

TIMI Risk Index (TRI) as a Predictor of Angiographic No-reflow Phenomenon after Primary Percutaneous Coronary Intervention in Patients with STEMI

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Background/aim: The thrombolysis in myocardial infarction (TIMI) risk score, global registry of acute coronary events (GRACE) risk score (GRS) and the TIMI risk index (TRI) have been reported in acute coronary artery disease patients. We investigated whether admission TRI is associated with no-reflow (NRF) Phenomenon, in-hospital major adverse cardiac events (MACE) and in-hospital mortality in patients underwent primary percutaneous coronary intervention (P-PCI). **Materials and methods:** ST-segment elevation myocardial infarction (STEMI) patients treated with p-PCI were included in the study. TRI was calculated on admission using specified variables. All patients were subjected to informed consent, detailed history taking, clinical evaluation, ECG analysis and coronary risk factor assessment. Additionally, Killip class examinations of all patients were recorded. We defined the angiographic NRF phenomenon as a coronary TIMI flow grade of ≤ 2 after the vessel was recanalized or a TIMI flow grade of 3 together with a final myocardial blush grade (MBG) of < 2 in a manner as described in previous studies. **Results:** A total of 319 patients who underwent p-PCI were enrolled in the study. In terms of age, NRF patients were older than reflow patients. Killip class III-IV designations were more common in NRF patients. TRI values were significantly greater in the NRF group. TRI was an independent predictor of NRF. **Conclusion:** TRI significantly related to no-reflow and in-hospital MACE and in-hospital mortality. TRI uses simple and inexpensive methods for evaluating patients with STEMI. In addition, high TRI may be helpful in identifying high risk patients and determining appropriate treatment strategies.

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1. Introduction

Coronary artery disease (CAD) and acute myocardial infarction are major causes of death and morbidity worldwide (1). Rapid restoration of coronary blood flow to the jeopardized myocardium is the crux of therapy after AMI. The invention and usage of stents have made percutaneous coronary intervention (PCI) a safe, effective, and preferred treatment of ST-segment elevation myocardial infarction (2). The success of a PCI procedure is best defined by 3 interrelated components: angiographic findings, procedural events, and clinical outcomes. Angiographic Success was defined in ACCF/AHA/SCAI 2011 As a minimum diameter stenosis of $< 10\%$ (with an optimal goal of as close to 0% as possible) With final TIMI flow grade 3, without occlusion of a significant side branch, flow-limiting dissection, distal embolization, or angiographic thrombus, the procedural success of PCI was defined as achievement angiographic success without associated in-hospital major clinical complications (e.g. death, MI, stroke, emergency CABG), while the clinically successful PCI requires

both anatomic and procedural success along with relief of signs and/or symptoms of myocardial ischemia (3).

However, even after patency of an infarcted artery was achieved via stent implantation, sufficient myocardial reperfusion was not observed in 2.3% to 29% of patients in the setting of AMI, often called the no-reflow (NRF) phenomenon (4). Factors associated with increased primary PCI complication rates include advanced age, diabetes, CKD, congestive heart failure, and multivessel CAD. A large number of scoring systems and laboratory parameters have been used in clinical practice to predict mortality with PCI. Nevertheless, those interested in cardiovascular medicine still need an easily accessible, cost effective, and noninvasive predictor of primary PCI success. In order to identify high-risk patients with STEMI, various risks classification systems and scoring systems are used frequently. Prediction of early and late mortality in hundreds of thousands of patients has been shown by the in-hospital death global registry of acute coronary events (GRACE) risk score (GRS) and the thrombolysis in myocardial infarction (TIMI) risk score (TRS) (5). Recently, the TIMI risk index (TRI) "which can predict mortality, may be easier to assess

and can be scored with fewer parameters in patients with STEMI" was improved.

2. Patients and Methods

2.1. Study population

This study is a cross sectional observational study, comprised 319 patients with STEMI presenting to National heart institute (NHI) from February 2017 to April 2018. Patients with STEMI eligible for PPCI according to European Society of Cardiology (ESC) guidelines were included. While the excluded Patients were those were not treated with PPCI, patients who were treated by thrombolytic therapy, patients who presented more than 12 hours after symptoms onset and patients with chronic kidney disease on medical treatment or in dialysis or those with Malignancy, bleeding diathesis, Hematological disease or severe liver disorder. Every patient's record included: Informed consent taken from patients. In case of incompetent patients, the informed consent was taken from the guardians. Thorough history taking with special emphasis on: Risk factors (Age, gender, diabetes, hypertension, smoking, dyslipidemia, family history). History of acute coronary syndromes (ACS) and revascularization, complete clinical examination, with demonstration of admission blood pressure, pulse, and killip class. Creatinine level and CKMB level were measured on admission. Standard 12 lead electrocardiogram (ECG) was performed and transthoracic two dimensional echocardiography was performed upon admission to CCU. Cardiac risk scores were calculated for all patients, Thrombolysis in myocardial infarction (TIMI) risk score (TRS) according to age, diabetes mellitus (DM), hypertension (HTN) or angina, heart rate of more than 100 bpm, systolic blood pressure (SBP) of less than 100 mmHg, Killip class II-IV, weight of less than 67 kg, anterior MI or LBBB presentation, and latency of more than 4 hours were recorded (6). Calculation of the TRS was performed using a computer program (<https://www.mdcalc.com/timi-risk-score-stemi>). Global registry of acute coronary events (GRACE) risk score (GRS) also was determined for all patients including age, creatinine, heart rate, SBP, Killip class, cardiac arrest on admission, elevated cardiac markers, and ST-segment deviation were recorded (7). Calculation of the GRS was performed using a computer program (<https://www.mdcalc.com/grace-acs-mortality-calculator>). Thrombolysis in myocardial infarction (TIMI) risk Index (TRI) of patients was calculated for all patients by the formula:

$$\{\text{Heart rate} \times (\text{age} \div 10)^2\} / \text{SBP} \quad (8).$$

All patients underwent selective coronary angiography using the Judkins technique. PCI procedures were performed with a standard femoral

approach using a 7 Fr. guiding catheter. Coronary blood flow patterns after p-PCI were subject to a thorough evaluation on the basis of TIMI flow grade, using grades 0, 1, 2, and 3 (9). The final TIMI flow grade and MBG were assessed using standard methods. We defined the angiographic NRF phenomenon as a coronary TIMI flow grade of ≤ 2 after the vessel was recanalized or TIMI flow grade 3 together with a final MBG of < 2 , in the same manner as described in previous studies (10,11). For all study, only one artery was identified as the IRA. CAD was defined as greater than 50% stenosis in one of the major coronary arteries. During the in-hospital follow-up period, patients were monitored for major adverse cardiac events (MACEs). Cardiogenic shock, new advanced heart failure, pulmonary edema, complete atrio-ventricular block (AVB) requiring a temporary pacemaker, severe ventricular arrhythmia, and in-hospital mortality during the post-PCI follow-up period were regarded as MACEs.

2.2. Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 23 and MedCalc version 15.4. Quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage. The tests were Independent-samples t-test of significance was used when comparing between two means, Mann Whitney U test was used when comparing two means of not normally distributed data, Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters, and Fisher Exact test is a test of significance that is used in the place of chi square test in 2 by 2 tables, especially in cases of small samples. The following regarding ROC curves were done:

- Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values. Area Under Curve (AUC) was also calculated, criteria to qualify for AUC were as follows: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at point of maximum accuracy.

- Sensitivity: Probability that a test result will be positive when the disease is present (true positive rate, expressed as a percentage).

$$\text{Sensitivity} = (\text{true +ve}) / [(\text{true +ve}) + (\text{false -ve})].$$

- Specificity: Probability that a test result will be negative when the disease is not present (true negative rate, expressed as percentage).

$$\text{Specificity} = (\text{true -ve}) / [(\text{true -ve}) + (\text{false +ve})].$$

- PPV (positive predictive value): probability that the disease is present when the test is positive

(expressed as a percentage of true positive cases to all positive). $PPV = (\text{true +ve}) / [(\text{true +ve}) + (\text{false +ve})]$.

- NPV (negative predictive value): probability that the disease is not present when the test is negative (expressed as a percentage of true negative subjects to all negative). $NPV = (\text{true -ve}) / [(\text{true -ve}) + (\text{false -ve})]$.

- Accuracy = $[(\text{true +ve}) + (\text{false +ve})] / [(\text{true +ve}) + (\text{false +ve}) + (\text{true -ve}) + (\text{false -ve})]$.

- Probability (P-value): P-value ≤ 0.05 was considered significant, P-value ≤ 0.001 was considered as highly significant and P-value > 0.05 was considered insignificant.

Table (1): Comparison between the studied groups regarding the demographic data.

Demographic data	Group A (Reflow)	Group B (No-reflow)	Test	P-value (Sig.)
Count (%)	249 (78.1%)	70 (21.9%)		
Age (years)				
Mean \pm SD	55.7 \pm 10.5	61.3 \pm 9.3	-4.696 •	<0.001 (HS)
Median (Range)	55 (28 – 81)	64.5 (34 – 76)		
Gender				
Male	189 (75.9%)	63 (90%)	6.544 ‡	0.011 (S)
Female	60 (24.1%)	7 (10%)		
Risk factors				
HTN	101 (40.6%)	34 (48.6%)	1.436 ‡	0.231 (NS)
DM	78 (31.3%)	24 (34.3%)	0.220 ‡	0.639 (NS)
Smoking	91 (36.5%)	25 (35.7%)	0.016 ‡	0.898 (NS)
Dyslipidemia	120 (48.2%)	33 (47.1%)	0.024 ‡	0.877 (NS)
Family history of IHD	107 (43%)	25 (35.7%)	1.186 ‡	0.276 (NS)
History of CAD	63 (25.3%)	17 (24.3%)	0.030 ‡	0.863 (NS)
History of PCI	34 (13.7%)	6 (8.6%)	1.287 ‡	0.257 (NS)

• Mann Whitney U test., ‡ Chi-square test., $p < 0.05$ is significant., Sig.: significance.

3. Results

A total of 319 patients were included in the data analysis.

Of all the study participants, 70 patients (21.9%) according to MBG flow were in the NRF group (group B), while the remaining (group A) were stratified into the reflow group. Baseline demographic characteristics, clinical, laboratory finding and cardiac risk scores on admission of patients after p-PCI results organized according to reflow grouping are shown in Tables 1,2,3,4 and 5. NRF patients were older than reflow patients. There was a significant difference regarding gender in both groups with statistically significant p value (0.011), with no significant difference regarding other atherogenic risk factors. Killip class III-IV designations were more common in NRF patients (P-value < 0.001). In this study, there is a significant difference between group A and group B regarding SBP (110.8 \pm 18.7mmHg vs. 95.9 \pm 11.4mmHg respectively), and pulse rate (88.8 \pm 17.5bpm vs. 96.0 \pm 17.8 bpm respectively), As regards the ECG, there was a significant difference between group A and B in the location of MI (anterior 69.5% vs. 30.5%, non-anterior, 88.6% vs. 11.4%

respectively). In our study, the time from onset of symptoms to presentation was relatively longer in group B than in group A (mean 4.5 \pm 2.5hours vs. 5.0 \pm 2.4hours) but with no significant P value 0.072.

In this study, we showed that increased TIMI risk index (TRI), TIMI risk score (TRS), and GRACE score (GRS) on admission were significantly associated with the development of angiographic no reflow phenomenon, Moreover, MACes, and increase in hospital duration.

The mean results of TIMI risk score, GRACE score, and TIMI risk index are higher in group B (6.4 \pm 2.5, 131.3 \pm 23.2, 40 \pm 15.0 respectively) than in group A (4.1 \pm 2.6, 113.6 \pm 23.9, 26.8 \pm 12.7 respectively). There was statistically significant difference between the two groups with the P value < 0.001 . In our study, there was a significant difference between groups A and B regarding IRA (**LAD** 69.1% vs. 84.3%, **LCX** 9.6% vs. 4.2%, and **RCA** 21.3% vs. 11.4% respectively). No significant difference was present between the two groups regarding the number of vessels occluded. In this study, in-hospital MACE, In-hospital mortality, cardiogenic shock, severe ventricular arrhythmia, and cardiopulmonary

resuscitations were more common in the no-reflow group; cardiac mortality occurred in 1.2% in reflow group vs. 8.6% in no reflow group, in reflow group 4.8% patients developed pulmonary edema vs. 18.6% in no reflow group. 0.4% of patients developed cardiogenic shock in group A (reflow group), vs. 17.1% of patients in group B (no reflow group). 3.2% of patients developed complete AV block in group A (reflow group), vs. 8.6% of patients in group B (no reflow group). In group A 3.6% patients had CPR at hospital stay, while in group B, 10% of patients had cardiopulmonary resuscitation. TRI significantly related to in-hospital MACEs and in-hospital mortality. TRI uses simple and inexpensive methods for evaluating patients with STEMI. In addition, high TRI may be helpful in identifying high-risk patients and determining appropriate treatment strategies. TRI can be readily calculated at point of care, thereby facilitating short- and long-term risk prediction for STEMI patients, even prior to revascularization.

4. Discussion

In the present study we showed that increased TRI, TR, and GRS on admission were significantly associated with the development of angiographic NRF phenomenon in patients with acute STEMI who underwent p PCI. Moreover, TRI was a significant and independent predictor of NRF. Primary PCI is the

recommended treatment for patients with acute STEMI. In 2008 the Stent for Life (SFL) initiative was launched by the European Association of Percutaneous Cardiovascular Interventions and EuroPCR in partnership with the European Society of Cardiology Working Group on Acute Cardiac Care and country-specific national cardiac societies. The aim was to promote the prioritization of PCI treatment for those who will benefit most, namely STEMI patients.

The following countries are currently participating: Bulgaria, France, Greece, Italy, Portugal, Romania, Serbia, Spain, and Turkey and Egypt (12). Preliminary reports suggest that major increases have been seen in the numbers of p-PCI treatments performed, with some countries reporting very significant increases in p-PCI use between 2008 and 2010. Improvements in STEMI mortality rates have also been observed. The number of p-PCI treatments performed in Europe has steadily increased over the past decade. However, a European survey from 2007 reported that only 40%–45% of European STEMI patients were treated with p-PCI, with large variations in treatment availability between countries (13). The challenges of introducing new technologies into clinical practice can be substantial and include a complex mix of medical, organizational, patient-related, regulatory, and economic factors (14).

Table (2): Comparison between the studied groups regarding the cardiac risk scores.

Cardiac risk scores	Group A (Reflow)	Group B (No-reflow)	Test	P-value (Sig.)
Count (%)	249 (78.1%)	70 (21.9%)		
TIMI risk score (points)				
Mean \pm SD	4.1 \pm 2.6	6.4 \pm 2.5	-5.982 •	<0.001 (HS)
Median (Range)	4.0 (0 – 11)	6.5 (1 – 11)		
GRACE score (points)				
Mean \pm SD	113.6 \pm 23.9	131.3 \pm 23.2	-5.501 *	<0.001 (HS)
Median (Range)	112 (62 – 191)	136 (73 – 184)		
TIMI risk index				
Mean \pm SD	26.8 \pm 12.7	40 \pm 15.0	-6.480 •	<0.001 (HS)
Median (Range)	24 (5 – 66)	43 (8 – 71)		

• Mann Whitney U test., * Independent samples Student's t-test., p< 0.05 is significant., Sig.: significance.

Rapid restoration of coronary flow to the jeopardized myocardium has become an essential part of therapy after STEMI. P-PCI has also been found to significantly improve the survival of these patients (15). Despite an open IRA, breakdown of obstruction to the coronary microvasculature can markedly decrease blood flow to the infarct zone. This effect is known as the NRF phenomenon (16, 17). Coronary

flow decreases in elderly patients, menopausal women, and patients with coronary risk factors (18). This phenomenon is strongly correlated with short and long-term morbidity and mortality in the settings of STEMI (19)

In our study, we showed that NRF was significantly related to in-hospital mortality and MACEs. Factors associated with increased primary

PCI complication rates include advanced age, diabetes, CKD, congestive heart failure, and multivessel CAD. The pathophysiology of the NRF phenomenon has not been fully clarified and its etiology appears to be multifactorial. Some of the contributing factors in the occurrence of NRF are distal atherothrombotic embolization, mechanical micro vascular leukocytes; platelet plugs in situ thrombosis, Ischemic endothelial edema and damage, vasospasm, free oxygen radicals, and susceptibility of the coronary microcirculation to injury (20, 21). The close interplay between inflammation, coagulation, and atherosclerosis progression has become a field of intensive research. An increased inflammatory activity in the setting of STEMI may be one of the underlying NRF mechanisms. In fact, an elevated leukocyte-platelet interaction at the site of the plaque rupture

may play a negative role in distal myocardial reperfusion by activating further inflammation. Botto et al. (22) showed an increased leukocyte-platelet functional interaction in STEMI at the site of plaque rupture relative to the systemic circulation, which may be one of the pathogenic mechanisms liable for NRF phenomenon. Thus, both locally increased inflammatory markers and leukocyte-platelet coaggregates at the site of the plaque rupture may be pathogenic mechanisms responsible for the angiographic NRF phenomenon after p-PCI in STEMI patients. Effective risk stratification is integral to the management of patients with ACS (23). Even among patients with STEMI for whom initial therapeutic options are well-defined, patient risk characteristics can affect early therapeutic decision making (24–26).

Table (3): Comparison between the studied groups regarding the clinical, ECG and laboratory data.

Clinical, ECG and laboratory data	Group A (Reflow)	Group B (No-reflow)	Test	P-value (Sig.)
Count (%)	249 (78.1%)	70 (21.9%)		
Killip class				
Class I & II	212 (85.1%)	28 (40%)	59.756 ‡	<0.001 (HS)
Class III & IV	37 (14.9%)	42 (60%)		
SBP (mmHg)				
Mean ± SD	110.8 ± 18.7	95.9 ± 11.4	5.946 •	<0.001 (HS)
Median (Range)	110 (80 – 190)	90 (80 – 140)		
Pulse (beat/min)				
Mean ± SD	88.8 ± 17.5	96.0 ± 17.8	-3.916 •	<0.001 (HS)
Median (Range)	90 (45 – 130)	100 (44 – 120)		
Chest pain duration (hours)				
Mean ± SD	4.5 ± 2.5	5.0 ± 2.4	-1.800 •	0.072 (NS)
Median (Range)	4 (1 – 10.5)	5.5 (1 – 9)		
ECG				
Non-anterior STEMI	76 (30.5%)	8 (11.4%)	10.269 ‡	0.001 (S)
Anterior STEMI	173 (69.5%)	62 (88.6%)		
CK-MB (U/L)				
Mean ± SD	72.4 ± 45.4	87.2 ± 52.5	-2.229 •	0.026 (S)
Median (Range)	60 (12 – 200)	73 (24 – 200)		
Creatinine (mg/dL)				
Mean ± SD	0.94 ± 0.21	0.92 ± 0.20	0.078 •	0.938 (NS)
Median (Range)	0.9 (0.4 – 1.6)	0.9 (0.4 – 1.6)		

• Mann Whitney U test., ‡ Chi-square test., p< 0.05 is significant., Sig.: significance.

Table (4): Comparison between the studied groups regarding the coronary angiographic data.

Coronary angiographic data	Group A (Reflow)	Group B (No-reflow)	Test	P-value (Sig.)
Count (%)	249 (78.1%)	70 (21.9%)		
The culprit artery				
LAD	172 (69.1%)	59 (84.3%)	9.338 ‡	0.009 (S)
LCX	24 (9.6%)	3 (4.2%)		
RCA	53 (21.3%)	8 (11.4%)		
Number of vessels				
One vessel	140 (56.2%)	31 (44.3%)	3.132 ‡	0.077 (NS)
More than one vessel	109 (43.8%)	39 (55.7%)		
TIMI flow				
1	0 (0%)	9 (12.9%)	168.877 ‡	<0.001 (HS)
2	0 (0%)	37 (52.9%)		
3	249 (100%)	24 (34.2%)		
MBG	<i>Only patients with TIMI 3 flow (N=273)</i>			
0 and 1	0 (0%)	24 (100%)	273.000 ‡	<0.001 (HS)
2 and 3	249 (100%)	0 (0%)		

‡ Chi-square test., ‡ Chi-square test using Linear-by-Linear Association., p< 0.05 is significant., Sig.: significance.

Table (5): Comparison between the studied groups regarding the in-hospital course.

In-hospital course	Group A (Reflow)	Group B (No-reflow)	Test	P-value (Sig.)
Count (%)	249 (78.1%)	70 (21.9%)		
Hospitalization duration (days)				
Mean ± SD	3.5 ± 1.3	3.7 ± 1.3	-1.496 •	0.135 (NS)
Median (Range)	3 (0 – 10)	3 (2.5 – 8)		
In-hospital MACE				
Advanced HF	3 (1.2%)	11 (15.7%)	27.413 F	<0.001 (HS)
Pulmonary edema	12 (4.8%)	13 (18.6%)	14.307 ‡	<0.001 (HS)
Cardiogenic shock	1 (0.4%)	12 (17.1%)	39.174 F	<0.001 (HS)
Complete AV block	8 (3.2%)	6 (8.6%)	3.739 F	0.090 (NS)
Ventricular arrhythmia	14 (5.6%)	4 (5.7%)	0.001 F	1.00 (NS)
CPR	9 (3.6%)	7 (10%)	14.716 F	0.004 (S)
Mortality	3 (1.2%)	6 (8.6%)	10.815 F	0.004 (S)

• Mann Whitney U test., ‡ Chi-square test., **F** Fisher's Exact test., p< 0.05 is significant., Sig.: significance.

A large number of scoring systems and laboratory parameters have been used in clinical practice to predict mortality with PCI. In order to identify high-risk patients with STEMI, various risks classification systems and scoring systems are used frequently. Prediction of early and late mortality in hundreds of thousands of patients has been shown by the in-hospital death global registry of acute coronary events (GRACE) risk score (GRS) and the thrombolysis in myocardial infarction (TIMI) risk score (TRS). We investigated whether pre intervention TRI, TRS, and GRS are related to coronary NRF in patients with STEMI who underwent primary

percutaneous coronary intervention (p-PCI). The study population consisted of 319 consecutive patients admitted at the national heart institute (NHI) for primary PCI from February 2017 to April 2018. The patients are divided into two groups according to the final TIMI flow grade and MBG after the primary PCI as follows: The reflow group (Group A): This group included 249 patients (78.1%), 189 patients were males (75.9%), while the remaining 60 patients were females (24.1%). The no-reflow group (Group B): This group included 70 patients (21.9%), 63 patients (90%) were males, while only 7 patients were females (10%). Our results demonstrated for the first time the

predictive value of these scores for NRF in patients with STEMI. In the present study, we think that with the help of the calculation of these scores in patients admitted to the emergency department with ACS, information about NRF of the CAD may be obtained. Some limitations of our study include relatively small number of patients and our study's population was also from a single center. Due to a male dominance in the patients in our study, the results may not be applicable to female patients. The TRI, GRS, and TRS are routinely used for stratification of patients with ACS. Our study showed that these scores were significantly associated with NRF in patients with STEMI. We think that these findings can guide further clinical practice.

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