l and Group 2: involved 50 participants with increased D-dimer level >0.5 mg/ l.

This work was performed in a six-month period starting from April 2022.

Inclusion criteria

All STEMI patients who were eligible for PPCI: participants have symptoms of continuous typical pain in the chest with a duration exceeding 30 minutes, accompanied with elevation of ST-segment of no less than 2 mm in two adjacent electrocardiography (ECG) leads within 12 hours after the start of symptoms, or within 24 hours. In the event that there was proof of ongoing ischemia or unstable hemodynamics.

Exclusion criteria

Aortic dissection, historical background of coronary artery bypass graft surgery (CABG) Adverse events such as death or hemorrhagic stroke occurred prior to the implantation of the stent throughout the surgery. Percutaneous trans-luminal coronary angioplasty (PTCA) is performed without implantation of stents in cases where the artery is narrow or there is a heavy burden of thrombus. Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA), VTE, Hypercoagulable state, Pregnancy and Patients reperfused with thrombolytic therapy.

Methods

The patients were subjected to

All participants provided a well-informed consent, Full taking of history, Full clinical examination (Vital signs, General, Local cardiac examinations and Resting 12 leads ECG Standard) and laboratory investigation.

Laboratory tests

That includes D-dimer using integra device and Roche kits by immunoturbidimetric method and fibrinogen equivalent units (FEU), in our study D-dimer was measured before PPCI. Serum creatinine and cardiac enzymes (troponin I) also was measured before PPCI.

Preparation before primary PCI: A loading dose of dual anti-platelet (Aspirin 300 mg chewable) plus P2Y12 inhibitor (Ticagrelor 180 mg or Clopidogrel 600 mg), plus IV unfractionated heparin (UFH) or low molecular weight heparin (LMWH) were used before the procedure. Glycoprotein IIbIIIa inhibitors (Eptifipatide or Tirofiban) were used during or after the procedure in selected cases [9].

Imaging

Left coronary imaging: A contrast injection in the left coronary cusp is a reasonable first step to define the ostium of the left main (LM) coronary artery, an antero-posterior (AP) view or a shallow right anterior oblique (RAO) caudal view may be useful to evaluate middle and distal LM coronary artery stenosis.

Right coronary imaging

The RCA should be approached in the 30-degree LAO projection.

Echocardiography

Measuring of left ventricular ejection fraction (LVEF) performed utilizing the Simpson method, as outlined in the 2015 guidelines provided by the European Association of Cardiovascular Imaging and the American Society of Echocardiography. This approach is utilized to quantify cardiac chamber size for adults via echocardiography.

Follow up was done during admission to detect in-Hospital MACES

MACES is defined as Cardiac arrest, Death, Re-infarction, Re-intervention for revascularization and Stroke.

Statistical analysis of the data

The computer received data and processed it utilizing the IBM SPSS software version 20.0. (IBM Corp, Armonk, NY). Quantitative data were expressed utilizing numerical values and percentages. The Kolmogorov-Smirnov test has been employed to validate the normality of the distribution. The quantitative data were characterized through different statistical measures, including the range (minimum and maximum), median, and interquartile range (IQR), mean, standard deviation. The significance of the obtained results was judged at the 5% level.

The used tests were

The chi-square test is utilized for contrasting qualitative data in both sets for categorical variables. either Fisher's Exact test or Monte Carlo correction can be used. Correction for the chi-square test is necessary when the predicted count in over 20 percent of the cells is below 5, The Student t-test is used for contrasting the mean of two sets that have normally distributed quantitative parameters. The Mann-Whitney test is used for contrasting two investigated groups when the quantitative parameters are not normally distributed. The Receiver Operating Characteristic curve (ROC): The graph is created by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values.

Results

No statistically substantial variation was existed among both groups based on demographic characteristics. Table 1.

Table 1: Comparison between the both groups under the study based on demographic data

	Group 1 (n = 150)		Group 2 (n = 50)		Test of Sig.	P
	No.	%	No.	%		
Gender						
Male	130	86.7	40	80.0	$\chi^2 = 1.307$	0.253
Female	20	13.3	10	20.0		
Age (years)						
Min.-Max.	37.0-70.0		36.0-72.0		t = 0.261	0.795
Mean ± SD.	56.84±6.34		57.16±7.87			
Median (IQR)	58.0 (53.0-61.0)		58.0 (50.0-62.0)			
BMI						
Over weight/ obese	80	53.3	28	56.0	$\chi^2 = 0.107$	0.743
Ideal body weight	70	46.7	22	44.0		

SD: Standard deviation, IQR: Inter quartile range, 1.Chi square test, t: Student t-test p: p value for comparing between both groups under the study, Group 1: D-dimer < 0,5, Group 2: D-dimer > 0,5

No statistically substantial variation was existed among the two groups according to comorbidity. Table 2.

Table 2: Comparison between both groups under the study based on comorbidity

Comorbidity	Group1(n=150)		Group2(n =50)		χ^2	P
	No	%	No	%		
Hypertension	93	62.0	36	72.0	1.638	0.201
DM	77	51.3	19	38.0	2.671	0.102
Hyperlipidemia	69	46.0	26	52.0	0.541	0.462
Smoking	101	67.3	26	52.0	3.804	0.051
Family history of premature CAD	40	26.8	22	44.0	5.136	0.023*

IQR: Inter quartile range, SD: Standard deviation, 1.Chi square test, t: Student t-test p: p value for comparing between both groups under the study, Group 1: D-dimer < 0,5, Group 2: D-dimer > 0,5

A substantially more participants presented with cardiogenic shock in group (2) as compared to group (1) 26% vs 6% respectively with p value <0.001. A substantially more participants presented with acute heart failure in group (2) as compared to group (1) 36% vs 8% respectively with p value <0.001. There were substantially more participants presented with cardiac arrest in group (2) as contrasted to group (1) 20% vs. 2.7% respectively with p value <0.001. There were significantly more patients survived from cardiac arrest in group (1) as contrasted to group (2) 50%vs 10% respectively with p value <0.001. Table 3.

Table 3: Comparison between both groups under the study based on clinical presentation

	Clinical presentation	Group 1 (n = 150)		Group 2 (n = 50)		χ^2	P
		No.	%	No.	%		
Cardiogenic shock	No	141	94.0	37	74.0	15.322*	<0.001*
	Shocked	9	6.0	13	26.0		
Acute heart failure	No	138	92.0	32	64.0	23.059*	<0.001*
	Yes	12	8.0	18	36.0		
Cardiac arrest at admission.	No	146	97.3	40	80.0	17.307*	<0.001*
	Yes	4	2.7	10	20.0		

2: Chi square test, p: p value for comparing between both groups under the study.
*: Statistically significant at $p \leq 0.05$, Group 1: D-dimer < 0,5, Group 2: D-dimer > 0,5

A substantially more participants presented with anterior STEMI in group (2) contrasted to group (1) 62% vs. 39% with p value 0.005. Table 4.

Table 4: Comparison between both groups under study according to ECG

ECG	Group 1 (n = 150)		Group 2 (n = 50)		χ^2	P
	No.	%	No.	%		
Inferior STEMI	61	40.7	14	28.0	2.567	0.109
Anterior STEMI	59	39.3	31	62.0	7.785*	0.005*
Lateral STEMI	24	16.0	4	8.0	1.993	0.158
Posterior STEMI	6	4.0	1	2.0	0.444	FEp=0.683

x2: Chi square test, p: p value for comparing between both studied groups.
Statistically significant at $p \leq 0.05$, Group 1: D-dimer < 0,5, Group 2: D-dimer > 0,5

D-dimer and peak troponin were substantially greater in group (2) contrasted to group (1) with p value <0.001. Table 5.

Table 5: Comparison between the both under study based on Labaratory testes

	Labs	Group 1 (n = 150)	Group 2 (n = 50)	Test of Sig.	P
D-dimer	Min. Max.	0.10-0.70	0.80-2.70	U=0.0*	<0.001*
	Mean ± SD.	0.43±0.15	1.24±0.53		
	Median (IQR)	0.40 (0.30-0.60)	0.90 (0.80-1.40)		
Peak Troponin	Min.-Max.	16.10-34.30	23.70-40.0	t=14.578*	<0.001*
	Mean ± SD.	21.32±3.99	32.77±5.06		
	Median (IQR)	20.40 (18.40-23.70)	32.60 (28.60-37.80)		
Cretinine	Min.-Max.	0.80-1.70	0.80-1.50	t=1.147	0.253
	Mean ± SD.	1.26±0.19	1.22±0.20		
	Median (IQR)	1.25 (1.10-1.40)	1.20 (1.10-1.40)		

IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, U: Mann Whitney test, p: p value for comparing between both groups under the study.
*: Statistically significant at $p \leq 0.05$

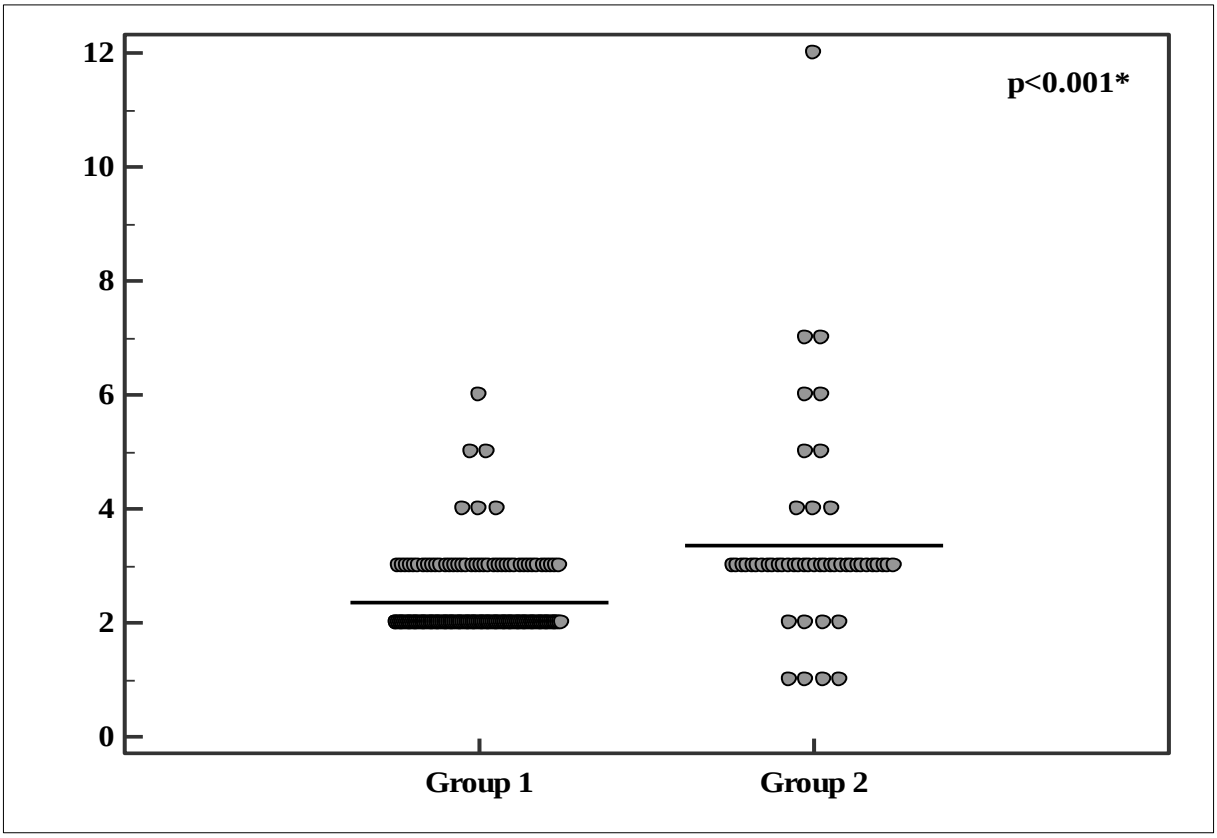

Fig 1: Comparison between both groups under study based on duration of hospital stay

D-dimer level was substantially higher in individuals with MACE as contrasted to individuals without MACE 1.46 vs 0.5 correspondingly ($p< 0.001$). Table 6.

Table 6: Relation between MACE and D-dimer (n= 200)

D-dimer	MACE		U	P
	No (n= 182)	Yes (n= 18)		
Min. Max.	0.10-1.89	0.40-2.70	419.0*	0.001*
Mean ±SD.	0.55±0.31	1.46±0.79		
Median	0.50	1.35		

We plotted ROC curve to assess the capability of D-dimer for predicting MACE, as demonstrated in Figure 2. The area of D-dimer under curve was 0.872 and the best cut off value was 0.6 with sensitivity 83.33% and specificity 73%.

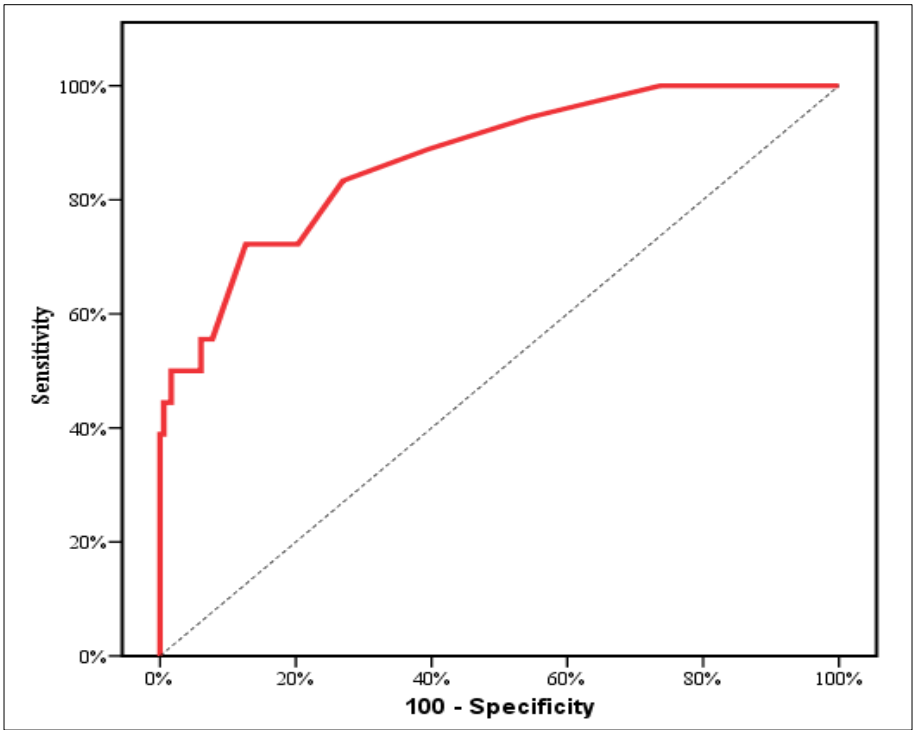

Fig 2: ROC curve for D-dimer for predicting MACE

Table 7: Prognostic performance for D-dimer to predict MACE

	AUC	P	95% C. I	Cut off	Sensitivity	Specificity	PPV	NPV
D-dimer	0.872	<0.001*	0.785-0.960	0.6	83.33	73.08	23.4	97.8
				0.8	72.22	87.36	36.1	97.0

AUC: Area Under a Curve, p value: Probability, value CI: Confidence Intervals, NPV: Negative predictive value, PPV: Positive predictive value, *: Statistically significant at $p \leq 0.05$

Case Scenario

Case number: 1.

Identification number: 64.

Male patient aged 64 years old. Known to be diabetic, not hypertensive. No previous cardiac history. However, he is a heavy smoker who smokes 20 cigarettes per day. He presented to Cardiology Department complaining of typical chest pain and sweating lasting approximately 3hours before presentation.

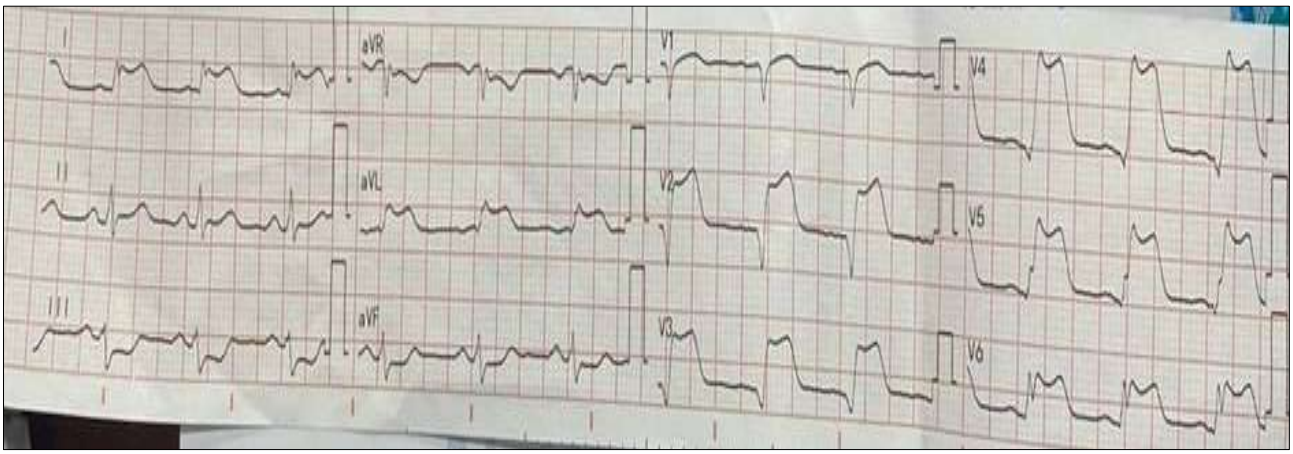

Fig 3: ECG show extensive anterior STEMI with ST segment elevation fromV1 toV6, I and AVL leads.

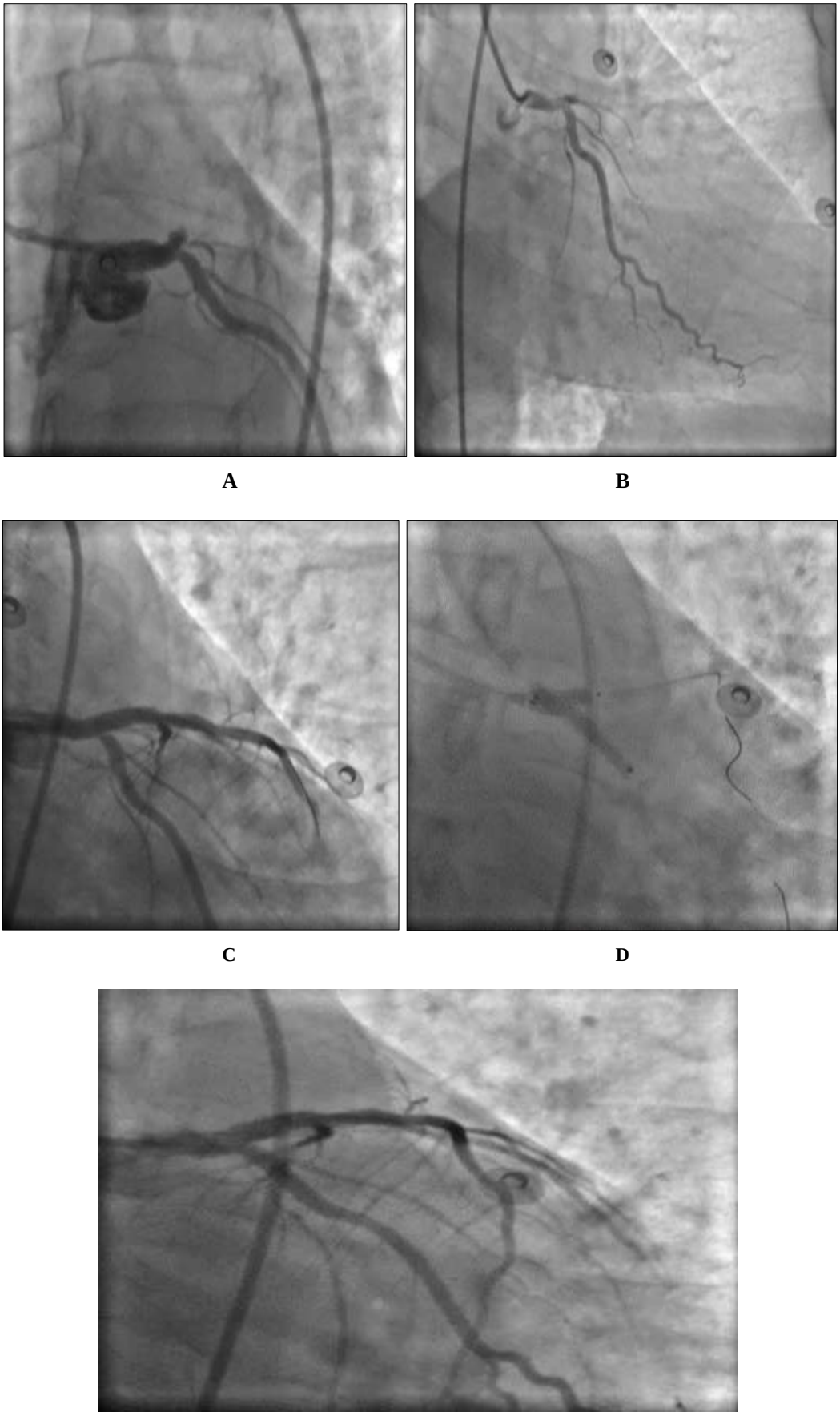

Fig 4: Acase of acute anterior STEMI (A):LAD proximal total occlusion (B) Distal L.M bifurcational lesion and total occlusion of LAD (C) PCI to LAD with DES with TIMI II (D) Bifurcational PCI to LM-LAD and LCX (E) Successful bifurcational PCI

Discussion

The plasma D-dimer levels is raised in certain individuals with AMI, but its value as a biomarker of diagnosis for AMI is still a subject of debate [3]. The reason for this is that the size and variety of ruptured plaque and thrombosis in the coronary arteries are relatively limited comparable to those seen in AD and VTE [4].

An elevated D-dimer levels may suggest a less stable blood clot structure and increased vulnerability to breakdown [10]. Thrombotic particles are formed after interventions on coronary arteries as a result of the fragmentation of components in the culprit lesion [11].

Regarding the demographics in this study There were significantly more male patients in both groups and This finding aligns with a work performed by Vaidya *et al.*, where the incidence of MI was five times higher in males compared to females in the studied population. Furthermore, this aligns with the findings of the AHA statistics annual revision released by Mozaffarian *et al.*, which concluded that the occurrence of STEMI is higher in men compared to women [12].

Regarding major adverse outcome during hospital admission In this study, 9% had in-hospital MACE but in a work performed by D. Huang *et al.* were 3.5%. The percentage of MACE in group 1 with normal d-dimer was 3.3% compared with group 2 with increased d-dimer was 26%.

Among those suffering from STEMI who received primary PCI, there is a positive relationship between increased levels of D-dimer and higher peak Troponin levels, reduced EF% and longer hospital stay. This came in agreement by D. Huang *et al.* [13].

In this work, the relation between D-dimer and MACE was during hospitalization but in HORIZONS-AMI study was within 3 years follow-up.

D-dimer assays exhibit significant variability in terms of the antibody utilized, capture method, needed instrumentation, and calibration standard [14].

In this study, the level of D-dimer was shown to be a substantial indicator of MACE occurring during hospitalization. MACE includes cardiac mortality, non-fatal AMI, revascularization, and stroke. The study specifically focused on patients with STEMI who received primary PCI. This finding was corroborated by Akgul *et al.* [5] and D. Huang *et al.* [13].

The development of the no-reflow phenomenon throughout PPCI intervention, which is correlated with AET and an unstable plaque, is indicative of a poor prognosis for patients with STEMI.

In the current investigation, the incidence of no-reflow was found to be 22%. The factors of risk associated with this condition were AET and a lower EF%. Oduncu *et al.* [15] established that levels of D-dimer upon admission was a reliable indicator of the likelihood of no-reflow following PCI, regardless of other factors. One of the most significant reasons contributing to no-reflow is a large thrombus burden.

The levels of D-dimer show a strong correlation with the amount of blood clot present in instances of venous thrombosis and acute pulmonary embolism [16]. In addition to the size of the blood clot, the chemical composition of the clot may also affect the delicate equilibrium between clot dissolution and the movement of clot fragments to distant areas.

A positive relationship was existed among D-dimer levels and lysis time in individuals who suffering from acute coronary syndrome (ACS) [17]. Therefore, increased levels of D-dimer may indicate a thrombus burden that is more susceptible to lysis, thereby increasing the chances of distal embolization.

Increased levels D-dimer have been proposed to indicate a widespread tendency for blood clot formation and the development of fibrin in the walls of certain blood vessels, which is associated with unstable activity of atherosclerotic plaque [18].

In an investigation using cardiac magnetic resonance imaging, researchers examined the relationship between the size of MI and the level of D-dimer in 208 individuals who received primary PCI for STEMI. They found that greater of D-dimer levels upon admission had been linked to a larger size of MI, a greater area at risk, and a decreased myocardial salvage index [19]. This suggests that D-dimer is an independent factor of risk for negative outcomes.

Limitations of the study

The work had certain inherent limitations, including a small sample size and a restricted observation period limited to the duration of the patients' hospitalization. Consequently, further investigation is necessary to analyze the long-term prognosis.

Conclusion

In this prospective work, increased levels of D-dimer were found to be an independent factor of risk for MACE during hospitalization among individuals with STEMI who received PPCI, which includes individuals with AET and no-reflow. The cutoff value was 0.6 mg/l

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Not available.

Author's Contribution

Not available.

Conflict of Interest

Not available.

Financial Support

Not available.

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