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Clinical and Laboratory Predictors of No-reflow during Primary Percutaneous Coronary Intervention

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ABSTRACT

Background: The phenomenon of no-reflow is defined as the occurrence of areas with very low tissue flow after the target vessel has reopened. Current knowledge suggests that the no-reflow phenomenon is caused by the damage to microvascular integrity established both during ischemia and during reperfusion. D-dimer is the end product of fibrin degradation by plasmin, as plasma concentrations increase in people with persistent or recent thrombosis. Its levels reflect the rate of fibrin turnover and give an indirect estimate of the size of the coagulant mass available for fibrinolysis and the severity of the hypercoagulable condition.

Objective: To investigate the Clinical and laboratory predictors of no-reflow on admission after primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) patients**.**

Patients and methods: A prospective single group observational study. A total of 100 patients presented with STEMI and eligible for primary PCI to the cardiology department in Ain Shams University hospital.

Results: Coronary angiography showed that (74%) had normal flow while (26%) showed no re-flow. Renal impairment, DM and delayed reperfusion (> 4 hr) were significantly associated with no reflow(P-values = 0.018,0.023,0.005) respectively. ROC curve showed that the best cut off point for D-dimer to predict cases with no reflow was found ≥ 560 with sensitivity of 96.15%, specificity of 79.73% and area under curve (AUC) of 86.5% where as the best cut off point for CRP was > 41 with sensitivity of 76.92%, specificity of 64.86% and area under curve (AUC) of 69.8.

Conclusion: Assessment of D-dimer and CRP levels on admission in STEMI patients might independently predicts no-reflow after primary PCI.

Keywords: D-dimer, CRP, No-reflow, STEMI, Primary PCI.

INTRODUCTION

The most important treatment goal for patients presented with STEMI is to maintain an effective and rapid myocardial reperfusion [(1)]. Primary PCI has considerably improved consequences in patients presented with STEMI and subsequently has become the preferred reperfusion approach in such patients [(2–4)]. However, the no-reflow phenomenon considerably decreases the usefulness of PCI treatment in STEMI [(5, 6)].

The phenomenon of no-reflow is clinically significant due to its independent association with elevated inpatient deaths, malignant arrhythmias, and heart failure [(7, 8)]. The phenomenon of no-reflow is associated with long-term poor prognosis due to post-procedure myocardial ischemia [(9)].

The main pathophysiological mechanisms of no-reflow are distal atherothrombotic embolization, ischemia/ reperfusion injury and susceptibility of microcirculation to injury. Previous studies have tested many different therapeutic strategies for the prevention and treatment of no-reflow [(10)]. However the results were inconsistent, possibly due to variable individual contribution of each pathophysiological mechanism in development of no-reflow in different patients.

Therefore, understanding the prevailing mechanisms in the development of no-reflow phenomenon in each individual patient may be important in selecting the most appropriate approach to the prevention and treatment of no-reflow phenomenon. Hence, it is important to define new indicators for each pathophysiological mechanism of no-reflow [(11)]. While some potential predictors of no-reflow phenomenon have been reported, such as the Platelet/lymphocyte ratio and monocyte count [(12)], more predictors are still urgently needed.

D-dimer levels reflect the rate of fibrin turnover and give an indirect estimate of the size of the blood clot mass available for fibrinolysis. It is known that elevated clot burden is associated with no-reflow phenomenon. Therefore, as an indirect estimate of the coagulant burden, the level of D-dimer in the plasma may predict the development of no-reflow phenomenon (13). Though, the data about the prognostic value of D-dimer in patients with acute coronary syndrome has been conflicting [(14)]. The role of admission CRP levels on the prediction of poor myocardial perfusion grades after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) has not been clearly elucidated [(15)]. Thus, we aimed to investigate whether plasma D-dimer and CRP

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levels on admission and other clinical parameters could predict no-reflow after primary PCI in STEMI.

PATIENTS AND METHODS

A prospective single group observational study. A total of 100 patients presented with STEMI and eligible for primary PCI to the cardiology department in Ain Shams University Hospital.

Inclusion criteria: Patients presented with chest pain associated with ECG changes fulfilling criteria for diagnosis of STEMI or elevated cardiac enzymes "elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit" who would be managed by primary PCI.

Exclusion criteria: Patients presented with STEMI after 48 hours from the onset of chest pain. Patients who underwent thrombolytic reperfusion therapy. Hematological disorders. Clinical suspicion of DVT and pulmonary embolism. Liver cell failure. Malignancy. Chronic renal disease on a hemodialysis program. Sepsis. Pregnancy. Patients with prior elevation of D-dimer.

All patients was subjected to the following:
Full history taking and clinical examination.
Surface Electrocardiogram (ECG): **12 lead. Routine laboratory investigation** with special concern to: Serum creatinine. Complete lipid profile. HbA1c. Cardiac enzymes. D-Dimer.

Coronary angiography: to identify their coronary anatomy, the culprit vessel causing the infarction and their thrombolysis in myocardial infarction (TIMI) grade, myocardial blush and TIMI myocardial perfusion (TMP) grade.
According to D-dimer level measured on admission and no-reflow phenomenon the patients were categorized into 4 groups:

- Group I: patient with no-reflow with high level of plasma D-dimer.
- Group II: patient with no-reflow with normal level of plasma D-dimer.
- Group III: patient with TIMI III flow with high level of plasma D-dimer.
- Group IV: patient with TIMI III flow with normal level of plasma D-dimer.

Myocardial reperfusion was judged upon using TIMI grade, Myocardial Blush Grade (MBG) and TIMI myocardial perfusion (TMP) grade [(6)].

No reflow is defined as TIMI flow grade < II or TIMI III with MBG 0 or I and normal reflow was defined as TIMI III flow grade and MBG II or III [(6)].

Ethical Considerations:
The study protocol was approved by the local Ethical Committee of the Faculty of Medicine of Ain Shams University. An informed written consent for accepting the participation in the study was obtained from every participating patient.

Statistical analysis

Data was analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY) and JMP® Version 13.2.1 (SAS© Institute Inc., Cary, NC). Continuous numerical data were presented as mean and standard deviation, range, median, and interquartile range (IQR) and intergroup differences were compared using the unpaired t-test.

Categorical data were presented as numbers and percentages and differences between groups and were compared using chi square or Fisher's exact test. ROC curve was used to assess the cut off value for D-dimer. The probability of error (P-value) at 0.05 was considered significant; while at 0.01 and 0.001 were considered highly significant.

RESULTS

Demographic data of patients' characteristics and risk factors are shown in table (1).

Table (1): Baseline patient characteristics

		No. = 100
Age (years)	Mean ± SD Range	53.33 ± 13.5 25 – 92
Gender	Male Female	86 (86%) 14 (14%)
Smoking	Non smoker Smoker Ex-smoker	47 (47%) 45 (45%) 8 (8%)
Hypertension	Negative Positive	55 (55%) 45 (45%)
Diabetes	Negative Positive	61 (61%) 39 (39%)
Family history	Negative Positive	94 (94%) 6 (6%)
Body mass index (BMI)	Healthy Overweight Obese class	20 (20%) 31 (31%) 49 (49%)
Dyslipidemia	No Yes	61 (61%) 39 (39%)
Previous MI	Negative Positive	74 (74%) 26 (26%)
PVD	Negative Positive	85 (85%) 15 (15%)
Stroke	Negative Positive	90 (90%) 10 (10%)
Reflow groups	No reflow Reflow	26 (26%) 74 (74%)
TIMI flow	TIMI 0 TIMI I TIMI II TIMI III	11 (11%) 7 (7%) 6 (6%) 76 (76%)
MBG grade	MBG 0 MBG I MBG II MBG III	18 (18%) 6 (6%) 2 (2%) 74 (74%)
Renal impairment	Negative Positive	78 (78%) 22 (22%)

The majority of the patients (74%), had reflow, as shown in table (2). Renal impairment, that was significantly higher in no reflow cases. More than half of no-reflow cases were diabetic, and this was significantly higher than reflow cases.

Table (2): Relation of no reflow and normal reflow groups with demographic data and risk factors of the studied patients

		No reflow	Normal Reflow	P-value	Sig.
		No. = 26	No. = 74		
Age (years)	Mean ± SD Range	56.96 ± 12.73 33 – 80	52.04 ± 13.62 25 – 92	0.111	NS
Gender	Male Female	22 (84.6%) 4 (15.4%)	64 (86.5%) 10 (13.5%)	0.813	NS
Smoking	Non smoker Smoker Ex-smoker	14 (53.8%) 12 (46.2%) 0 (0.0%)	33 (44.6%) 33 (44.6%) 8 (10.8%)	0.205	NS
Hypertension	Negative Positive	10 (38.5%) 16 (61.5%)	45 (60.8%) 29 (39.2%)	0.049	S
Diabetes	Negative Positive	11 (42.3%) 15 (57.7%)	50 (67.6%) 24 (32.4%)	0.023	S
Family history	Negative Positive	25 (96.2%) 1 (3.8%)	69 (93.2%) 5 (6.8%)	0.591	NS
BMI	Healthy Overweight Obese class I Obese class II Obese class III	6 (23.1%) 7 (26.9%) 7 (26.9%) 5 (19.2%) 1 (3.8%)	14 (18.9%) 24 (32.4%) 13 (17.6%) 19 (25.7%) 4 (5.4%)	0.805	NS
Dyslipidemia	No Yes	16 (61.5%) 10 (38.5%)	45 (60.8%) 29 (39.2%)	0.948	NS
Previous MI	Negative Positive	18 (69.2%) 8 (30.8%)	56 (75.7% 18 (24.3%)	0.519	NS
PVD	Negative Positive	21 (80.8%) 5 (19.2%)	64 (86.5%) 10 (13.5%)	0.482	NS
Stroke	Negative Positive	23 (88.5%) 3 (11.5%)	67 (90.5%) 7 (9.5%)	0.761	NS
Renal impairment	Negative Positive	16 (61.5%) 10 (38.5%)	62 (83.8%) 12 (16.2%)	0.018	S

There was a statistically highly significant increase in the level of D-dimer in no reflow groups than normal reflow groups. Moreover, there was a highly significant correlation between C-reactive protein (CRP) level with no reflow .There was a significant decrease in the level of hemoglobin in cases with no reflow than those with normal reflow. Also, longer reperfusion time > 4 hours was higher in cases with no reflow than those with normal reflow while early reperfusion (< 4 hr) was associated with a significant reduction in no reflow as shown in table (3).

Table (3): Relation of no reflow and normal reflow groups with different parameters

		No reflow		Normal Reflow		P-value	Sig.
		No. = 26		No. = 74			
D-dimer	Mean ± SD	590.92 ± 135.04		353.66 ± 125.69		0.001	HS
D-dimer groups	D-dimer < 500 D-dimer > 500	3 (11.5%) 23 (88.5%)		52 (70.3%) 22 (29.7%)		0.001	HS
TLC	Median (IQR)	11.60 (9 - 14.3)		10.80 (8.3 - 13.2)		0.191	NS
HB	Mean ± SD	12.46 ± 2.50		13.62 ± 2.25		0.030	S
PLTs	Mean ± SD	280.96 ± 107.03		256.82 ± 76.75		0.219	NS
CRP	Median (IQR)	58.5 (42 – 77)		9 (2.8 – 55)		0.003	HS
CKMB	Median (IQR)	32 (19 - 107)		52.50 (31 - 120)		0.128	NS
Loading	Ticagrelor Clopidogrel	11 15	42.3% 57.7%	47 27	63.5% 36.5%	0.059	NS
Reperfusion time	< 4 hours > 4 hours	7 14	33.3% 66.7%	53 26	67.1% 32.9%	0.005	HS

There was a statistically significant relation between D-dimer level and renal impairment, and CRP level as shown in table (4). Moreover, D-dimer<500 ng/dl was associated with ECG features of successful reperfusion (ST-segment resolution > 70 % from the baseline after 2 hr from PCI) while D-dimer (>500 ng/dl) was associated with ECG features of no-reflow.

Table (4): Relation between D-dimer level and demographic and risk factors of the studied patients

		D-dimer < 500	D-dimer > 500	P-value	Sig.
		No. = 55	No. = 45		
Age (years)	Mean ± SD Range	53.02 ± 14.04 25 – 92	53.71 ± 12.97 28 – 80	0.801	NS
Gender	Male Female	49 (89.1%) 6 (10.9%)	37 (82.2%) 8 (17.8%)	0.325	NS
Smoking	Non smoker Smoker Ex-smoker	21 (38.2%) 27 (49.1%) 7 (12.7%)	26 (57.8%) 18 (40.0%) 1 (2.2%)	0.053	NS
Hypertension	Negative Positive	32 (58.2%) 23 (41.8%)	23 (51.1%) 22 (48.9%)	0.480	NS
Diabetes	Negative Positive	36 (65.5%) 19 (34.5%)	25 (55.6%) 20 (44.4%)	0.313	NS
Family history	Negative Positive	52 (94.5%) 3 (5.5%)	42 (93.3%) 3 (6.7%)	0.800	NS
Dyslipidemia	No Yes	36 (65.5%) 19 (34.5%)	25 (55.6%) 20 (44.4%)	0.313	NS
CRP	Median (IQR)	9 (2.5 – 54)	50.0 (6 – 74)	0.014	S
ST-segment resolution > 70% from baseline	Negative Positive	4 (14.3%) 6 (10.9%)	24 (85.7%) 4 (8.9%)	0.001	HS
Renal impairment	Negative Positive	47 (85.5%) 8 (14.5%)	31 (68.9%) 14 (31.1%)	0.047	S

Moreover there were a highly significant correlations between D-dimer value and TIMI flow, No reflow, and MBG grade (Table 5).

Table (5): Relation of D-dimer level with TIMI flow, Reflow groups and MPG grade

		D-dimer < 500		D-dimer > 500		Test value*	P-value	Sig.
		No.	%	No.	%			
TIMI flow	TIMI 0 TIMI I TIMI II TIMI III	1 1 1 52	1.8% 1.8% 1.8% 94.5%	10 6 5 24	22.2% 13.3% 11.1% 53.3%	23.149	<0.001	HS
Reflow groups	No reflow Reflow	3 52	5.5% 94.5%	23 22	51.1% 48.9%	26.815	<0.001	HS
MBG grade	MBG 0 MBG I MBG II MBG III	2 1 0 52	3.6% 1.8% 0.0% 94.5%	13 5 2 25	28.9% 11.1% 4.4% 55.6%	21.415	<0.001	HS

ROC curve for the relation of no-reflow, TIMI flow and MBG grade, showed that the best cut off value for D-dimer to predict cases with no reflow was found ≥ 560 and the best cut off point for CRP to detect cases with no reflow was found > 41 (Table 6 and Fig. 1).

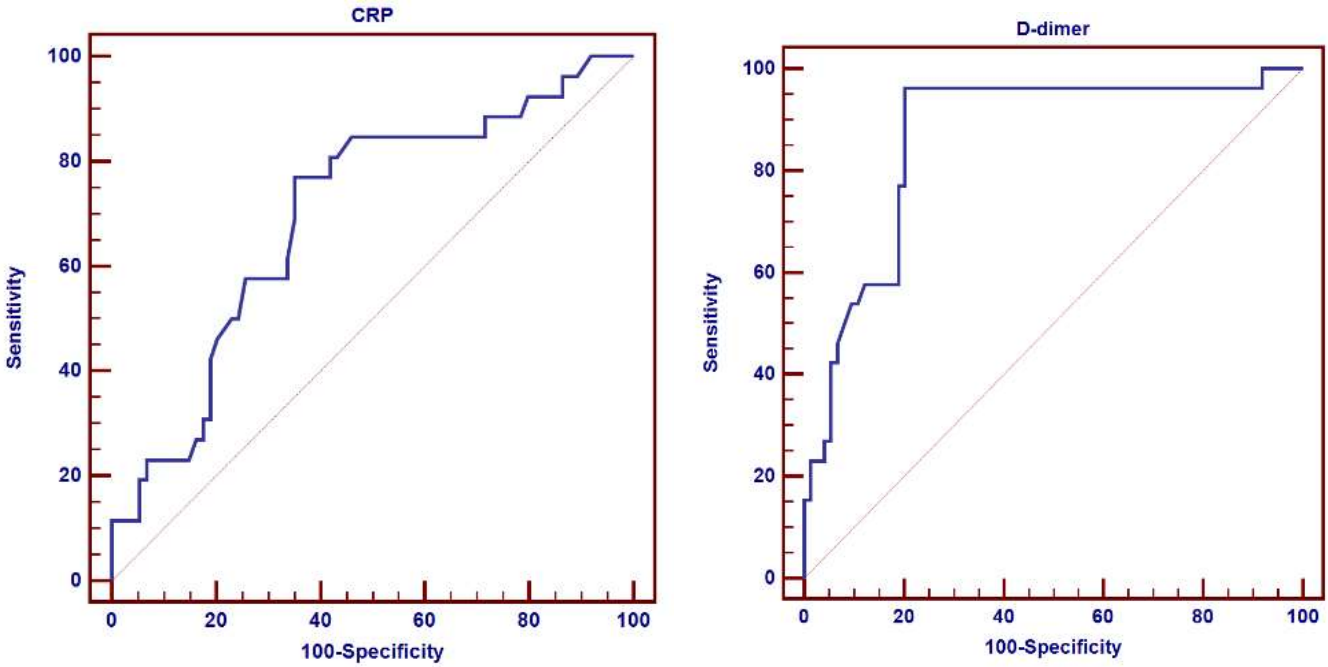

Fig. (1) ROC curves between CRP, D-dimer and no-reflow

Table (6): Cut-off values for D-dimer and CRP to predict no-reflow

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
D-dimer	**0.865**	**>560**	**96.15**	**79.73**	**62.5**	**98.3**
CRP	**0.698**	**≥41**	**76.92**	**64.86**	**43.5**	**88.9**

DISCUSSION

The current study aimed to determine the value of plasma D-dimer level in predicting no-reflow after primary PCI in patients presented with acute STEMI, among 100 patients admitted to Ain Shams university Hospital. Most of the patients (86%) were males, with the age ranged from 25 to 92 years with a mean ± SD was 53.33 ± 13.50. More than half of the patients (55%) were either current or ex-smokers. More than half of the patients had negative history for hypertension (55%), diabetes (61%) and dyslipidemia (61%). BMI results showed that only 20% of the patients had healthy/normal BMI and the rest were overweight and obese, with 31% overweight, and 49% obese.

The demographic and clinical data came in line with **Erkol *et al.*** [16] study results, in which, males were 84% of the included patients, with mean age was 56 ± 12. **Gao *et al.*** [17] who investigated the value of plasma D-dimer and endothelin-1 (ET-1) levels on admission in predicting no-reflow after primary PCI and long-term prognosis in STEMI patients with type 2 diabetes mellitus (T2DM), the results showed that the average age of the patients was 62.5 years. While (47%) of patients were females, which was higher than the current study results. Similarly, the average age of the patients in **Zhang *et al.*** [18] study was 52.6 years with a standard deviation of 7.81 years. However, females were more than half of the participants (53.7%), which was discordant with our study results.

Most of the patients achieved post-procedural TIMI flow grade III (76%), consequently they had high percentage of both reflow and MBG-III (74%). This came in agreement with **Erkol *et al.*** [16]**,** study in which the study population consisted of 569 STEMI patients undergoing primary PCI. The majority of patients (82 %) achieved post-procedural TIMI flow grade III**.**

The percentage of patients with reflow in the current study was higher than that reported by **Zhang *et al.*** [18]**,** in which no-reflow phenomenon after primary PCI was found in 47.9% after PCI which may be related to different demographic distribution of populations in both studies.

In the current study, as regards no reflow there was a statistically highly significant correlation with D-dimer level compared with normal reflow group. Moreover, there were significant correlations between creatinine, CRP levels and no reflow. Also, longer reperfusion time > 4 hours and anemia (Hb < 11) were higher in cases with no reflow than those with normal reflow with. These results came in agreement with the previous literature, in which patients with angiographic no-reflow had higher levels of D-dimer compared with those achieved normal reflow (P < 0.001) [17].

In current study diabetes and longer reperfusion time were found to be independently

predictors of no-reflow. There was an agreement with **Niccoli *et al.* [11]** study, which showed that both reperfusion time and diabetes affected TIMI flow. Also another study was done on 212 patients diagnosed with STEMI who underwent primary PCI in 2012-2013 at JFK medical Center. The glucose on admission were significantly higher in the no-reflow group[19].

In our study pretreatment with P2Y12 inhibitors either ticagrelor or clopidogrel had no significant reduction in the incidence of no reflow. This showed disagreement with **Erkol *et al.* [16]** study, which declared that patients who took clopidogrel had a higher prevalence of no-reflow phenomenon. The difference with our study might be attributed to our smaller sample size and our patients' late presentation compared to **Erkol *et al.* [16]** study.

The mean D-dimer level in the current study was 415.35 ng/ml which came in agreement with **Gao *et al.* [17]** study, which reported a mean D-dimer level of 430.0 (ng/mL).

In the current study, TIMI flow and MBG grade, showed that the best cut off point for D-dimer to predict no reflow was ≥ 560 with sensitivity of 96.15%, specificity of 79.73% and area under curve (AUC) of 86.5%. It also showed that the best cut off point for CRP to detect cases with no reflow was >41 with sensitivity of 76.92%, specificity of 64.86% and area under curve (AUC) of 69.8%. In a study that investigated the value of the combination of plasma D-dimer level upon admission and pre-infarction angina (PIA) in predicting no-reflow phenomenon in STEMI patients after initial PCI; a total of 926 STEMI patients who underwent initial PCI showed that the plasma D-dimer level on admission had an AUC of 0.604 (95% CI: 0.568 ~ 0.641, with a sensitivity of 0.526 and a specificity of 0.682) [18].

In the current study there was no statistically significant relation between level of D-dimer with age, gender, smoking, hypertension, diabetes mellitus, dyslipidemia and BMI. Whereas, there was a statistically significant relation between the increased D-dimer level in patients with renal impairment and CRP. This came in partial disagreement with **Erkol *et al.* [17]** study as there were statistically significant correlations between plasma D-dimer levels and age ($P < 0.001$), reperfusion time ($P < 0.001$), TIMI thrombus score ($P< 0.001$), creatinine ($P < 0.001$), CRP ($p < 0.001$), mean platelet volume ($P= 0.016$), and hemoglobin ($P = 0.003$).

In the current study, there was a statistically significant correlation between D-dimer level (< 500 ng/dl) and ECG features of successful reperfusion (ST-segment resolution > 70 % from the baseline after 2 hr from PCI) and moreover high level of plasma D-dimer (>500ng/dl) could predict ECG features of no-reflow phenomenon.

There was an agreement with the previous literature, in which D-dimer levels were higher in the patients with electrocardiographic no-reflow ($P < 0.001$). The univariate analysis declared that plasma D-dimer level was significantly predictive of both angiographic ($P < 0.001$) and electrocardiographic no-reflow phenomenon ($P < 0.001$) [19].

Limitations of our study were:

- Short duration of follow up.
- Single center study and small number of cases.
- Other methods, besides TIMI flow and MBG might be used in the assessment of myocardial flow such as cardiac MRI or myocardial contrast echocardiography

CONCLUSION

As regards clinical predictors; DM, renal impairment, decreased hemoglobin level, delayed perfusion were associated with higher percentage of no-reflow phenomenon. Whereas the laboratory predictors; D-dimer and CRP levels on admission could independently predicts no-reflow after Primary PCI.

RECOMMENDATIONS

Further studies including a scoring system might be needed to investigate thoroughly whether such clinical parameters &or high D-dimer levels & or CRP on admission might be a selection criterion for more aggressive complementary treatment strategies to improve microvascular perfusion after Primary PCI.

Conflict of interest: The authors declare that they have no competing interests.

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