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The Relationship between the Levels of Serum Cystatin C and the Occurrence of the No-Reflow Phenomenon during Primary Percutaneous Coronary Interventions

HOSSAM EL-DIN E.M. FARRAG, M.B.B.Ch.; AHMED Sh. ELSERAFY, M.D.; ABDELRAHMAN E. ATTIA, M.D. and ADEL M. SHABANA, M.D.

The Department of Cardiology, Faculty of Medicine, Ain Shams University

Abstract

Background: The best treatment of ST-segment elevation myocardial infarction (STEMI) is reperfusion of ischemic myocardium as soon as possible. Primary percutaneous coronary intervention (PPCI) has become the preferred strategy for reperfusion and the current standard care for STEMI. No-reflow is clinically important as it is associated with cardiac failure, malignant arrhythmias and in-hospital and long-term mortality. Cystatin C is a potent inhibitor of lysosomal proteinases and found in virtually all tissues and body fluids.

Aim of Study: To assess the relationship between the level of Cystatin C and the occurrence of no-reflow during primary PCI in the setting of STEMI.

Patients and Methods: This study was carried out at the Cardiology Department Ain Shams University. This prospective clinical trial study was conducted on 68 patients with acute STEMI who were undergoing PPCI who were subdivided into 2 groups: Group 1: Patients with TIMI III flow. Group 2: Patients with no reflow. Serum cystatin c level was assessed in the group with TIMI III flow VS No reflow group from May 2022 till October 2022.

Results: There was statistically significant difference between reflow and no reflow regarding cystatin c level found higher in no reflow cases than reflow cases.

Conclusion: In conclusion, data of this study suggest that Cystatin C is a useful marker for prediction of no-reflow after PCI in STEMI as it can help in screening of STEMI patients with high risk of development of no-reflow on admission and help to choose the best treatment.

Key Words: *Cystatin C – No reflow – ST elevation myocardial infarction.*

Introduction

ACUTE myocardial infarction (AMI) is defined as myocardial necrosis in a clinical setting consistent with myocardial ischemia. These conditions can be satisfied by a rise of cardiac markers (preferably cardiac troponin [cTn]) above the 99 th percentile of the upper reference limit (URL) plus at least one of the following: Symptoms of ischemia, ECG changes indicative of new ischemia (significant ST/T changes or left bundle branch block), development of pathologic Q waves, imaging evidence of new loss of myocardium or new regional wall motion abnormality, and Angiography or autopsy evidence of intracoronary thrombus **[1]**.

AMI can be classified into 5 types based on etiology and circumstances: Type 1: Spontaneous MI caused by ischemia due to a primary coronary event (e.g., plaque rupture, erosion, or fissuring; coronary dissection), Type 2: Ischemia due to increased oxygen demand (e.g., hypertension), or decreased supply (eg, coronary artery spasm or embolism, arrhythmia, hypotension), Type 3: Related to sudden unexpected cardiac death and Types 4 and 5 MIs are related to coronary revascularization procedures like Percutaneous Coronary Intervention (PCI) or Coronary artery Bypass Grafting (CABG) respectively **[2]**.

The most serious form of the acute coronary syndrome, ST segment elevation myocardial infarction, or STEMI, most often occurs from occlusion of one or more of the coronary arteries that supply the heart with blood. The cause of this abrupt disruption of blood flow is usually plaque rupture, erosion, fissuring or dissection of coronary arteries that results in an obstructing thrombus. The major risk factors for ST-elevation myocardial infarction are dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of coronary artery disease **[3]**.

STEMI is a life-threatening, time-sensitive emergency. Early accurate diagnosis and prompt

Correspondence to: Dr. Hossam El-Din E.M. Farrag, E-Mail: drhossamfarrag@gmail.com

treatment to restore coronary perfusion, usually by percutaneous coronary intervention (PCI), are critical to effective management. Primary percutaneous coronary intervention (PPCI) is the gold standard of treatment of ST segment elevation myocardial infarction (STEMI). PPCI restores thrombolysis in myocardial infarction flow 3 (TIMI 3) in over 90% of patients **[4]**.

Despite re-establishing epicardial coronary vessel patency, primary PCI may fail to restore optimal myocardial reperfusion within the myocardial tissue, a failure at the microvascular level known as no-reflow (NR). NR has been reported to occur in up to 60% of STEMI patients with optimal coronary vessel reperfusion. When it does occur, it significantly attenuates the beneficial effect of reperfusion therapy, leading to poor outcomes **[5]**.

No reflow is regarded as independent predictor of death or recurrent myocardial infarction. No reflow is a multi-factorial phenomenon. However, micro embolization of atherothrombotic debris during PCI remains the principal mechanism responsible for microvascular obstruction **[6]**.

Cystatin-C (Cys-C) is a cysteine protease inhibitor produced by almost all human cells. It is excreted into the bloodstream, filtered in the renal glomerulus, and metabolized by the proximal tubule [7].

In recent years, cystatin C has emerged as a more reliable biomarker of renal dysfunction than serum creatinine, in particular for the detection of small reductions in glomerular filtration rate (GFR) [8].

Apart from its established role in evaluating renal function, cystatin C has also proven to be a powerful predictor of mortality and adverse cardiovascular events in postmenopausal women with angiographically documented coronary artery disease, in patients with heart failure and in patients with non-ST elevation acute coronary syndrome, and in stable CAD patients with preserved eGFR after elective PCI **[9]**. Furthermore, elevated systemic cystatin C levels have been reported to predict a poor prognosis in patients with STEMI treated by PPCI **[10]**.

Aim of the work:

The aim of the present study is to assess the relationship between the level of Cystatin C and the occurrence of no-reflow during primary PCI in the setting of STEMI.

Patients and Methods

This study was carried out at the Cardiology Department Ain Shams University. This prospective clinical trial study was conducted on 68 patients with acute STEMI who were undergoing PPCI who were subdivided into 2 groups: Group 1: patients with TIMI III flow. Group 2: Patients with no reflow. Serum cystatin c level was assessed in the group with TIMI III flow VS No reflow group from May 2022 till October 2022.

The inclusion criteria were: Patients with their first STEMI within 12 hours of symptom onset who underwent PPCI, ST segment elevation (measured at the J. point) was considered suggestive of ongoing coronary artery acute occlusion in the following cases: 2 contagious leads with ST-segment elevation 2.5mm n men <40 years, 2mm in men 40 years, or 15mm in women in leads V2-V3 and –or 1mm in the other leads. In patients with inferior myocardial infarction, it was recommended to record right precordial leads (V3R and V4R) seeking ST-segment elevation, to identify concomitant right ventricular (RV) infarction. Likewise, ST-segment elevation in leads V7-V9 should be considered as a means to identify posterior myocardial infarction **[11]**.

While the exclusion criteria: Age 80 years, Cardiogenic shock, Previous MI or coronary bypass surgery, Rescue PCI after thrombolytic therapy, Contraindication to the use of adenosine, Significant left main coronary artery disease, Chronic liver disease and chronic inflammatory disease, Patients on dialysis therapy and those with end-stage renal disease (creatinine clearance <15ml/min), Malignant life-threatening diseases and Inability to provide informed consent.

Intervention studies:

Primary PCI: All patients received loading oral dose of aspirin (300mg) and clopidogrel (600mg) on admission. All PPCI procedures were performed through the radial OR femoral approach with a 6 French guiding catheter. An intravenous bolus of weight-adjusted unfractionated heparin was administered. Use of either intracoronary or systemic bolus of tirofiban followed by a 12-24h continuous infusion was left at the operator's discretion, supervisors experts will do the percutaneous coronary intervention **[9]**.

Following-up patient hemodynamics and transthoracic Echo have been done in CCU after PCI.

Post-PCI medication: Consists of double antiplatelet therapy with aspirin 100mg/day for lifelong

and clopidogrel 75mg/day for at least 12 months; beta-blockers, angiotensin-converting enzyme inhibitors, and statins were also given **[9]**.

Angiographic assessment of microvascular perfusion: Coronary flow was graded using standard thrombolysis in myocardial infarction (TIMI) criteria. Myocardial blush grade (MBG), based on the visual assessment of contrast opacification of the myocardium supplied by the IRA, was evaluated according to, Angiographic no-reflow was defined as a coronary TIMI flow grade 2 after vessel reopening or TIMI flow 3 together with a final MBG 2.

Laboratory assays: The venous blood samples were drawn from patients of both groups after performing PCI. The amount of blood needed for the research is 1.5 c.c, Blood samples were collected using standardized sterile tubes and centrifuged at 3000 rpm for 5min at 4°C, and the serum and plasma was immediately frozen and stored at –80°C until being assayed, Serum cystatin C concentration was measured by high sensitive latex particle-enhanced immunoturbidimetric assay with an automatic biochemical analyzer (Hitachi 7600; Tokyo, Japan), which was also used for the measurement of high-sensitivity C-reactive protein (hsCRP) and Other blood tests including lipids, troponin I, and creatinine, etc. were assayed using routine laboratory methods **[12]**.

Statistical analysis:

Quantitative data will be presented as mean and standard deviation. Comparing means of the groups (with and without burnout) will be done using two independent samples *t*-test. Categorical data will be presented as counts and appropriate proportions and comparison between the two groups will be done using chi-squared test. A p-value of 0.05 or less is considered statistically significant to assess the relationship between the level of Cystatin C and the occurrence of no-reflow during primary PCI in the setting of STEMI.

Results

The Pervious table shows that there was statistically significant difference between reflow and no reflow groups regarding mean age which was found higher in no reflow cases than reflow cases.

While there was no statistically significant difference between both groups regarding gender of the studied patients. Table (5).

The Pervious table shows that there was statistically significant difference between reflow and no reflow groups regarding presence of DM which was found higher in no reflow cases than reflow cases while there was no statistically significant difference between both groups regarding presence of HTN and smoking. Table (6).

The previous table shows that there was statistically significant difference between reflow and no reflow groups regarding BMI which was found higher in no reflow cases than reflow cases. Table (7).

The previous table shows that there was statistically significant difference between reflow and no reflow groups regarding SBP and DBP which were found lower in no reflow cases than reflow cases while there was no statistically significant difference between both groups regarding HR. Table (8).

Table (1): Demographic data of the studied patients.

Personal history	Total No.=68
Age (years):	
Mean ± SD	55.57±8.44
Range	37-74
Gender:	
Female	16 (23.5%)
Male	52 (76.5%)
Major risk factors:	
HTN:	
No	27 (39.7%)
Yes	41 (60.3%)
DM:	
No	27 (39.7%)
Yes	41 (60.3%)
Smoking:	
No	18 (26.5%)
Yes	50 (73.5%)

Table (2): Anthropometric measurements and vital signs of studied patients.

Anthropometric measurements	Total No.=68
BMI:	
Mean ± SD	29.25±3.00
Range	23.7-37.8
Vital signs:	
HR:	
Mean ± SD	87.88±14.11
Range	58-118
SBP:	
Mean ± SD	132.46±18.88
Range	90-170
DBP:	
Mean ± SD	80.46±10.96
Range	60-110

Table (3): Echocardiography, ECG, Cardiac catheterization of studied patients.

Echocardiography	Total No.=68
LVEF:	
Mean ± SD	52.93±8.99
Range	35-66
ECG:	
Infarct location:	
Anterior STEMI	36 (52.9%)
Inferior STEMI	30 (44.1 %)
Lateral STEMI	2 (2.9%)
Cardiac catheterization:	
Lesion location:	
RCA	22 (32.4%)
LAD	36 (52.9%)
LCX	10 (14.7%)
Post-intervention TIMI flow grade:	
0	3 (4.4%)
I	12 (17.6%)
II	19 (27.9%)
III	34 (50.0%)
Reflow vs no reflow:	
Reflow	34 (50.0%)
No reflow	34 (50.0%)

Table (4): Total Ischemic time (hours) and Cystatin C among all studied patients.

	Total No.=68
Total ischemic time (hours):	
Median (IQR)	5 (3-7)
Range	1-12
Cystatin:	
Median (IQR)	4.1 (2.5-10.13)
Range	0.8-21

Table (5): Comparison between reflow and no reflow regarding personal history (age and gender) of the studied patients.

Personal history	Post-intervention TIMI flow grade		Test value	*p*-value	Sig.
	Reflow	No reflow			
	No.=34	No.=34			
Age (years):					
Mean ± SD	53.09±8.33	58.06±7.90	–2.524•	0.014	S
Range	37-74	39-72			
Gender:					
Female	8 (23.5%)	8 (23.5%)	0.000*	1.000	NS
Male	26 (76.5%)	26 (76.5%)			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
*: Chi-square test.
•: Independent *t*-test.

Table (6): Comparison between reflow and no reflow regarding major risk factors (HTN, DM and smoking) of the studied patients.

Major risk factors	Post-intervention TIMI flow grade		Test value	*p*-value	Sig.
	Reflow	No reflow			
	No.=34	No.=34			
HTN:					
No	17 (50.0%)	10 (29.4%)	3.010*	0.083	NS
Yes	17 (50.0%)	24 (70.6%)			
DN:					
No	20 (58.8%)	7 (20.6%)	10.381*	0.001	HS
Yes	14 (41.2%)	27 (79.4%)			
Smoking:					
No	9 (26.5%)	9 (26.5%)	0.000*	1.000	NS
Yes	25 (73.5%)	25 (73.5%)			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.

Table (7): Comparison between reflow and no reflow groups regarding BMI of the studied patients.

	Post-intervention TIMI flow grade		Test value	*p*-value	Sig.
	Reflow	No reflow			
	No.=34	No.=34			
BMI:					
Mean ± SD	28.41±2.79	30.33±2.97	–2.553•	0.013	S
Range	23.7-33.5	24.2-37.8			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
•: Independent *t*-test.

Table (8): Comparison between reflow and no reflow groups regarding Vital signs (HR, shocked on nor-adrenaline infusion, SBP and DBP) of the studied patients.

Vital signs	Post-intervention TIMI flow grade		Test value	*p*-value	Sig.
	Reflow	No reflow			
	No.=34	No.=34			
HR:					
Mean ± SD	88.97±15.02	86.79±13.27	0.633•	0.529	NS
Range	58-118	65-118			
SBP:					
Mean ± SD	144.55±15.23	120.00±13.44	6.882•	0.000	HS
Range	120-170	90-150			
DBP:					
Mean ± SD	87.58±9.02	73.13±7.38	7.055•	0.000	HS
Range	70-110	60-90			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
*: Chi-square test.
•: Independent *t*-test.

The previous table shows that there was statistically significant difference between reflow and no reflow groups regarding LVEF which was found Lower in no reflow cases than reflow cases while there was no statistically significant difference between both groups regarding Infarct location and Lesion location. Table (9).

Table (9): Comparison between reflow and no reflow groups regarding Echocardiography, ECG and Cardiac Catheterization (LVEF, Infarct location, Lesion location) of the studied patients.

Echocardiography	Post-intervention TIMI flow grade		Test value	*p*-value	Sig.
	Reflow	No reflow			
	No.=34	No.=34			
LVEF:					
Mean ± SD	60.26±4.86	45.59±5.44	11.735•	0.000	HS
Range	49-66	35-56			
ECG:					
Infarct location:					
Anterior STEMI	19 (55.9%)	17 (50.0%)	2.644*	0.267	NS
Inferior STEMI	13 (38.2%)	17 (50.0%)			
LATERAL STEMI	2 (5.9%)	0 (0.0%)			
Cardiac catheterization:					
Lesion location:					
RCA	11 (32.4%)	11 (32.4%)	0.511*	0.774	NS
LAD	19 (55.9%)	17 (50.0%)			
LCX	4 (11.8%)	6 (17.6%)			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
*: Chi-square test.
•: Independent *t*-test.

The previous table shows that there was statistically significant difference between reflow and no reflow groups regarding cystatin C level which was found higher in no reflow cases than reflow cases. Table (10).

Table (10): Comparison between reflow and no reflow groups regarding Total Ischemic time (hours) of the studied patients.

Total ischemic time (hours)	Post-intervention TIMI flow grade		Test value	*p*-value	Sig.
	Reflow	No reflow			
	No.=34	No.=34			
Median (IQR)	3 (2-4)	6.5 (6-7)	–6.177	0.000	HS
Range	1-8	4-12			

p-value >0.05: Non significant.
p-value <0.05: Significant.
p-value <0.01: Highly significant.
: Mann-Whitney test.

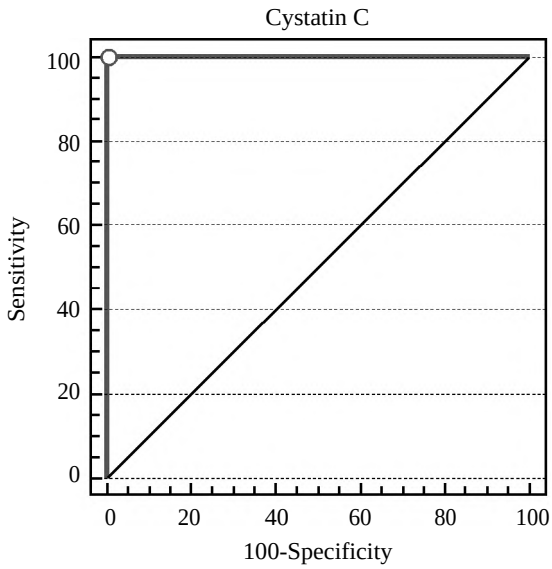

Fig. (1): ROC curve for cystatin C to detect no reflow.

The following ROC curve shows that the best cut off point of cyctatin C to detect no reflow was >3.7 with sensitivity 100%, specificity 100% and area under curve of 100% Table (11).

Table (11): ROC curve for cystatin C to detect no reflow.

Cut off point	AUC	Sensitivity	Specificity	+PV	–PV
>3.7	1.000	100.00	100.00	100.0	100.0

The previous table shows that there was statistically significant difference between reflow and no reflow groups regarding Total Ischemic time (hours) which was found longer in no reflow cases than reflow cases. Table (12).

Table (12): Comparison between reflow and no reflow groups regarding cystatin c level of the studied patients.

Cystatin C	Post-intervention TIMI flow grade		Test value	*p*-value	Sig.
	Reflow	No reflow			
	No.=34	No.=34			
Median (IQR)	2.5 (2-3.1)	10.13 (8-12)	–7.099	0.000	HS
Range	0.8-0.37	4.5-21			

p-value >0.05: Non significant. *p*-value <0.01: Highly significant.
p-value <0.05: Significant. : Mann-Whitney test.

The previous table shows that there was a negative correlation for cytatin C with SBP, DBP and LVEF and also a positive correlation with total ischemic time (hours) while there was no statistically significant correlation with age, BMI and HR. Table (13).

Table (13): Correlation between Cystatin C and other studied parameters.

	Cystatin C	
	r	*p*-value
Age (years)	0.229	0.060
BMI	0.165	0.213
HR	–0.033	0.787
SBP	–0.593**	0.000
DBP	–0.571 * *	0.000
LVEFF	–0.795**	0.000
Total ischemic time (hours)	0.625**	0.000

p-value >0.05: Non significant. Spearman correlation coefficient.
p-value <0.05: Significant.
p-value <0.01: Highly significant.

The previous table shows that there was a positive correlation for cytatin C with the presence of DM and also a negative correlation with post intervention TIMI flow grade increasing from TIMI flow III to TIMI flow 0, while there was no statistically significant correlation with gender, hypertension, smoking, shock state, infarct location and lesion location. Table (14).

The previous univariate logistic regression analysis shows that all the previous parameters were associated with post-intervention no reflow also the multivariate logistic regression analysis shows that LVEF <=52 the most associated factor with post-intervention no reflow. Table (15).

Table (14): Relation between Cystatin C and other studied parameters.

	Cystatin C		Test value	*p*-value	Sig.
	Median (IQR)	Range			
Gender:					
Female	4.1 (2.65-10.5)	0.8-19.5	–0.203•	0.839	NS
Male	4.1 (2.5-9.73)	1.5-21			
HTN:					
No	3 (2.5-9.75)	1.5-18	–1.211•	0.226	NS
Yes	7.5 (2.8-10.5)	0.8-12			
DM:					
No	3 (2.2-4.5)	1.5-18	–3.000•	0.003	HS
Yes	8.2 (2.8-11.2)	0.8-21			
Smoking:					
No	4.1 (2.5-10.5)	0.8-19.5	–0.334•	0.738	NS
Yes	4.1 (2.5-9.7)	1.5-21			
Shocked on levophed:					
No	3.7 (2.5-9.75)	0.8-21	–1.675•	0.094	NS
Yes	12 (3.7-18)	3.7-18			
Infarct location:					
Anterior STEMI	3.6 (2.35-9.75)	1.5-18	3.599	0.165	NS
Inferior STEMI	6.1 (2.5-10.5)	1.8-21			
Lateral STEMI	1.65 (0.8-2.5)	0.8-2.5			
Lesion location:					
RCA	4.1 (2.5-9)	1.8-17	0.610	0.737	NS
LAD	3.6 (2.35-9.75)	1.5-18			
LCX	9.1 (2.5-12)	0.8-21			
Post-intervention TIMI flow grade:					
0	12 (9.5-18)	9.5-18	51.005	0.000	HS
I	10.5 (8.85-13.25)	5-21			
II	9 (8-11.2)	4.5-19.5			
III	2.5 (2-3.1)	0.8-3.7			

p-value >0.05: Non significant. •: Mann-Whitney test.
p-value <0.05: Significant. : Kruskal-Wallis test.
p-value <0.01: Highly significant.

Table (15): Univariate and Multivariate logistic regression analysis for factors associated with Post-intervention no reflow.

	Univariate				Multivariate (Backward: Wald)			
	p-value	Odds ratio (OR)	95% C.I. for OR		*p*-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Age >60 years	0.011	4.579	1.427	14.691	–	–	–	–
DM	0.002	5.510	1.879	16.159	–	–	–	–
BMI >28.3	0.024	3.953	1.202	13.000	–	–	–	–
SBP <=130	0.000	19.333	4.807	77.751	–	–	–	–
DBP <=70	0.000	46.769	5.661	386.412	–	–	–	–
LVEF <=52	0.000	165.333	25.838	1057.944	0.000	118.833	18.338	770.048
Total ischemic timme >4 hours	0.000	107.250	12.600	912.885	–	–	–	–

Discussion

In patients with myocardial ischemia symptoms, STEMI is defined as the combination of persistent ST segment elevation and the release of biomarkers of myocardial necrosis **[13]**.

PCI is the main reperfusion strategy for eligible patients with STEMI, but the no-reflow phenomenon is an important cause of adverse PCI outcomes, ventricular remodeling, and poor cardiac function recovery after ischemia-reperfusion **[14]**. No reflow significantly increases hospitalization and mortality rates. To date, there is no clear evidence of the reversal of the no-reflow phenomenon, but early monitoring and screening for high risk patients before PCI could reduce the occurrence of the no-reflow **[15]**.

Cystatin C is the most important inhibitor of endogenous cysteine proteases and serves as a marker of renal function **[16]**. Epidemiological studies show that Cystatin C is associated with cardiovascular diseases, such as astherosclerosis, heart failure, ischemic stroke and acute coronary syndrome **[17]**. High Cystatin C level is indicated as a useful marker for identifying an elevated risk of cardiovascular diseases, and is independent of renal function determined by creatinine.

The current study was performed on 68 patients with acute STEMI undergoing PPCI who were subdivided into 2 groups; group 1: Patients with TIMI III flow and group 2: Patients with no reflow to assess serum cystatin C level and its value in prediction of no reflow after PPCI.

It revealed male predominance among the included patients with STEMI who underwent PCI (76.5%). As regards history of chronic diseases, Almost 60% had history of HTN, and similar percentage had history of DM, while about three fourth of the subjects were smokers. Half of the included patients had post intervention TIMI flow grade III, followed by grade II (27.9%), grade I (17.6%), and less than 5% had grade 0. The commonest infarction location among the included subjects was anterior STEMI (52.4%), followed by inferior infarction (44.1 %), and lateral infarction (2.9%). Also, the commonest lesion location among the included subjects was LAD (52.4%), followed by RCA (32.4%), and LCX (14.7%).

These results are in agreement with a recent study that was conducted on 656 patients diagnosed with STEMI and reperfused through PCI. The investigators reported that 36 patients developed no reflow. They also reported that anterior STEMI and left anterior descending artery were common among the included subjects (53.5%). Also male gender, DM and HTN were common predisposing factors for development of no-reflow with *p*-values <0.001 **[18]**.

The current study found that older age patients were more susceptible to development of no reflow after PCI with *p*-value=0.014. Similarly, Yu et al. **[19]** who conducted a study on 902 STEMI patients after PCI, revealed that patients who developed no reflow were older (mean age=59±11 years) compared to patients with TIMI III flow with near significant *p*-value=0.051 **[19]**. The previously mentioned study **[18]** stated older age as one of the predisposing factors for development of no-reflow with *p*-value 0.029. A meta-analysis done by Fajar and colleagues found similar results with a *p*-value <0.001 **[20]**.

Our study also revealed that patients who had DM were more susceptible to development of no reflow with *p*-value=0.001. In the meta-analysis mentioned above, Fajar et al. **[20]** reported statistically significant increased history of having DM among patients with no reflow with *p*-value=0.001 **[19,20]**. Also found higher incidence of no-reflow in hyperglycemia group than those with normal blood glucose level, among 121 STEMI patients

after PCI [19]. Hospitalized hyperglycemia was also found to increase the risk of stent restenosis during follow-up [21]. This can be explained as hyperglycemia can trigger endothelial dysfunction leading to vascular damage and microvascular obstruction, and is also known to increase oxidative stress, inflammation and platelet aggregation [22]. Endothelial dysfunction is also correlated with advancing age, hypertension and male gender [23]. Another explanation is that hyperglycemia aggravate leukocyte blockage in microcirculation and hyperglycemia will increase the level of intercellular adhesion molecule 1 or P-selectin, Also hyperglycemia may increase thrombosis and microthrombosis in capillaries that play a key role in re flow after AMI [24].

In the current study, PCI STEMI patients with no reflow had statistically significant lower SBP and DBP during PCI in spite of many of them were known hypertensive. In agreement with Cheng et al. [25] study that revealed statistically significant lower SBP among no reflow group with *p*-value= 0.024 [25].

In the current study, patients with no reflow had statistically significant longer duration of ischemic time with *p*-value=0.000. This could be explained as delayed reperfusion (long duration from symptom to reperfusion) must have probably increased risk of no reflow. Gupta and Gupta reported that "the symptom onset to balloon time longer than 12h" was an essential factor for no reflow development [26]. The time interval between the diagnosis of STEMI and myocardial reperfusion should be as short as possible. Ideally, we should aim at less than 120 minutes and acceptably less than 12 hours from the onset of typical MI symptoms until reperfusion [27]. Patients' prognosis remains closely related to the time elapsed from the onset of typical symptoms to PCI. Other studies reported correlation between no reflow and prolonged myocardial ischemia and subsequent extension of the necrosis area [28,29] in an Egyptian study, reported that the main factor for a prolonged total ischemic time was the patient s delay [29]. The absence of general awareness regarding chest pain differentiation, delay in looking for medical advice, particularly in women and poverty were factors prompting the occurrence of patients delay, the same reasons were demonstrated by [30]. In contrary, [31] found no statistically significant association between time interval from the onset of STEMI to PCI and occurrence of no-reflow in their study [31]. However, other several studies showed that a period less than 12 hours after the onset of MI still be associated with no-reflow especially in patients with multiple risk factors, such as diabetes, high blood pressure and chronic kidney disease [18].

The possible mechanism underlying this outcome is microembolization, as has been disclosed that prolonged ischemia triggers distal capillary beds edema, myocardial cells, swelling, neutrophil plugging, alterations of capillary integrity and microvascular bed disruption [20]. This leads to the thrombus takes on more erythrocyte and becomes more rigid, which may lead to distal coronary embolization [32].

In the current study, patients with no reflow had statistically significant lower LVEF with *p*-value=0.000. In agreement with us, Pantea-Rosan and coworkers revealed statistically significant decreased LVEF among PCI patients with no reflow with *p*-value=0.009 [33,34] in their study, considered that the occurrence of no-reflow in STEMI patients contributed to subsequent severe myocardial dysfunction and thus to increased mortality at 2 years [33]. Similarly, [20] reported that low LVEF was proven to be associated with no reflow. Another study by [35] that was performed on 189 patients who had no reflow after PCI of 781 patients and revealed that age >60 years, thrombus score 4 and duration interval between symptom to balloon intervention >360min were independent predictors of no reflow [20]. Lower left ventricular EF (LVEF) of 11 studies [35] was correlated with the possibility of the development of no-reflow, additionally, low EF of LV was correlated with poor prognosis [36]. In [29] study, lower EF was found among no reflow group (45.67%) vs (47.57%) in reflow cases [29].

As regards our marker of importance; Cystatin C, our study revealed statistically significant elevated serum Cystatin C in patients with no reflow group compared to reflow group with *p*-value =0.000. In agreement with us, a study by Cheng and colleagues conducted on 218 STEMI patients who underwent PCI and revealed statistically significantly higher serum Cystatin C in no reflow group compared to reflow group (1.1±38 vs. 89±.21) with *p*-value=0.001 [25].

Similarly, Tang et al. [9] study which was conducted on 108 patients with STEMI who underwent PCI to evaluate the association of baseline serum Cystatin C with myocardial perfusion after PCI-revealed that elevated Cystatin C levels at admission were independently associated with impaired myocardial perfusion, poor cardiac functional recovery and development of CHF in patients with anterior STEMI underwent PCI [9].

One of the important results of our study is the determination of the best cut off point for serum Cystatin C for prediction of no reflow after PCI in STEMI patients, which was estimated to be more than 3.7 with sensitivity 100%, specificity 100%, and AUC of 100%. Cheng et al., reported that Cystatin C at cutoff point >1.055 had 54% sensitivity, 83% specificity in predicting no-reflow (95% CI AUC 0.688 (0.557-0.780) **[25]**.

The current study revealed statistically significant negative correlation between Cystatin C and post intervention TIMI flow grade with increasing from TIMI III to 0. This agrees with(36)study that was conducted on 127 patients who underwent coronary angiography after ACS and revealed statistically significant negative correlation between serum Cystatin C being higher among TIMI 0 (1.52) than TIMI 3 (0.9) with *p*-value <0.001 **[37]**.

It is worthnoting that Ichimoto and colleagues conducted a study on 71 patients with STEMI, also suggested that Cystatin C was associated with greater frequency of rehospitalization and acute heart failure episodes **[38]**. In AMI, the prognostic significance of Cystatin C may be attributable to multiple underlying mechanisms including, its suggested active role in physiological process of atherosclerosis plaque formation. Furthermore, being an endogenous cathepsin inhibitor, it maintains the balance between proteases and their disruption of this relationship, therefore accelerating atherosclerosis development **[39]**. In addition, elevated Cystatin C value may lead to no-reflow phenomenon due to its correlation with impaired renal function and inflammation which are associated with oxidative stress, microvascular endothelial dysfunction, pro-coagulant cytokines and free radicals. Therefore, this biomarker is useful predictor for no reflow event in STEMI patients treated with PCI **[25]**.

Also, our study revealed statistically significant negative correlation between Cystatin C and LVEF with *p*-value=0.000. Recently, Lou et al., presented Cystatin C levels at admission as a biomarker of cardiac function and they showed a negative relationship with EF with *p*-value <0.001 **[41]**.

The current study found statistically significant association between Cystatin C and DM with *p*-value=0.003. Such finding was similar to a study conducted by Mao and coworkers that involved 422 patients with acute coronary syndrome to investigate the association of Cystatin C with metabolic syndrome and cardiovascular outcomes. It revealed statistically significant association between higher Cystatin C level and risk for DM with *p*-value 0.036. Similarly, Fu et al., reported statistically significant higher cytatin C level among ACS patients with DM with *p*-value <0.05 **[42]**.

Conclusion:

Cystatin C is a useful marker for prediction of no-reflow after PCI in STEMI as it can help in screening of STEMI patients with high risk of development of no-reflow on admission and help to choose the best treatment.

Recommendations:

Several studies with large sample size are needed for further evaluation of the role of Cystatin C in prediction and screening for no-reflow after PCI, The association and changes in Cystatin C overtime are needed to be studied and The prognostic impact of Cystatin C in re-flow of STEMI remains to be examined in future studies.

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العلاقة بين مستويات السيستاتين فى الدم وحدوث ظاهرة عدم الانحسار أثناء التدخلات التاجية الأولية عن طريق الجلد فى احتشاء عضلة القلب المرتفع للقطعة ST

المقدمة والهدف من البحث : أفضل علاج لاحتشاء عضلة القلب الناجم عن ارتفاع المقطع ST هو إعادة ضخ عضلة القلب الإقفارية فى أسرع وقت ممكن. أصبح التدخل التاجى الأ و لى عن طريق الجلد هو الاستراتيجية المفضلة لإ عادة التروية والرعاية القياسية الحالية لاحتشاء عضلة القلب المرتفع فى المقطع ST. ومع ذلك، فإن حوالى ١٢٪ إلى ٣٢.٨٪ من مرضى احتشاء عضلة القلب المرتفع للجزء الذين تم إجراؤهم بالتدخل التاجى الأولى عن طريق الجلد لا يحققون تدفق الدم التاجى المرغوب، والذى يشار إليه بظاهرة عدم الانسياب. يعد عدم إعادة التدفق أمراً مهماً من الناحية السريرية لأنه يرتبط بفشل القلب وعدم انتظام ضربات القلب الخبيث والوفيات داخل المستشفى والوفيات طويلة الأجل. قد تساهم العوامل متعددة العوامل فى تطوير عدم إعادة التدفق بما فى ذلك الانصمام البعيد، والتشنج الوعائى، وتلف الأوعية الدموية الدقيقة، الإجهاد التأكسدى، وإصابة نقص التروية–ضخة . لكن العوامل المؤهبة لظاهرة عدم إعادة التدفق لا تزال غير مفهومة تماماً. Cystatin C هو أهم مثبط لبروتياز السيستين الداخلى ويعمل كمشر لوظيفة الكلى. تظهر الدراسات الوبائية أن سيستاتين سى مرتبط بأمراض القلب والأوعية الدموية، مثل تصلب الشرايين وفشل القلب والسكتة الدماغية ومتلازمة الشريان التاجى الحادة. يشار إلى ارتفاع مستوى السيساتين كعلامة مفيدة لتحديد ارتفاع مخاطر الإصابة بأمراض القلب والأوعية الدموية، وهو مستقل عن وظيفة الكلى التى يحددها الكرياتينين. فى هذه الدراسة، قمنا أيضاً بالتحقيق فى العلاقة بين Cystatin C وعدم إعادة التدفق فى المرضى الذين يعانون من احتشاء عضلة القلب المرتفع ST والذين يخضعون للتدخل التاجى الأولى عن طريق الجلد.

المرضى والطرق : أجريت الدراسة الحالية على ٦٨ مريضاً يعانون من احتشاء عضلة القلب الحاد المرتفع ST والذين كانوا يخضعون للتدخل التاجى الأولى عن طريق الجلد والذين تم تقسيمهم إلى مجموعتين، المجموعة ١: المرضى الذين يعانون من تدفق TIMI III والمجموعة ٢: المرضى الذين لا يعانون من إنحسار التدفق لتقييم مستوى السيستاتين فى الدم وقيمته فى التنبؤ بعدم الانسياب بعد التدخل التاجى الأولى عن طريق الجلد. كشفت الدراسة الحالية عن غلبة الذكور بين المرضى المشمولين باحتشاء عضلة القلب المرتفع ST والذين خضعوا للتدخل التاجى الأولى عن طريق الجلد (٧٦.٥٪). فيما يتعلق بتاريخ الأمراض المزمنة، كان ٦٠.٣٪ لديهم تاريخ من ارتفاع ضغط الدم، و ٦٠.٣٪ لديهم تاريخ من مرض السكرى و ٧٣.٥٪ لديهم تاريخ من التدخين. كان لدى معظم المرضى المشمولين بعد تدخل TIMI من الدرجة الثالثة (٥٠٪)، تليها الدرجة الثانية (٢٧.٩٪)، والصف الأول (١٧.٦٪). كان موقع الاحتشاء الأكثر شيوعاً بين الأشخاص المشمولين هو احتشاء عضلة القلب المرتفع ST (٣٢.٤٪)، يليه احتشاء سفلى (٤٤.١٪)، واحتشاء جانبى (٢.٩٪). وجدت الدراسة الحالية أن المرضى الأ كبر سناً كانوا عرضة للإصابة بعدم إعادة التدفق بعد التدخل التاجى الأولى عن طريق الجلد بقيمة p=0.014. كشفت دراستنا أيضاً أن المرضى الذين يعانون من داء السكرى كانوا أكثر عرضة للإصابة بعدم إعادة التدفق بقيمة p=0.001. فى الدراسة الحالية، أدى التدخل التاجى الأولى عن طريق الجلد ST إلى ارتفاع ضغط الدم الانقباضى وضغط الدم الانبساطى.

النتائج : فى الدراسة الحالية، كان لدى المرضى الذين لا يعانون من إ عادة التدفق جزء مهم من الناحية الإحصائية من البطين الأيسر القذفى للبطين الأيسر بقيمة p=0.000. فى الدراسة الحالية، كان لدى المرضى الذين لا يعانون من إعادة التدفق فترة زمنية أطول ذات دلالة إحصائية من الو قت الإقفارى مع قيمة p=0.000 حيث أن إعادة التروية المتأخرة (المدة الطويلة من الأعراض إلى ضخه) تزيد من خطر عدم إعادة التدفق. كشفت الدراسة الحالية عن احتشاء عضلة القلب البطين الأيسر السفلى ذو دلالة إحصائية بين مجموعة عدم إعادة التدفق مع قيمة p=0.000. فيما يتعلق بعلامتنا، Cystatin C ، كشفت دراستنا عن ارتفاع معتد به إحصائياً فى مصل Cystatin C فى المرضى الذين لا يعانون من إعادة تدفق مع قيمة p=0.000 . وثقت دراستنا أن أفضل نقطة قطع لمصل Cystatin C لتنبؤ بعدم الانسياق بعد تصوير الأوعية التاجية عن طريق الجلد فى مرضى احتشاء عضلة القلب المرتفع ST كانت > ٣.٧ مع حساسية ١٠٠٪ ونوعية ١٠٠٪ و AUC بنسبة ١٠٠٪. كشفت الدراسة الحالية عن وجود علاقة سلبية ذات دلالة إحصائية بين Cystatin C ودرجة تدفق TIMI بعد التدخل مع زيادة من TIMI III إلى ٠ . كشفت دراستنا أيضاً عن وجود علاقة سلبية ذات دلالة إحصائية بين Cystatin C وجزء طرد البطين الأيسر بقيمة p=0.000. وجدت الدراسة الحالية ارتباطاً ذا دلالة إحصائية بين Cystatin C ومرض السكرى مع قيمة p=0.003.