

Combining Biomarkers and TIMI Score for Prediction of Left Ventricular Systolic Dysfunction Among Patients with STEMI

E.V. Sid’

State Institution “Zaporizhzhia Medical Academy of
Postgraduate Education of the Ministry of Health of Ukraine”, Ukraine

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Abstract

The aim of the study was to evaluate possibility combining biomarkers and Thrombolysis In Myocardial Infarction score for prediction of the left ventricular systolic dysfunction among patients with ST-segment elevation myocardial infarction.

Methods: the results of the study are based on data obtained from a comprehensive survey of 280 patients with ST-segment elevation myocardial infarction, the average age was 60,0 [53,0 ; 64,0] years. All persons were comparable in age, social status, and gender.

Results: We found that the basic model was determined by Thrombolysis In Myocardial Infarction score, Se 24,00 % and 86,96 % at Area Under the ROC curve = 0,58 (95% confidence interval 0,515-0,634) with cut off 4 points for the left ventricular systolic dysfunction. To determination of the baseline model with simultaneous three biomarkers (troponin I, metalloproteinase-9, interleukin-6) allowed us to improve the prognosis of left ventricular systolic dysfunction in patients with ST-segment elevation myocardial infarction.

Introduction

Even the use of modern reperfusion methods of treatment does not guarantee the avoiding of a frequent complication among patients with ST-segment elevation myocardial infarction (STEMI) such as the left ventricular systolic dysfunction (LVSD). The development of LVSD is determined by a de-

crease in the left ventricular ejection fraction (LVEF), and can be either a consequence of a decrease in the contractile function of the heart, due to extensive myocardial damage, or a consequence of left ventricular dilation caused by the spread of the myocardial infarction zone. In any case, the mechanism of left ventricular systolic dysfunction in patients with STEMI is a multifactorial pathophysiological process. [1, 2].

Predicting the course in patients with STEMI is one of the most important and difficult tasks that practical Cardiology solves. A convenient tool for assessing risk in clinical practice is special scales that allow to quantify the risk of an adverse event. One of the simplest and most well-known is the TIMI (Thrombolysis in Myocardial Infarction) scale, which allows to determine the probability of death of acute myocardial infarction among patients within 30 days from the onset of the disease [3].

However, the use of scales is not always accompanied by optimal prediction of the risk of an unfavorable outcome, which actualizes the search for new markers to assess the risk of complications. Currently, the researchers' interest is focused on the possibility of predicting the development of LVSD after STEMI using biomarkers. Matrix metalloproteinases contribute to development of the LVSD and have the prognostic value according to studies. An increase in their activity leads to a more aggressive breakdown of intercellular matrix components, which contribute to the further progression of the left ventricular dilation. The process of inflammation plays an important role in the pathophysiology of post-infarct left ventricular repair. However, hyperactivation or prolonged inflammatory response can lead to further heart damage, as well as the development of LVSD. The matrix metalloproteinases and markers of inflammation may improve prediction development of the LVSD among patients with STEMI, which determined the aim of this study [4, 5].

The aim of the study was to evaluate possibility combining biomarkers and TIMI score for prediction of the left ventricular systolic dysfunction among patients with ST-segment elevation myocardial infarction.

Material and methods

The results of the study are based on data obtained from a comprehensive survey of 280 patients with STEMI, the average age was 60,0 [53,0 ; 64,0] years. The sample of patients was carried out in the period from 2015 to January 2018 on the basis of the the MI "Regional medical center of cardiovascular diseases" of the Zaporizhzhia regional Council. All persons were comparable in age, social status, and gender.

Criteria for inclusion in the study: male and female patients from 46 to 75 years of age; for women postmenopausal period is more than 1 year; presence of STEMI in the first 12 hours from the onset of the disease; informed consent of the patient to participate in the study.

Criteria for exclusion from the study: atrioventricular block of II-III degree; permanent form of atrial fibrillation; detection of congenital and acquired hemo-

dynamically significant heart defects; III stage of chronic heart failure; detected left ventricular aneurysm; decompensated concomitant pathology; acute inflammatory diseases or exacerbation of chronic ones; history of coronary artery bypass grafting; oncological diseases.

All patients underwent a comprehensive clinical, instrumental and laboratory examination. AMI diagnosis verification was performed based on the ESC/ACCF/AHA/WHF Third universal definition of myocardial infarction (2012), taking into account the recommendations of the ESC Fourth universal definition of myocardial infarction (2018) [6, 7].

Echocardiography. Echocardiographic study was carried by conventional techniques EACVI (European Association of Cardiovascular Imaging), ASE (the American Society of Echocardiography). Calculated the LVEF using Simpson's method. Determination of the left ventricular systolic function was performed during screening and after 12-14 days [8].

The level of metalloproteinase-9 (MMP-9) and tissue metalloproteinase-2 (TIMP-2) in blood plasma was determined by immunoassay method using standard kits: Human MMP-9 (TIMP-2) ELISA kit (RayBiotech, USA) and highly sensitive C-reactive protein (hs-CRP), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-10 (IL-10) «ELISA-Best» kits (Vektor-Best, Russia). The analysis was carried out using the immunoassay enzyme «SUNRISE TS» (Austria).

Treatment of patients. Patients was after successful reperfusion (postprocedural TIMI-3 flow or ST-segment resolution by >50%): pharmacoinvasive reperfusion strategy were among 66 patients, systemic thrombolytic therapy was performed among 75 patients, primary percutaneous coronary interventions was (PPCI) among 109 patients. Conservative treatment was among 30 (10.7 %) patients. The follow-up treatment was carried out with the anticoagulants, antiaggregants, selective β -blocker, inhibitors of angiotensin converting enzyme, lipid-lowering drugs and nitrates.

Statistical analysis

Statistical processing of the received data was performed on a personal computer using the PSPP application software package (version 1.0.1, GNU Project, 1998-2017, GNU GPL license). For dichotomous division of variables, ROC analysis (Receiver Operating Characteristic curve analysis) was used. We calculated the area under the ROC curve (AUC - Area Under the ROC curve), and its 95% confidence interval (CI), sensitivity (Se), specificity (Sp), the likelihood ratio for positive (+LR) and negative (-LR) results. The Cut off point was found using the J-Youden index.

Results and Discussion

Using two data sets: the first group of patients with LV EF >45 % (n = 230) and the second group with LV EF <45 % (n = 50), ROC analysis was performed. The results are presented in table 1.

Table 1. Comparison of models for predicting the left ventricular systolic dysfunction (n = 280)

Variable	Cut off	AUC	95 % CI AUC	Se, %	Sp, %	P-value
Baseline model	4	0,58	0,515 - 0,634	24,00 %	86,96 %	-
Troponin I, ng/ml	4,75	0,54	0,479 - 0,599	64,00 %	47,39 %	P = 0,59
MMP-9, PG/ml	5247,9	0,69	0,615 - 0,763	88,24 %	53,79 %	P = 0,23
TIMP-2, PG/ml	483,7	0,69	0,617 - 0,764	76,47 %	62,07 %	P = 0,28
IL-6/IL-10	3,71	0,66	0,581 - 0,723	58,33 %	68,32 %	P = 0,69

The baseline model was determined by TIMI score, Se 24,00 % and 86,96 % at AUC = 0,58 (95% CI 0,515-0,634) with cut off 4 points for the left ventricular systolic dysfunction. Comparisons were made with the baseline TIMI score model by selecting biomarkers that had the highest AUC values for the development of left ventricular systolic dysfunction. The AUC values for troponin and MMP-9, TIMP-2, and the IL-6/IL-10 ratio were no better than the baseline model ($p > 0.05$).

Then the procedure was performed adjusting data, rated the baseline model among patients with pharmaco-invasive reperfusion strategy and PPCI by ROC analysis. The first group include patients with LV EF >45 % (n = 156) and the second group with LV EF <45 % (n = 19). The results are presented in table 2.

Table 2. Comparison of models for predicting the left ventricular systolic dysfunction after adjusting data procedure (n = 175)

Variable	Cut off	AUC	95 % CI AUC	Se, %	Sp, %	P-value
Baseline model	4	0,52	0,441 - 0,594	21,05 %	88,46 %	-
Troponin I, ng/ml	2,25	0,58	0,507 - 0,657	42,11 %	58,97 %	P = 0,59
MMP-9, PG/ml	5633,70	0,63	0,531 - 0,721	80,00 %	59,80 %	P = 0,24
IL-6, PG/ml	10,80	0,59	0,497 - 0,675	80,00 %	51,28 %	P = 0,28

Troponin and MMP-9 and IL-6 had the highest AUC values for the development of left ventricular systolic dysfunction. When compared with the baseline model, these biomarkers weren't better ones ($p > 0.05$).

Then the simultaneous determination of troponin and >2.25 ng/ml, MMP-9 >5633.70 PG/ml, and IL-6 >10.80 PG/ml with a TIMI score >4 for predicting left ventricular systolic dysfunction by ROC analysis was evaluated. The results are presented in table 3.

Table 3. Comparison of the improved model with the baseline model for predicting the left ventricular systolic dysfunction

Models	AUC	95 % CI AUC	Se, %	Sp, %	+LR	-LR	P-value
Baseline model	0,52	0,441-0,594	21,05 %	88,46 %	1,82	0,89	P < 0,05
Baseline model + 3 biomarkers*	0,81	0,744-0,865	68,42 %	93,59 %	10,67	0,34	

* - troponin I $>2,25$ ng/ml, MMP-9 $>5633,70$ PG/ml, IL-6 $>10,80$ PG/ml.

To determination of the baseline model with simultaneous three biomarkers (troponin I, MMP-9, IL-6) allowed us to improve the prognosis of left ventricular systolic dysfunction in patients with STEMI. An increase in the quality of the improved model by AUC = 0.81 was accompanied by an increase in Se from 21.05% to 68.42 %, as well as an increase in the likelihood ratio for positive results from 1.82 to 10.67.

The TIMI score risk assessment may have some variability in AUC, since the populations in which it was developed, relates to clinical trials, and it may not correspond to local reality. A higher quality of the defined model for our population composed patients with different treatment strategies. Then, it is known that the quality of the TIMI score model can be influenced by the treatment strategy [9].

For many years, one of the most pressing challenges in cardiology has been predicting outcomes for patients with STEMI. Single-marker models do not have an advantage over scales in predicting the development of complications, since this is a multi-factor process. Currently, discrete risk stratification, which is based only on the definition of one indicator, has lost its relevance due to its low prognostic significance [10].

Conclusions

1. For patients with STEMI who receive successful reperfusion, with an AUC of 0.52, 95% CI of 0.441-0.594, the TIMI score is of poor model quality.

2. A discrete model based on the definition of only one biomarker has advantages over the baseline TIMI score model.

3. In patients with STEMI, a multi-marker strategy that combines biomarkers of necrosis, extracellular matrix degradation, and inflammation along pathobiological axes provides additional prognostic information for predicting the left ventricular systolic dysfunction and improves the baseline model.

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Ethical declaration. The study was approved by the local ethics committee of State Institute «Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine». The study was carried out in conformity with the Declaration of Helsinki.

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