The relationship between the hematologic indices   after thrombolysis in patients with myocardial infarction

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ABSTRACT

The objective of the present study was to determine the relationship between the hematologic indices including MPV and WBC count at the admission time of patients with ST resolution index in patients with STEMI who were treated by thrombolytic agents. In this prospective study, venous blood samples of 114 patients with STEMI were taken to determine PDW, MPV and WBC count at patients' referral time and before thrombolytic therapy. According to ST resolution index in 90 minutes after thrombolytic therapy, patients were classified in two groups with ST resolution less than 50% and ST resolution of 50% or more. In assessing through ROC curve analysis, it was determined that measuring MPV is not considered as an accurate and effective index in predicting ST resolution after thrombolysis (Area Under Curve: 0.574). WBC count was not an applicable indicator for predicting ST resolution after thrombolysis, as well (Area Under Curve: 0.660). Finally, the results of multiple logistic regression model showed that the only predictor of ST resolution less than 50% is the history of using statins so that history of using statin increased the probability of ST resolution less than 50% for 7 times (P: 0.028, OR: 7.306). There is not a relationship between the occurrence of complete ST resolution (more than 50%) and the values of both MPV and WBC indices. So, measuring these two indicators may not have the enough validity for predicting ST resolution after thrombolysis.

Keywords: Hematologic indices, thrombolysis, myocardial infarction, ST segment

Introduction

In the recent decade, several observations led to the confirmation of the benefits of evaluation and monitoring of ST resolution indices after occurrence of STEMI. For the first time, Schroder et al found that ST resolution predicts the risk of mortality and congestive heart failure in patients treated by fibrinolytic therapy, effectively [1, 2]. Another studies confirmed the relationship between the degree of ST resolution and mortality. In another study by Ito et al., it was determined that epicardial normal blood store is not sufficient for evaluation and providing adequate myocardial reperfusion [3, 4]. In fact, new reperfusion regimens were developed to improve the

limitations of two fibrinolytic and anticoagulant therapies [5, 6] and these therapies may be particularly useful in providing coronary micro-circulation [7].

ST resolution is currently evaluated in many clinical trials and managing patients. Primary studies on ST resolution showed this fact that patients with sharper ST resolution had a lower level of infarction compared to the patients with stable ST-elevation [8]. Further studies confirmed that there is a significant relationship between ST resolution and clinical outcomes of the patients. In a large study on 7426 patients, it became clear that two third of patients with ST resolution more than 50% were four hours after thrombolysis therapy so that these patients had a thirty-day mortality rate of 3.5% against the mortality of 7.4% in patients with ST resolution less than 50% [9]. On the other hand, Schorder et al. developed a new three-part definition for the total resolution of 180 minutes ST elevation after thrombolysis which was included complete resolution (more than 70%), relative (between 30 to 70%) and without resolution (less than 30%). In trials on fibrinolytic treatments, a strong relationship between ST resolution and the reduction in the mortality of patients was observed [10]. In newer studies, it was determined that evaluation of ST resolution even in 3 to 4 first hours after the beginning of fibrinolytic therapy, can determine the risk of death as well as heart failure in patients [11-14]. In addition, it has been determined that patients with

complete ST resolution within 60 minutes had a much lower risk for these two consequences than those patients with ST resolution within 90 minutes [15]. Due to the slower beginning of fibrinolytic streptokinase activation, 90 minutes is a very limited time for the creation of ST resolution and therefore 180 minutes is considered as an acceptable time to assess streptokinase activity in the creation of reperfusion [10]. In addition, along with predicting mortality, the degree of ST resolution is capable to predict the left ventricular dysfunction and heart failure. So that the more complete ST resolution is related to the more limited size of infarction and more improvement of left ventricular function [16-18]. Similar to mortality, the risk of heart failure in a wider and faster ST resolution cases, has been associated with a reduction in the risk of heart failure [19].

The special importance of predicting ability of ST resolution is mainly related to its relationship with epicardial blood flow. In a study, it was determined that under thrombolysis and 90 minutes after it, patients with ST resolution less than 70% had 10-fold higher mortality than the patients with ST resolution more than 70% [20]. Interestingly, there was no difference between two groups with TIMI II and TIMI III and ST resolution in terms of being complete or relative. It was observed through monitoring that patients with faster recovery of stable ST had faster improvement and restoration of infarction that this issue has been independent from TIMI degree. In another study, ST resolution and not the grade of TIMI was the predictor of mortality and heart failure [19, 20].

Other evidences showed the prognostic value of ST resolution derived from the experiences related to primary PCI in patients with STEMI. After the successful primary PCI in patients with STEMI, continuous ST elevation had been associated with weaker recovery of left ventricular function and therefore increased mortality [19-21]. Risk of death and heart failure in patients with increased level of ST after PCI had been increased because of increased extent of infarction [22-24]. In addition, it is proposed that ST resolution is associated with providing tissue reperfusion. By creating the ST resolution at 90 minutes after fibrinolysis, reperfusion has been completely developed in both epicardial and microvascular levels that leads to an excellent outcome in the patient. Another important point in this regard was the companying role of other risk factors in patients with STEMI including age, high weight, infarction, the onset of treatment, evidences of brain involvement, diabetes and hypertension with the history of coronary heart disease [25]. Interestingly, in both groups of patients with and without any of mentioned risk factors, the presence of ST resolution has still been a predictor of lower mortality in these patients [26]. Recently, it has determined that some factors such as previous cardiac biomarker level before fibrinolytic therapy can be stronger predictors of mortality alongside the lack of ST resolution [27-29]. It has also been shown that the evaluation of myoglobin immediately before fibrinolysis along with evaluation of ST resolution 60 to 90 minutes before the therapy can provide more complete information on predicting undesirable outcomes in patients that increased myoglobin associated with the lack of 90-minutes ST resolution increase the risk of mortality up to 25 times [28].

Recently, the role of other factors and biomarkers especially hematologic factors related to ST resolution has been evaluated. As we know, platelets play a basic role in the pathogenesis of atherosclerosis and the spread of thrombotic coronary events. Platelets are mainly produced in stressful conditions such as acute coronary syndrome that platelets will be the high stimulator of B2 thromboxan production [30]. The Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) are considered as the risk factors of MI occurrence and stroke and finally mortality in patients with STEMI [31-33]. Also, leukocytosis plays an important role in the occurrence and progression of atherosclerosis and acute coronary syndrome [34]. But, what has been still unclear for the researchers is the role these hematologic indices in evaluating the adequacy of reperfusion following the thrombolytic therapy especially in relation to or in association with occurrence of ST resolution.

Acute myocardial infarction is a clinical syndrome in which evidences of myocardial ischemia is associated with symptoms of myocardial necrosis in the electrocardiogram, biochemical tests and imaging modalities. One of the types of acute myocardial infarction is determined by ST segment elevation in the electrocardiogram and necrosis of all walls [35-38]. Using the rapid, accurate and non-invasive methods to evaluate the efficacy of reperfusion and thrombolysis therapies in patients with acute myocardial infarction is an essential issue. In the recent decade, many observations have been made about the efficacy of monitoring of ST segment changes as a simple and accessible method in patients with acute myocardial infarction treated by reperfusion and ST resolution was significantly considered in this regard [39-43]. For the first time in 1994, it was determined that this index can even predict the risk of death and occurrence of congestive heart failure in patients under fibrinolytic therapy. In this regard, further studies showed that there is a strong significant relationship between the degree and severity of ST resolution and the risk of mortality following the above mentioned therapies and therefore this indicator was really considered as a prognostic measure in patients treated by reperfusion (thrombolytic and also interventional).

Both inflammatory and coagulative hematologic indicators play essential roles in the occurrence and pathogenesis of acute coronary syndrome. It has been approved in studies that there is a significant relationship between the platelet size considered as mean platelet volume and the platelet activity. On the other hand, the platelets with higher mean platelet volume (MPV) are more active in terms of metabolic and enzymatic ranges and therefore have more thrombotic effects. In addition, an increase in MPV level has been an independent risk factor for the clinical reverse-outcomes in patients with acute myocardial infarction. However, the relationship between MPV and myocardial reperfusion disorders is not still fully understood [41, 44-48].

On the other hand, the role of inflammation has been fully known as a potential risk factor for developing cardiovascular events. Leukocyte response observed during STEMI indicates the role and is considered as an essential component of systemic inflammatory response to myocardial injury. WBC count in time of admission of the patients is a strong predictor for increasing mortality and morbidity of patients with STEMI. In this regard, it is found that there is a relationship between the increase in WBC count and the reduction of epicardial and myocardial blood flow in patients with STEMI.

Along with the above studies, the present study was conducted aimed to evaluate the relationship between the hematologic indices including MPV and WBC count in the time of admission and ST resolution index in patients with STEMI treated by thrombolytics. This study was carried out in Azerbayjan Province for the first time, but its similar studies have been done in Tabriz and Yazd which are mentioned in scientific literature section.

Method

In this prospective case-control study, basic details of the patients such as demographic information, height, weight and body mass index (BMI), history of heart disease risk factors such as familial history of heart diseases, hypertension, hyperlipidemia, diabetes mellitus and smoking, history of drug use especially using heart drugs, previous history of cardiovascular interventions, history of myocardial infarction, history of heart failure, previous history of cerebrovascular events, history of renal failure, history of peripheral arterial hypertension and history of chronic obstructive pulmonary disease were extracted from the patients' records data and registered in the special questionnaire of the project. At the patients' referral time and prior to thrombotic therapy, venous blood samples were taken to measure PDW, MPV indices and WBC count and data were registered in the patients' records. Patients were treated by thrombolysis in an equal condition (including streptokinase 1.5 million units in 20-30 minutes) with a German-made Streptase drug. ST elevation was measured from the J point in ST segment as well as in two electrocardiograms during the initial hospitalization and 90 minutes after thrombotic therapy. According to ST resolution index, 90 minutes after thrombotic therapy, patients were classified in two groups of ST resolution less than 50% and ST resolution of 50% or more. Finally, values of the above laboratory indices were compared between two ST resolution groups.

Criteria to enter the study:

The presence of STEMI diagnostic criteria are based on clinical symptoms (continues typical chest angina for more than 30 minutes), ECG changes (ST segment elevation more than 2 mm in pre-cordial lids and more than 1 mm in limb lids in more than two adjacent lids) and increased cardiac enzymes, 2) receiving thrombolytic treatments, 3) the first occurrence of myocardial infarction.

Criteria to exit the study:

1)Delay to visit for more than 6 hours from the onset of symptoms, 2) presence of LBBB, 3) presence of ventricular tachycardia arrhythmias and ventricular fibrillation, 4) rhythm resulted from the pacemaker, 5) incomplete or non-judgmental electrocardiogram, 6) cases of thrombolytic inhibition including fibrinolytic therapy within the recent 24 hours, anti-coagulant therapy, having congenital hemorrhagic factors, renal insufficiency, history of malignancy, history of chronic inflammatory disease and or active infection, intra-ventricular conduction abnormalities, aortic dissection, systolic hypertension higher than 180 mmHg, history of trauma to the head or any surgery during the recent 3 months, history of thrombocytopenia, presence of cardiogenic shock, 7) presence of concurrent internal or infectious diseases effective on the laboratory parameters under the study, 8) patients who already have aspirin and clopidogrel.

Finally, SPSS version 21 software was used to analyze the data of above study.

Results

A total of 114 patients were evaluated. In terms of ST resolution, 43 cases (37.7%) and 70 cases (61.3%) had resolution of less than 50% and resolution of more than 50%, respectively. In the comparison of basic details between the patients with the resolutions less than 50% and more than 50%, we found that in terms of sexual distribution, frequency of men in people with resolution less than 50% was 69.8% and in people with resolution higher than 50% was 90.1% that the difference was statistically significant (P: 0.006). In terms of the mean age, mean ages in the groups of resolution less than 50% and resolution higher than 50% were 62.07±12.96 years and 56.32±9.29 years old that the difference was statistically significant, as well (P: 0.007). In terms of frequency of the risk factors of heart diseases, prevalence of diabetes was 23.3% and 9.9% in the groups with resolutions less than 50% and more than 50%, respectively that was significantly higher in the first group (P: 0.052). The prevalence of hypertension in the groups with the resolutions less and more than 50% were 44.2% and 18.3% respectively and it was significantly higher in the first group (P" 0.003). In terms of the smoking history, the prevalence of smoking in the groups with resolutions less and more than 50% were 37.2 and 35.2%, respectively that no difference was seen in those groups (P: 0.829). In terms of using opium in the groups with resolutions less and more than 50%, it was 11.6% and 8.5% respectively and without a difference between those groups, as well (P: 0.745). In terms of hyperlipidemia, the prevalence of this complication in the groups with resolutions less and more than 50% was 11.6% and 7%, respectively and without a difference between those groups, as well (P: 0.402). Prevalence of MI in the groups with resolutions less and more than 50% was 14% and 4.2%, respectively and without a difference between those groups, as well (P: 0.07). Prevalence of pulmonary diseases in the groups with resolutions less and more than 50% was 4.7% and 5.6.2%, respectively and without a difference between those groups, as well (P: 0.999). In terms of familial cardiovascular diseases, this history in the groups with resolutions less and more than 50% was 4.7% and 12.7%, respectively and without a difference between those groups, as well (P: 0.209). Also, in terms of prevalence of peripheral vascular disease, this prevalence in the groups with resolutions less and more than 50% was 4.7% and 0%, respectively and without a difference between those groups, as well (P: 0.14).

Table 1: Basic details of patients with ST resolution of less and more than 50%			
Details	Resolution less than 50%	Resolution more than 50%	p-value
Frequency of men	69.8%	90.1%	0.006
Mean age (years old)	62.07 ±12.96	56.32 ±9.29	0.007
Prevalence of diabetes	23.3%	9.9%	0.052
Prevalence of hypertension	44.2%	18.3%	0.003
Prevalence of smoking	37.2%	35.2%	0.829
Prevalence of using opium	11.6%	8.5%	0.745
Prevalence of hyperlipidemia	11.6%	7.0%	0.402
Prevalence of pulmonary diseases	4.7%	5.6%	0.999
History of cardiac diseases	4.7%	12.7%	0.209
History of peripheral vascular diseases	4.7%	0%	0.140
Using of statins	16.3%	2.8%	0.026
Using β blockers	0	4.2%	0.289
Using ACE inhibitors	18.6%	9.9%	0.181
Using Ca blockers	0	8.5%	0.082
Using anti-diabetic	14.0%	5.6%	0.174

drugs			
Frequency of using diuretic drugs	0	1.4%	0.999
Mean of MPV	9.42 ±0.77	9.59 ±1.00	0.377
Mean of WBC count	10027.91 ±2433.04	10520.00 ±2800.03	0.343

In terms of using the cardiovascular drugs, the prevalence of using statins in the groups of resolution less and more than 50% was 16.3% and 2.8%, respectively that in the first group was significantly higher than the second group (P:0.026). Frequency of beta blockers in the groups of resolution less and more than 50% was 0% and 4.2%, respectively that there was no difference between both groups (P: 0.289). Frequency of using ACE inhibitors in the groups of resolution less and more than 50% was 18.6% and 9.9%, respectively and without any difference between two groups (P: 0.181). Similarly, using the Ca blockers in the groups of resolution less and more than 50% was evaluated as 0% and 8.5%, respectively and with no difference between two groups, as well (P: 0.082). Frequency of using anti-diabetic drugs in the groups of resolution less and more than 50% was 14% and 5.6%, respectively that the difference between the groups was not significant (P: 0.174). Also, frequency of using diuretic drugs in the groups of resolution less and more than 50% was 0% and 1.4%, respectively and without any difference between two groups, again (P: 0.999) (Table 1).

Mean of MPV in patients with resolution less than 50% was 9.42±0.77 as well as 9.59±1.00 in the patients with resolution more than 50% that the difference between two groups was not significant (P: 0.377). Means of WBC count in patients with resolution less and more than 50% were 1027.91±2433.04 and 10520.00±2800.03, respectively and the difference between two groups was not significant (P: 0.343) (Table 1).

In the evaluation with multiple logistic regression, the only predictor of ST resolution less than 50% was using statins so that the history of using statin increased the probability of ST resolution less than 50% for about 7 times (P: 0.028, OR: 7.306).

Table 2: Logistic regression model in determining the factors related to resolution less than 50%

Index	Beta coefficient	SE	p-value	OR
Gender	-0.584	0.630	0.354	0.558
Age	-0.032	0.022	0.150	0.969
diabetes	0.299	0.651	0.646	1.349
Hypertension	0.837	0.517	0.105	2.310
Using statin	1.989	0.902	0.028	7.306

In the evaluation by ROC curve analysis, it was found that determination of MPV is not considered as an accurate and efficient indicator in predicting ST resolution after thrombolysis (area under curve: 0.574). Determining WBC count was not an applicable indicator for predicting ST resolution after thrombolysis, as well (area under curve: 0.660) (charts 1, 2).
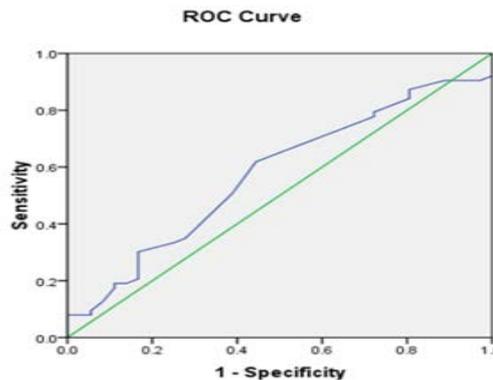

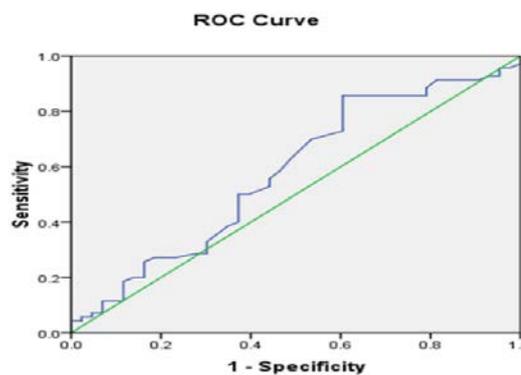**Chart 1:** AUC-ROC for MPV to differentiate the resolutions less and more than 50%

Chart 2: AUC-ROC for MPV to differentiate the resolutions less and more than 50%

Discussion and conclusion

First of all, the purpose of this study was to evaluate the difference between MPV and WBC indices in two groups of patients with ST resolution less and more than 50% after thrombolysis. In fact, the objective was to find if these two measures have an acceptable value to differentiate ST resolutions less and more than 50% after thrombolysis or not or on the other hand, whether a cut-off point is obtained that considering that cut-off point for two MPV and WBC indicators, ST resolution less and more than 50% can be differentiated with acceptable sensitivity and specificity or not. Despite the observed numerical difference in two MPV and WBC indicators between two groups of ST resolution less and more than 50%, this difference was not statistically significant according to this study. Also, in the evaluation of area under ROC curve (AUC-ROC), it was shown that none of these indicators are valuable enough to differentiate ST resolutions less and more than 50% and therefore a cut-off point with acceptable sensitivity and specificity for such this differentiation ability cannot be determined. Unlike some conducted studies, our study was not able to determine the relationship between MPV as well as WBC with ST resolution. In Ghaffari et al. study, patients with MPV higher than 8.2 fl had lower ST resolution and fewer acute heart failures. In the evaluation with regression model, MPV was the predictor for ST resolution as well as MACE occurrence [35] that was completely contrary to our study. In the study of Kirbas et al., MPV value in patients with ST resolution less than 50% was lower than it in patients with ST resolution more than 50% and based on ROC curve analysis, the cut-off point of 9.3 fl for MPV was the strong

predictor for predicting ST resolution with the sensitivity of 66.7% and 77.9% [49] that was not contrary to our study, as well. In Varasteh et al. study, patients with ST resolution less than 70% had higher values of MPV, PDW and WBC count. The best cut-off point of MPV for predicting ST resolution less than 70% was 10.05 fl with the sensitivity and specificity of 71.8% and 80.9%, respectively. Also, the best cut-off point of WBC count for predicting ST resolution less than 70% was 12.65 per thousand with the sensitivity and specificity of 42.9% and 82.7%, respectively [50]. Of course, the studies conducted about the relationship between ST resolution and values of the laboratory indicators are very few. In general, it seems that the disapproval reason of the relationship between ST resolution and values of MPV and WBC indicators can be the following items. First, determination of cut-off point for ST resolution has been different in various studies so that in some studies the cross section of 50% was considered and in the others, 70% was considered that can be very effective in the significance of differences between the groups. Second, the time range was mainly 1 to 4 hours in order to determine resolution after thrombolysis which affects the laboratory indices and occurrence of a complete resolution (which was less than 6 hours in our study). Third, type of thrombolysis therapy as well as its associated treatments may be effective on the occurrence of complete resolution after thrombolysis. It is important to mention that in the above studies, the history of using aspirin and clopidogrel was not included in the exclusion criteria while in our study, patients with history of using these drugs excluded from the study and this point can be effective in the results of the study. Also, type of using technique and its accuracy estimating the laboratory indices will be an important and effective factor in determining the relationship among the indices and occurrence of a complete resolution. So, with the presence of possible contingency indicators mentioned above, it is not possible to find a significant relationship between two MPV and WBC laboratory indices and the occurrence of a complete resolution.

In this regard, history of using statin was only related to resolution occurrence among all basic indices of patients and multiple logistic regression. The obtained result was the reverse finding of Varasteh et al. in which among all patients' indices, only the history of using statins was different between two groups of with and without resolution was different, but the group with the use of statin ST resolution more than 50% [51]. Of course, the cause of this relationship was not evaluated in their study, as well. In some studies, using statins was associated with the improvement of ST resolution [52]. Although, in some other studies, there was not a significant relationship between the history of using statins and occurrence of improving complete ST resolution [53,62]. Maybe, the relationship between using statin and ST resolution is due to the effect of drug on the inflammatory indices and predicting the occurrence and development of ischemia in myocardial tissue; however, it requires further studies and evaluation.

Finally, it can be said that in our study, there is no relationship between the occurrence of complete ST resolution (more than 50%) and the values of both MPV and WBC indicators. Therefore, there are not enough evidences that show the assessment of these indicators have the enough value for predicting ST resolution after thrombolysis based on this study. According to our study, patients with history of using statins have lower prevalence of complete ST resolution (more than 50%).

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