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Predictors of No-reflow Phenomenon in ST-elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention

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Abstract: Background Primary Percutaneous coronary intervention (PPCI) is an established mainstay in treatment of patients presenting with acute ST elevation myocardial infarction (STEMI). However, successful revascularization of the culprit coronary vessel does not always mean ideal myocardial reperfusion in a portion of patients, mainly because of the no-reflow phenomenon. Myocardial no-reflow is associated with worse contractile dysfunction and higher incidence of complications and is an independent predictor of death and myocardial infarction after PPCI. Objective: To study the relationship between admissions CRP, Albumin, CRP/Albumin ratio, Monocyte, HDL, and Monocyte/HDL ratio, in patients presenting with acute STEMI and angiographic no-reflow after PPCI. Material and Methods: From October 2018 to February 2019, of the 1500 patients who presented with STEMI for PPCI to any of the Ain Shams University Hospitals' cath labs, we enrolled 150 consecutive patients who had post revascularization angiographic no-reflow. They were allocated to group A. we allocated 150 age, gender, and baseline characteristics matched STEMI patients who had TIMI III flow post revascularization to group B. this was set as the control group. Results: The study population was divided into 2 groups: no-reflow "A" (n = 150) and reflow "B" (n = 150) groups. CRP and Monocytes were significantly higher in the no-reflow group; Albumin and HDL were significantly lower in the no-reflow group. The novel indices, CRP/Albumin ratio (CAR) and Monocytes/HDL ratio (MHR) were both significantly higher in the no-reflow group (p value = 0.000) for both. The tow indices were found to be independent predictors of no-reflow development. Conclusion: Our results suggested that CAR and MHR on admission before PPCI though cheap, and easily measurable laboratory tools, have a significant predictive value with an odds ratio of 0.182 with a p value = 0.000 and 0.321 with a p value = 0.002 respectively. They could help to risk stratify STEMI patients who might suffer from no-reflow phenomenon after PPCI.

Keywords: No-reflow, CRP/Albumin Ratio, Monocytes/HDL Ratio

1. Introduction

Acute myocardial infarction (MI) is the leading cause of death worldwide. It has been widely accepted that it is due to the insufficient blood supply to the cardiac tissue. Early revascularization with primary percutaneous coronary intervention (PPCI) after acute ST elevation myocardial infarction (STEMI) is associated with high success rates for Thrombolysis in Myocardial Infarction (TIMI) III flow attainment and improved prognosis [1]. However, successful revascularization of the epicardial coronary artery does not always mean optimal myocardial reperfusion in a sizeable portion of patients, mostly because of no-reflow phenomenon.

The hallmarks of the 'no-reflow' phenomenon are myocyte swelling, endothelial cell swelling with luminal protrusions, and intravascular red blood cell aggregates [2]. Later findings

included presence of capillary leukocyte plugging [3] and to a lesser extent, platelet and fibrin accumulation [4, 5]. Myocardial damage always precedes the microvascular abnormalities in the presence of total coronary occlusion caused by a coronary thrombus and not vice versa [3].

No-reflow is a multifactorial phenomenon and five mechanisms have been recognized [6]: (A) pre-existing microvascular dysfunction, (B) distal micro-thrombo-embolization, (C) ischemic injury, (D) reperfusion injury, and (E) individual susceptibility. All these factors are inter-related in a complex manner.

Recently, clinical researches had focused on the predictive values of blood cell-related biomarkers on admission and their usefulness in modifying the clinical approach of no-reflow phenomenon in patients with acute myocardial infarction (AMI). Recent investigations have suggested that CRP, monocytes, albumin, and HDL may be involved in the pathogenesis of coronary artery disease [7, 8]. The present study aimed to investigate the relationship between on admission CRP, albumin, monocyte count, and HDL; and post-intervention no-reflow in patients treated by PPCI, because it would be valuable to be able to predict and risk stratify STEMI patients who might suffer from no-reflow phenomenon after PPCI.

2. Aim of Study

To study the relationship between admissions CRP, Albumin, CRP/Albumin ratio, Monocyte, HDL, and Monocyte/HDL ratio, in patients presenting with acute STEMI and angiographic no-reflow after PPCI.

3. Patients and Methods

This was an observational case control study conducted in the coronary care units in Ain Shams University Hospitals.

From October 2018 to February 2019, of the 1500 patients who presented with STEMI for PPCI to any of the Ain Shams University Hospitals' cath labs, we enrolled 150 consecutive patients who had post revascularization angiographic no-reflow; They were allocated to group "A". We then allocated 150 age, gender, and baseline characteristics matched STEMI patients who had TIMI III flow post revascularization to group "B"; This was set as the control group. We excluded patients with late presentation (chest pain onset >48hrs), patients who received thrombolytic therapy, and patients with chronic inflammatory, hematological, or Chronic Kidney disease (CKD) stage 4/5.

STEMI was defined as: typical chest pain > 30 min with ST elevation > 1 mm in at least two consecutive leads on the electrocardiogram or new onset left bundle branch block, and more than two-fold increase in serum cardiac biomarkers [9]. The institutional review board approved this study and all patients provided written informed consent to participate.

After history, clinical examination, and 12 lead surface ECG; STEMI patients who met inclusion criteria were screened for the admission results of: 1) CRP (n<6), 2) serum albumin (n=3.4-4.8g/dL), 3) monocyte count (n=0.20-1.00 10^3/uL), 4) HDL (n>40mg/dL), and 5) eGFR (All samples were withdrawn on admission in the emergency room prior to the administration of antiplatelets). Study blind expert operators assessed Echocardiography data (on admission and pre-discharge), measuring EF in the parasternal long axis, and apical 4 chamber views, using 2D eyeballing. We graded the Angiographic flow in the culprit vessel post revascularization using TIMI flow score as follows: TIMI 0: No perfusion, TIMI 1: penetration with no perfusion, TIMI 2: partial perfusion, TIMI 3: complete perfusion [10].

Primary PCI was performed after patients were loaded with dual anti-platelets (DAPT) using the standard procedural protocol for PPCI as approved by the Cardiology Department Ain Shams University. No-reflow after PPCI was defined as TIMI flow grade 2 or less after stent deployment in the culprit lesion despite the absence of angiographic residual stenosis, spasm, dissection, or thrombosis. Normal-reflow was defined as post-revascularization TIMI grade III flow.

Statistical analysis: Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented in the form of numbers and percentages for the qualitative data; mean, standard deviations, and ranges for the quantitative data with parametric distribution. *Chi-square test* was used in the comparison between two groups with qualitative data. The comparison between two groups with quantitative data and parametric distribution were done by using *Independent t-test.* Multi-variate *logistic regression analysis* was used to assess predictors of no reflow among the studied patients. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: $p \geq 0.05$: Non-significant (NS), $p < 0.05$: Significant (S), $p < 0.01$: Highly significant (HS)

4. Results

This study recruited 300 patients, and according to the patients' PPCI outcome, patients were divided into two groups; the first group was the patients who suffered from no-reflow "A". The second group included patients with normal reflow outcome "B". The two groups were matched regarding age, gender, hypertension, diabetes mellitus, previous history of IHD, smoking, and family history of CAD with p value > 0.05, *table 1*.

Table 2, depicts the relationship between the laboratory parameters from blood samples withdrawn before primary PCI and the TIMI flow outcome of the primary intervention. There was no difference between the two groups regarding eGFR [75.08 vs 75.56 mL/min per 1.73 m^2, p = 0.893]. However, all other parameters showed significant statistical differences between the 2 groups. CRP was significantly higher in the no-reflow group showing a median (IQR) of 27.50 against 6.00 in the reflow group (P value= 0.000).

Albumin was lower in the no-reflow group with a mean of 3.58 g/dL in contrast to 4.00 g/dL in the reflow group (P value = 0.000). Other acute phase reactant (Monocytes and HDL) also showed highly significant difference between the 2 groups. The novel indices, CRP/Albumin ratio (CAR) and Monocytes/HDL (MHR) were both significantly higher in the no-reflow group in contrast to the reflow group, (P value = 0.000) for both. *Figure 1*.

Table 1. *Comparison between group A and group B regarding age, gender, and CAD risk factors.*

		No-Reflow group		Reflow group		Test value*	P-value	Sig.
		No.	%	No.	%			
Age	Mean ± SD	64.10 ± 10.60		61.50 ± 8.66		1.343•	0.182	NS
	Range	31 – 82		37 – 84				
Gender	Female	30	(20.0%)	39	(26.0%)	0.508*	0.476	NS
	Male	120	(80.0%)	111	(74.0%)			
DM	No	84	56.0%	54	48.0%	4.026	0.145	NS
	Yes	66	44.0%	96	52.0%			
HTN	No	66	44.0%	60	40.0%	0.164	0.685	NS
	Yes	84	56.0%	90	60.0%			
Smoking	No	54	36.0%	75	50.0%	1.999	0.157	NS
	Yes	96	64.0%	75	50.0%			
History of IHD	No	132	88.0%	132	88.0%	0.000	1.000	NS
	Yes	18	12.0%	18	12.0%			
FH	No	141	94.0%	141	94.0%	0.000	1.000	NS
	Yes	9	6.0%	9	6.0%			

DM: Diabetes Mellitus, HTN: Hypertension, FH: Family history of IHD, P-value ≥0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), *: Chi-square test, •: Independent t-test; ‡: Mann Whitney test.

Table 2. *Comparison between group A and group B as regards to Laboratory parameters and indices.*

		No Reflow group	Reflow group	Test value	P-value	Sig.
		No. = 50	No. = 50			
eGFR	Mean ± SD	75.08 ± 19.59	75.56 ± 15.57	-0.135•	0.893	NS
	Range	30 – 110	45 – 120			
CRP	Median (IQR)	27.50 (19 - 53)	6.00 (6 - 8)	-8.312‡	0.000	HS
	Range	8 – 185	6 – 18			
Albumin	Mean ± SD	3.58 ± 0.38	4.00 ± 0.35	-5.764•	0.000	HS
	Range	2.8 – 4.4	3.4 – 4.6			
CRP / Albumin	Median (IQR)	7.17 (5.58 - 16.18)	1.62 (1.46 - 2)	-8.303‡	0.000	HS
	Range	2.16 – 44.05	1.3 – 4.74			
Monocytes	Mean ± SD	2.44 ± 0.71	0.48 ± 0.16	19.894•	0.000	HS
	Range	1.39 – 3.7	0.2 – 1.25			
HDL	Mean ± SD	35.32 ± 5.95	39.28 ± 7.76	-2.864•	0.005	HS
	Range	27 – 51	28 – 65			
Monocytes / HDL	Mean ± SD	0.063 ± 0.027	0.0135 ± 0.011	8.899•	0.000	HS
	Range	0.019 – 0.082	0.003 – 0.026			

P-value ≥0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), *: Chi-square test, •: Independent t-test; ‡: Mann Whitney test.

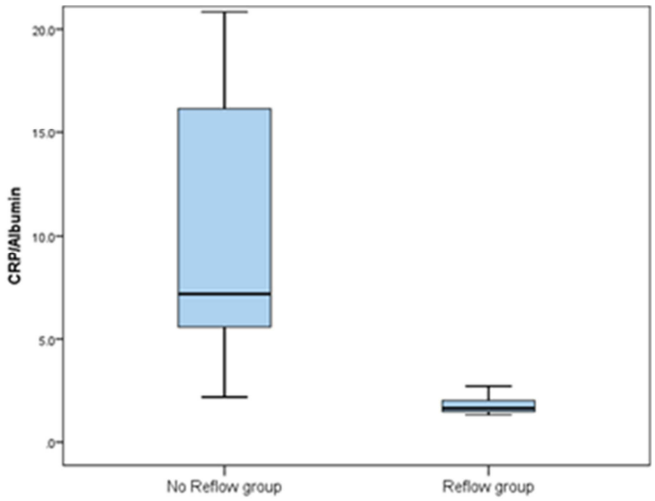

Figure 1. *Comparison between the both groups regarding CRP/ Albumin ratio (CAR).*

Logistic regression analysis:

Table 3, display the multivariate logistic regression analyses for the laboratory predictors of no-reflow in STEMI patients. Only the ratios CAR and MHR showed a significant predictive value with an odds ratio of 0.182 with a p value = 0.000 and 0.321 with a p value = 0.002 respectively.

Table 3. *Multivariate logistic regression analysis for predictors of No-reflow in patients with STEMI.*

	B	S.E.	Wald	P-value	Odds ratio (OR)	95% C.I. for OR	
						Lower	Upper
CRP	0.074	1.020	0.005	0.943	1.076	0.146	7.946
Albumin	2.271	3.718	0.373	0.541	9.690	0.007	14169.139
CRP/Albumin (CAR)	-1.705	0.436	15.301	0.000	0.182	0.077	0.427
HDL	0.191	0.112	2.914	0.088	1.211	0.972	1.508
Monocytes	0.032	0.026	1.824	0.103	1.392	0.063	1.320
Monocytes/HDL (MHR)	-1.267	0.321	12.231	0.002	0.321	0.054	0.519

Tables 4 and 5, show the cut-off values suggested for prediction of no-reflow in STEMI patients. The suggested cut-off values were as follows: CRP ≥ 9, albumin < 3.6, monocytes ≥ 0.75, HDL < 36, CAR ≥ 3.26 with area under curve (AUC) 0.974 and MHR ≥0.023 with AUC 0.872.

Table 4. *Cut-off values for CRP, albumin and CRP / Albumin ratio.*

	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
CRP	≥ 9	0.966	79.49	97.44	96.9	82.6
Albumin	< 3.6	0.763	82.05	56.41	65.3	75.9
CRP/Albumin (CAR)	≥ 3.26	0.974	92.31	89.74	90.0	92.1

Table 5. *Cut-off values for monocytes, HDL and monocytes / HDL ratio.*

	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Monocyte	≥ 0.75	0.72	74.3	61.5	63.2	65.5
HDL	< 36	0.660	64.1	64.1	64.1	64.1
Monocyte/HDL (MHR)	≥ 0.023	0.872	81.2	76.3	76.2	78.1

5. Discussion

The goal of primary PCI in STEMI patients is the rapid restoration of coronary blood flow to the jeopardized myocardium and to improve overall survival. However, in up to 12–39% of patients, myocardial tissue perfusion does not occur despite the presence of normal epicardial flow [11, 12]. This effect is known as the no-reflow phenomenon. In a recent work published by Hassan et al., 2018, they reported a 30 % no-reflow in patients with PPCI in Assuit University [13] while Mazhar et al, 2016 [14] reported 25% no-reflow in their patients' group. In this study we chose to examine patients who experienced no-reflow as a case control study.

No-reflow phenomenon strongly affects the outcome of PPCI and may limit the benefits of reopening of the infarct-related artery. Early risk stratification in order to detect patients at high risk of no-reflow is very important for the anticipation, prevention, and treatment of this condition.

No-reflow has been clearly linked to increased mortality, poor outcome and increased 30 days readmission rates [15, 16]. There is plethora of published work examining various predictors of no-reflow [17-19]. To the best of our knowledge, this is the first published data on Egyptian patients. It adds to the work by Hassan et al., 2018 [13].

We didn't report any difference between the two groups with regards to gender or other risk factors (DM, HTN, smoking), this contrast the work of Celik et al., 2016 who found female gender to be an independent predictor of no-reflow [17]. This can be attributed to delayed reperfusion time, as evidenced from Hassan et al. analysis of positive predictors [13]. Hence in the current study the control group was selected to match the study group as regard gender; these differences were not applicable for the current study.

In group A, (no-reflow) CRP was significantly higher reflecting ongoing inflammation associated with thrombosis. This is comparative to the data reported by Karabag et al. in 2018 [20]. Our data showed a lower Albumin level in patients who had no-reflow. In multivariate logistic regression analyses CAR showed a significant predictive value with an odds ratio of 0.182 (p value = 0.000).

We also examined monocyte/HDL ratio (MHR) as another marker reflecting acute inflammation, which proved to be a strong predictive factor with an odd ratio of 0.321 (p value=0.002). This is similar to the data reported from Balta et al., 2016 [19].

6. Conclusion

No-reflow can be predicted by systemic inflammatory markers including CRP, monocytes, albumin, and HDL. Our results suggested that CAR and MHR on admission before PPCI though cheap, and easily measurable laboratory tools, have a significant predictive value with an odds ratio of

0.182 with a p value = 0.000 and 0.321 with a p value = 0.002 respectively. They could help to risk stratify STEMI patients who might suffer from no-reflow phenomenon after PPCI.

Limitations

A larger randomized controlled trial is needed to verify the results achieved in the current study.

Myocardial blush grading was not evaluated in this study, which is important for assessment of tissue perfusion; and hence, contractility.

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