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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ
ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

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3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალებების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემაში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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რეს და $4,04 \pm 0,44$ მმ მარჯვნივ. ლოყის მიდამოს საშუალო სისქემ შეადგინა $9,79$ მმ და ცხიმოვანი ბურთულის სისქემ - $5,4$ მმ.

ნატარებელი კვლევიით მიღებული მონაცემები დაეხმარება ყბა-სახის ქირურგებს ცხიმოვანი ბურთუ-

ლის სინჯის ეფექტურ შერჩევაში პაციენტებისათვის სხვადასხვა სახის ტიპით პირის ღრუს ქსოვილების დეფექტების რეკონსტრუქციისათვის მზადების პერიოდში, რაც უზრუნველყოფს შესაძლებელი გართულებების თავიდან აცილებას.

BIOMARKER sST2 AS AN EARLY PREDICTOR OF ACUTE RENAL INJURY IN PATIENTS WITH ST-SEGMENT ELEVATION ACUTE MYOCARDIAL INFARCTION

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One of the serious complications of acute myocardial infarction (AMI) is acute kidney injury (AKI) [2,3,13,19]. The frequency of AKI development in AMI according to various authors differs from 10 to 27% [7]. Modern methods of AMI treatment also contribute to the formation of AKI, namely, contrast-induced nephropathy. It is known that AKI significantly deteriorates the prognosis of the disease and raises mortality during the first year [18].

To reveal this formidable complication, new markers of cardio-renal dysfunction, which level elevates before the development of AKI, are being investigated.

Promising in this respect is the stimulating growth factor ST2 (its soluble form sST2). It is a peptide belonging to the family of interleukin-1 receptors, which secreted when cardiomyocytes and heart fibroblasts subjected to mechanical stress [11]. The main function of ST2 is potentiating of IL-33 effects, which has an antihypertrophic anti-fibrotic effect on cardiomyocytes under biomechanical stretching conditions. However, a sharp increase in the ST2 level in case of injury accompanied by inhibition of IL-33 favorable antihypertrophic effects [9].

Role of biomarker sST2 in heart failure formation studied well. Elevated concentration of sST2 predicts mortality in patients with heart failure and stable ischemic heart disease [5]. Elevated ST2 level is a predictor of major adverse cardiac events in acute coronary syndrome patients [20] AMI patients undergoing PCI [21], higher sST2 concentration at baseline predicts poor clinical outcome in ACS patients, including all-cause mortality, HF events, and MACEs [6].

Limited number of studies regarding the role of biomarker sST2 in AKI prediction performed. One of the first study in 2011 indicated that IL-33 promotes AKI in cisplatin-induced model. [1; 4]. Nowadays, there is not enough data to convincingly talk about the role of the sST2 biomarker in predicting acute renal damage.

The purpose of our study is to analyze the prognostic significance of sST2 biomarker in identifying the risk of AKI development in patients with ST-segment elevation myocardial infarction (STEMI).

Material and methods. The study included 103 patients with STEMI, of which 75 patients were male (72.8%) and 28 female (27.2%), the mean age of participants was 61.85 ± 12.23 years.

Patients were hospitalized in the intensive care unit during the first day of the disease. Patients were subjected to selective coronary angiography (SCAG) with subsequent stenting of the infarct-related artery. The control group consisted of 10 practically healthy persons, comparable by gender and age to the patients under examination.

The diagnosis of STEMI was established based on clinical, electrocardiographic and biochemical studies in compliance with European guidelines for the diagnosis and treatment of STEMI (2017). The study was carried out in compliance with the provisions of the Helsinki Declaration, the protocol was approved by the local Ethics and Deontology Commission (protocol No. 12 of 21.10.15).

Criteria for inclusion into the study concerned patients with STEMI, who arrived in the hospital during 24 hours after the onset of the symptoms and agreed to participate in the study. The exclusion criteria were: refusal to sign the Patient Informed Consent, infectious and inflammatory diseases at the stage of exacerbation, acute renal failure (need for hemodialysis), acute liver failure, and inability to follow the protocol of the study.

Conventional coronary angiography performed using Digital X-Ray system "Integris Allura" (Philips Healthcare, Best, The Netherlands), managed by radial or femoral access. Coronary arteries visualized with two-to-three orthogonal projections. In this study, the contrast "Ultravist-370" (Bayer Pharma GmbH, Germany), automatic contrast injector used. The contrast amount used in coronary angiography in each injection was 8 – 10 mL for the left coronary artery and 6 mL for the right coronary artery. The coronary arteries were divided into segments according to the American Heart Association classification

Reperfusion therapy was performed as follows: primary percutaneous coronary intervention (PCI) - 28 (27.2%), thrombolysis - 28 (27.2%), thrombolysis with subsequent PCI - 27 (26.2%), 20 (19, 4%) patients refused reperfusion for personal reasons or because of contraindication. According to (SCAG) data, the damage to coronary arteries with stenosis of more than 50% was considered significant. Stenosis of a single vessel was observed in 17 patients (32.7%), multi-vessel coronary artery injuries - in 35 patients (67.3%). During the whole treatment period, STEMI patients received treatment according to the standard protocol.

According to SCAG, 16 (29.1%) patients had a single vessel

lesion, 16 (29.1%) had a two-vessel lesion and 23 (41.8%) patients had a multi-vessel lesion (three or more vessels). Coronary Artery Bypass Grafting (CABG) was not performed urgently after CAG for any single patient; this treatment recommended for two patients with multivascular damage (3 or more vessels with stenosis of more than 70% and in the range of 50-70%). CABG performed to the one patient in a delayed period (after the next two years), the second patient reached the endpoint (death).

Echocardiography was performed during hospitalization of a patient in hospital with the MedisonSonoAceX6 device (Korea), end-diastolic (ED) and end-systolic (ES) left ventricle (LV) volume, end-systolic (ES) and end-diastolic (ED) LV dimension, myocardial LV weight (LVM), left ventricular ejection fraction – LVEF by Simpson, left atrium (LA) diameter, LV diastolic dysfunction - maximal velocity of early diastolic filling E (m/s), maximum velocity of atrium diastolic filling A (m/s), their ratio E/A were assessed.

With the help of the AKI network classification (KDIGO, 2013), the kidney function deterioration evaluated. A group of patients selected (n = 68), by which the creatinine level determined over 48 hours. These patients divided into 2 groups depending on the dynamics of serum creatinine level. The first group included 23 patients with an increase in serum creatinine level by more than 26.4 $\mu\text{mol/l}$ for 48 hours, corresponding to the first and higher stages of AKI. The second group included the remaining 45 patients, where the above-indicated dynamics of creatinine were not obtained.

All patients were determined standard and additional clinical and biochemical parameters on the first day of the disease.

Troponin I (Tn I) level was measured by chemoluminescent immunoassay (Humalyzer 2000, HUMAN GmbH, Germany) according to the manufacturers' recommendations. The average of Tn I level was 0.5-50 ng/mL to all included patient to confirm STEMI diagnosis. In the whole group of patients the troponin level was equal to 3.83 [1,14-10,65] ng/ml.

The level of sST2 was determined by the enzyme-linked immunoassay using the "Presage ST2 Assay" reagent kit, Critical Diagnostics, (USA), the N-terminal pro B-type natriuretic peptide level was determined using a set of "NT pro BNP-IFA-BEST" (RF) during the first 24 hours after the event.

Statistical processing of the obtained data was carried out using «STATISTICA® for Windows 6.0» (StatSoft Inc., №AXXR712D-833241FAN5). Categorical variables were expressed as numbers and percentages, and the χ^2 -Pearson test was used to compare the

variables between the groups under study. To determine the correlation between sST2 level and the indices studied, a correlation analysis (correlation coefficient (r) by Pearson, Spearman) was used. Intergroup differences in qualitative characteristics were assessed using the Mann-Whitney U-criterion. "ROC" receiver operating system was used to assess the biomarkers discriminatory capacity. The regression analysis was used as a statistical method for determining the effect of an independent variable on the dependent variable. For all types of analysis, differences were considered statistically significant at $p < 0.05$.

Results and their discussion. In patients of the control group, the sST2 level was 19.4 [15.9-29.1] ng/ml and significantly differed from the ST2 level in the AMI group (38.28 [26.90-72.81] ng/ml) ($p < 0.05$).

Comparative characteristics of patients depending on their reaching the endpoint - death from all causes within the 6 months - is presented in Table 1.

It was found that the level of creatinine during hospitalization in patients who died was reliably higher than that in patients who survived ($p=0.05$), the same reliability was maintained when comparing creatinine level after 48 hours ($p=0.02$). Additionally, in the studied groups, the level of sST2 biomarker ($p=0.008$) and NTproBNP ($p=0.0001$) differed reliably. We did not find a significant difference in the levels of troponin I in the studied groups; there was no relationship between the level of the sST2, NT-pro BNP, and the level of troponin I.

As a result of the ROC analysis performed, it was found that creatinine was an independent predictor of an adverse outcome within the 6 months period (AUC 0.664, CI 0.552-0.764, sensitivity 90%, specificity 50%, associated limit $> 108 \mu\text{mol/l}$), Pic. 1.

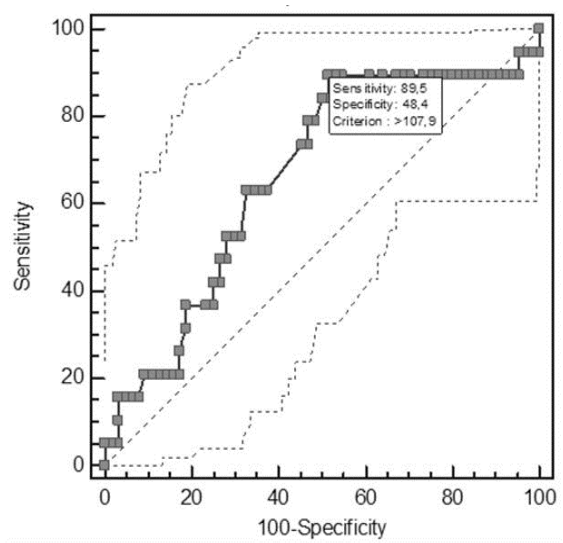
The construction of the Kaplan-Meier curve for the included patients depending on the level of creatinine and their achievement of the endpoint (death after 6 months) was performed, Pic. 2.

Accumulation of endpoints, depending on the factors above, led to an early (1 month) divergence of survival curves, and by the end of the observation period reached a prognostically significant level ($p=0.0003$). To determine the degree of creatinine level effect on reaching the endpoint within 6 months, a stepwise regression analysis of proportional Cox risks was used ($T1=8.64$; $T2=11.35$; $F=6.47$; $p = 0.00053$).

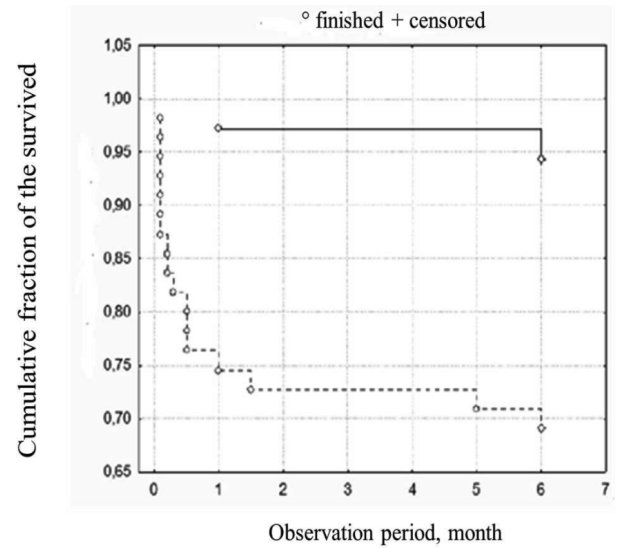
A direct correlation between the level of sST2 and blood serum

Table 1. Comparative characteristic of patients with MI depending on the prediction after 6 month

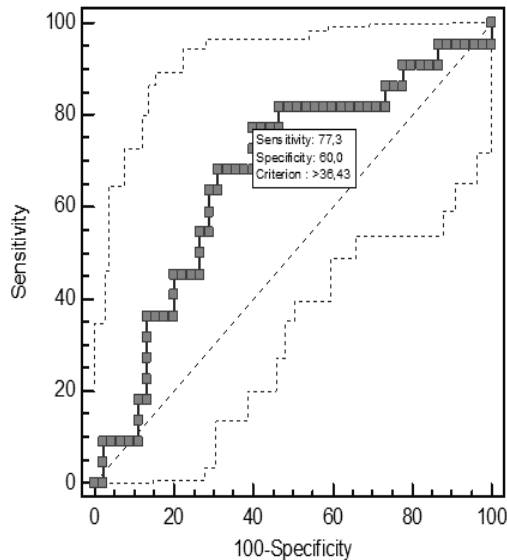
Indices	Patients, who died (n = 20), median, upper, lower quartile	Patients, who survived (n = 83) median, upper, lower quartile	*p
Blood serum creatinine (at hospitalization), $\mu\text{mol/l}$	130 [115;140]	118 [100;135]	0.05
Blood serum creatinine (after 48 hours), $\mu\text{mol/l}$	161 [115;213]	122 [104;131]	0.02
sST2 at hospitalization, ng/ml	111 [38.5;140]	62.46 [26;66]	0.008
Blood serum glucose, mmol/l	11.3 [7;15]	9.29 [6.3;9.9]	0.16
NTpro-BNP, ng/ml	1432,97 [147,70 -2548,26]	63,68 [29,93-597,77]	0.0001
Hemoglobin, g/l	136 [127;143]	137 [130;148]	0.4
LVEF, %	45 [38;50]	53 [48.5;60]	0.01
Heart, beats per minute	91 [78;104]	77 [65;90]	0.04



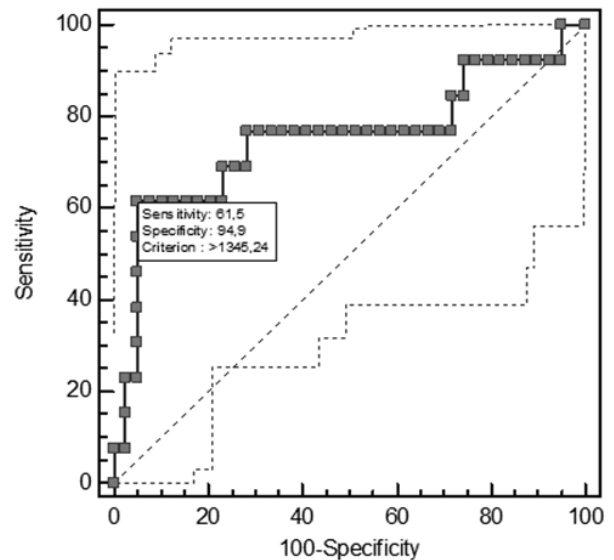
Pic. 1. ROC curve for blood serum creatinine defined in patients depending on the disease outcome within the 6 months period



Pic. 2. Kaplan-Meier curve



Pic. 3. ROC curve for sST2 defined in patients depending on the disease outcome within the 6 months period



Pic. 4. ROC curve for blood NT-pro BNP defined in patients depending on the disease outcome within the 6 months period

creatinine was revealed ($r=0.4$; $p=0.0006$). On this basis, it can be assumed that an increase in the level of a biomarker is associated with the renal function decrease in patients with STEMI.

The constructed ROC curve showed that the optimal threshold sST2 value for predicting the renal function deterioration is 36 ng/ml with sensitivity (Se) and specificity (Spe) of 77% and 60% respectively (Area under the curve (AUC) being 0.67; Confidence Interval (DI) being 95% 0.53-0.8; $p=0.02$), Pic. 3.

ROC-curve for NT-pro BNP has determined its threshold val-

ue as 1345 ng/ml (AUC=0.75; 95% CI 0.56-0.94; Se 60%; Spe 95%; $p=0.0089$), Pic. 4.

In multivariate regression analysis, we found that sST2 and blood glucose are the only significant predictors of acute kidney injury during the first 48 hours ($R^2=0.437$, $P<0.001$) among the parameters included into the study, such as the NT-pro BNP biomarker, ejection fraction, E/A ratio, end diastolic volume and hemoglobin level.

In patients, the strongest connection with decreased renal function during the first 48 hours from the onset of the disease

Table 2 Factors associated with decreased renal function in patients with STEMI

STEMI patients, n=103	Factors	Odd Ration	Beta	β	p
	sST2, pg/ml	0.103	0.44	0.2	0.0006
	Glucose, mmol/l	0.1048	0.28	2.45	0.008

was found in sST2 and blood glucose indices. Factors associated with decreased renal function in patients with STEMI are presented in Table 2.

The problem of AKI in STEMI patients is very actual because PCI is main treatment for this condition and using a contrast leads to deterioration of kidney function.

In previous studies reported that the AKI incidence was 6.2% in STEMI patients with preserved EF before PPCI [17]. In our study such complication were reached by 23% of patients. In this article, we discussed the importance of timely diagnosis of AKI, since this condition is significantly associated with the mortality of patients in the intensive care unit. We have selected the sST2 biomarker, since its levels are not influenced by age, initial renal function, body mass index, which gives sST2 a practical advantage over NT-pro BNP for predicting AKI [16].

In current study elevated level of creatinine associated with high mortality, that means that deterioration of renal function strongly connect with surveillance. In this study, we first demonstrated the prognostic ability of sST2 biomarker in selecting patients with high risk of AKI formation. We consider our results relevant, since this condition significantly complicates the treatment of patients with myocardial infarction, because AKI makes it difficult use a contrast for PCI, to prescribe such drugs as ACE inhibitors. We managed to confirm, using various statistical methods, that sST2 biomarker is really a powerful tools in the AKI prediction.

Thus, in our study, we first proved that rises of the sST2 biomarker level has a prognostic power in predicting the formation of acute renal injury in patients with STEMI. There is a small amount of research studying the role of sST2 biomarker in this problem. So, Lobdell K.W.et al. have proven that in patients undergoing coronary artery bypass grafting, the level of the above biomarker prior to the operation is a predictor of AKI after the intervention [10].

The sST2 biomarker, in the result of a multivariate analysis, turned to be the most significant marker for predicting the AKI development, despite the fact that NT-pro BNP had a higher sensitivity, but its specificity was slightly inferior to ST2.

In this study, the sST2 biomarker has outweighed the predictive power of the NT-pro BNP biomarker, which is the reference marker of left ventricular dysfunction. We have proved that the use of two biomarkers gives us a more complete picture to predict the AKI formation.

In 2018, a study on the role of sST2 biomarker in a cohort of patients with a terminal stage of kidney disease was published in the Clinical Chemistry journal. It has been found that its increase by more than 35 ng / ml is associated with cardiovascular mortality, overall mortality [15, 8, 14, 12]. These findings made us think about high actuality of chosen topic. In our study equal level of sST2 independently predicted AKI formation.

In the study, 27 patients had a history of type 2 diabetes mellitus; the average blood glucose level in the first 24 hours from the onset of AMI was 9.68 ± 5.20 mmol / L. In this case, an increase in glucose considered as stressful hyperglycemia of critical conditions, which was AMI. Well-known that stressful hyperglycemia leads to an increase in apoptosis of myocardial cells, suppression of stem cell activity in the peri-infarction zone, impaired effectiveness of myocardial pre- and postconditioning, an increase in the damage zone, and a worse prognosis. These all explain the presence of glucose in the results of the multivariate analysis as a predictor of AKI.

Our study has several limitations. First, we acknowledge all limitations associated with the study design (i.e., single-center, retrospective study). Second, the incidence of AKI may have been underestimated in patients who died within the first few hours of hospital admission, as changes in serum creatinine levels were not assessed in those patients. Third, I.V. crystalloid infusion was based on the hemodynamic status of each STEMI patient individually. Finally, we generally defined AKI as at least.

Conclusions.

1. The role of the biomarker ST2 in the early stratification of reduced kidney function in patients with STEMI suggests the development of AKI.

2. We showed that level of sST2 > 36 pg/ml could predict deterioration of kidney function in STEMI patient with sensitivity 77% and specificity 60%. The biomarker was significant and independent predictor of AKI.

3. The first time a prognostic model has developed and this model used simple, but important factors. Routine measures should be recommended.

Prospects for further research: further observation of patients with the assessment of their condition over a longer follow-up period, 5-year after STEMI, seems perspective. A comparative evaluation of therapy approaches, its influence on renal function and effectiveness depending on the level of sST2 at admission, as well as in dynamics, is promising.

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SUMMARY

BIOMARKER sST2 AS AN EARLY PREDICTOR OF ACUTE RENAL INJURY IN PATIENTS WITH ST-SEGMENT ELEVATION ACUTE MYOCARDIAL INFARCTION

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One of the serious complications of ST-segment elevation myocardial infarction (STEMI) is acute kidney injury (AKI). Promising in this respect is the stimulating growth factor sST2. A sharp increase of ST2 level in case of injury is accompanied by inhibition of IL-33 favorable antihypertrophic effects.

The purpose - to analyze the prognostic significance of sST2 biomarker in identifying the risk of AKI development in patients with STEMI.

The study included 103 patients with STEMI, of which 75 patients were men (72.8%) whose mean age was (61.85±12.23) years. Patients were hospitalized at the intensive care unit during the first day of the disease. Patients were subjected selective coronary angiography (SCAG) with subsequent stenting of the infarct-related artery. Criteria for inclusion into the study concerned patients with STEMI, who arrived in the hospital during 24 hours after the onset of the symptoms and agreed to participate in the study. The level of sST2 was determined during the first 24 hours after the event.

In multivariate regression analysis, we found that sST2 and blood glucose are the only significant predictors of acute kidney injury during the first 48 hours (R²=0.437, P<0.001) among the parameters included into the study, such as the NT-pro BNP biomarker, ejection fraction, E/A ratio, end diastolic volume and hemoglobin level. The first time a prognostic model has developed and this model used simple, but significant factors.

The role of the biomarker ST2 in the early stratification of reduced kidney function in patients with STEMI suggests the development of AKI.

Keywords: acute renal injury, myocardial infarction, prognostic factors, biomarkers.

РЕЗЮМЕ

БИОМАРКЕР sST2 КАК РАННИЙ ПРЕДИКТОР ОСТРОГО ПОЧЕЧНОГО ПОВРЕЖДЕНИЯ У БОЛЬНЫХ ОСТРЫМ ИНФАРКТОМ МИОКАРДА С ПОДЪЕМОМ СЕГМЕНТА ST

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Одним из серьезных осложнений острого инфаркта миокарда с подъемом сегмента ST (ОИМп ST) является острое повреждение почек (ОПП). Перспективным в этом отношении

