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Стаття надійшла до редакції
11.04.2022

UDC 616.127-005.8-036.11-078-037:616.12-008.46 https://doi.org/10.26641/2307-0404.2022.3.265932

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A MODEL FOR PREDICTING ACUTE HEART FAILURE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION BY TAKING INTO ACCOUNT ENERGY AND ADIPOKINE METABOLISM INDICATORS

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Цитування: Медичні перспективи. 2022. Т. 27, № 3. С. 64-71
Cited: Medicni perspektivi. 2022;27(3):64-71

Key words: *adipokine, energy homeostasis, myocardial infarction, heart failure, prognosis*
Ключові слова: *адипокін, енергетичний гомеостаз, інфаркт міокарда, серцева недостатність, прогнозування*

Abstract. A model for predicting acute heart failure in patients with acute myocardial infarction by taking into account energy and adipokine metabolism indicators. Koteliukh M.Yu. *Acute heart failure (AHF) is one of the most common complications of acute myocardial infarction (AMI). Currently, adropin, irisin, fatty acid binding protein 4 (FABP 4) and C1q/TNF-binding protein 3 (CTRP 3) are considered to be valid markers of energy homeostasis and the adipokine system in AMI patients. The aim of the study was to predict the development of AHF in AMI patients by taking into account indicators of energy homeostasis and adipokine system using generalized linear mixed model. The study examined 189 patients with acute ST-segment elevation myocardial infarction. Concentrations of adropin, irisin, insulin, FABP4 and CTRP3 were determined by enzyme-linked immunosorbent assay. Fasting capillary blood glucose level was measured by glucoseoxidase method. Insulin resistance (IR) was assessed using homeostasis model assessment of insulin resistance (HOMA-IR). The study identified thrombolysis in myocardial infarction (TIMI) grade before intervention. A generalized linear mixed model was used to develop a method for predicting AHF in AMI patients. The study showed decreased levels of adropin, irisin and CTRP3 and increased levels of FABP4 in AMI patients. A mathematical model for predicting AHF development in AMI patients was proposed. The model consisted of fixed effects, namely, two one-factor indicators (HOMA-IR and systolic blood pressure (BP)), one two-factor indicator (systolic and diastolic BP) and one three-factor indicator (adropin, irisin and CTRP3) and random effects such as four one-factor indicators (FABP4, TIMI Grade Flow, platelets, total cholesterol). The accuracy of predicting the absence of Killip class I AHF was 100%, Killip class II AHF – 0%, Killip class III AHF – 11%, Killip class IV AHF – 82%. It should be noted that systolic BP on day 1 was a strong negative prognostic factor, while HOMA-IR, the combined effect of adropin, irisin and CTRP3, the combined effect of systolic and diastolic BP were positive prognostic factors. Thus, the model showed a very high sensitivity in predicting Killip class IV AHF. The overall accuracy of the model was 89.4%.*

Реферат. Модель прогнозування гострої серцевої недостатності в пацієнтів з гострим інфарктом міокарда з урахуванням показників енергетичного й адипокінового обміну. Котелюх М.Ю. *Однією з частих ускладнень гострого інфаркту міокарда (ГІМ) є гостра серцева недостатність (ГСН). Сьогодні актуальними маркерами енергетичного гомеостазу та адипокінової системи є адропін, ірисин, білок, що зв'язує жирні кислоти 4 (FABP 4), і C1q/TNF-зв'язуючий білок 3 (CTRP 3) у хворих з ГІМ. Метою дослідження було спрогнозувати розвиток ГСН у хворих з ГІМ з урахуванням показників енергетичного й адипокінового обміну за допомогою узагальненої лінійної змішаної моделі. Проведено обстеження 189 пацієнтів з ГІМ та елевацією сегмента ST. Вміст адропіну, ірисину, інсуліну, FABP 4, CTRP 3 визначено за допомогою імуноферментного методу. Рівень глюкози проведено глюкооксидантним методом у капілярній крові натщесерце. Інсулінорезистентність визначено за допомогою гомеостатичної моделі оцінки інсулінорезистентності (HOMA-IR). У дослідженні застосовано шкалу тромболізису при інфаркті міокарда (TIMI) до втручання. Для розробки способу прогнозування ГСН у пацієнтів з ГІМ було застосовано генералізовану лінійну змішану модель. Констатовано зниження вмісту адропіну, ірисину і CTRP 3 та збільшення концентрації FABP 4 у пацієнтів з ГІМ. Запропоновано математичну модель прогнозування розвитку ГСН у пацієнтів з ГІМ. Модель складається з фіксованих ефектів: двох однофакторних: індекс HOMA-IR і систолічний артеріальний тиск (АТ), одного двофакторного: систолічний та діастолічний АТ і одного трифакторного показника: адропін, ірисин і CTRP 3 та випадкових ефектів – чотирьох однофакторних показників: FABP 4, шкала TIMI, тромбоцити, загальний холестерин. Точність прогнозу відсутності розвитку ГСН I класу за Кілліпом становить 100%, прогноз ГСН II класу за Кілліпом – 0%, прогноз ГСН III класу за Кілліпом – 11%, прогноз ГСН IV класу за Кілліпом – 82%. Слід зазначити, що сильним негативним прогностичним фактором є систолічний АТ на 1 добу, а позитивним прогностичним фактором є індекс HOMA-IR, спільний вплив адропіну, ірисину і CTRP 3, спільний вплив систолічного й діастолічного АТ. Отже, установлений дуже високий рівень чутливості моделі до передбачення ГСН IV класу за Кілліпом. Загальна точність моделі становила 89,4%.*

Acute heart failure (AHF) is a major cause of mortality and reduced quality of life in patients with acute myocardial infarction (AMI). Despite the implemented interventional methods of treatment and reduction of the overall mortality rate in AMI patients, the mortality rate among individuals with AHF remains quite high and stable. During a 5-year follow-up period of AMI patients, the AHF-related mortality was 40.8% [4]. A multifactorial mechanism of development of changes in patients with AMI complicated by AHF has been determined based on the study of clinical and functional predictors of AHF development [1]. V.D. Syvolap et al. [15] have found that hyperglycemia and left ventricular systolic dysfunction are independent risk factors for AHF in AMI patients. Adropin and irisin are currently considered to be markers of energy homeostasis, whereas fatty acid-binding protein 4 (FABP4) and C1q/TNF-binding protein 3 (CTRP 3) – of the adipokine system [2, 10, 12, 13]. Indicators of energy homeostasis and the adipokine system influence the development and course of AMI via suppression of numerous inflammatory signaling pathways. An imbalance in energy homeostasis and the adipokine system can have an impact on the development of AMI complications, in particular AHF. To date, the role of energy homeostasis and the adipokine system markers in AHF development following AMI is still

insufficiently studied and therefore it is of research interest to scientists.

The aim of the study was to predict the development of AHF in AMI patients by taking into account indicators of energy homeostasis and adipokine system using generalized linear mixed model that would improve diagnostic accuracy in the examination of these patients.

MATERIALS AND METHODS OF RESEARCH

The study involved examination of 189 patients aged 58.85±7.83 years with ST-segment elevation AMI (STEMI), hospitalized to the Government Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" and the Kharkiv Railway Clinical Hospital No. 1 of the branch "Center of Healthcare" of Public Joint Stock Company "Ukrainian Railway". The study was conducted between 01 September 2018 and 31 December 2020.

The study was performed in accordance with the principles of the World Medical Association Declaration of Helsinki "Ethical principles for medical research involving human subjects". All patients signed an informed consent to participate in the study. The study was approved by Minutes No. 2 of the Ethics Commission of Kharkiv National Medical University dated 02.04.2018. The article is part of the research work "Prediction of the course, improvement of diagnosis and treatment of coronary heart disease and hypertension in patients with metabolic disorders" (registration number 0120U102025).

An inclusion criterion was STEMI with the presence of AHF in patients.

Exclusion criteria were type 1 and 2 diabetes, COVID-19, autoimmune diseases, pituitary and hypothalamic diseases, thyroid disease, symptomatic hypertension, valvular heart disease, IV functional class chronic heart failure to myocardial infarction, chronic obstructive pulmonary disease, severe liver and kidney dysfunction, severe anemia, malignancy.

We followed the 2017 European Society of Cardiology Guidelines on the diagnosis and management of patients with STEMI [9]. All the patients underwent percutaneous coronary intervention (PCI) with stent implantation in the coronary artery. Patients received the following medication treatment during: anticoagulants, acetylsalicylic acid, ticagrelor or clopidogrel, high doses of statins, nitrates, beta-blocker (depending on heart rate), angiotensin-converting enzyme inhibitor (for blood pressure control), eplerenone or spironolactone (for patients with reduced left ventricular ejection fraction and signs of heart failure).

Blood serum was collected on day 1-2 of follow-up. General clinical and biochemical methods of examination were applied in the study [1]. Serum concentration of insulin, troponin I, adropin, irisin, FABP 4, CTRP 3 of patients was determined by enzyme-linked immunosorbent assay using commercial test systems "Human Insulin" (Monobind Inc, Lake Forest, USA), "Human troponin I" (Xema-Medica Co. Ltd, Moscow, Russia), "Human Adropin", "Human FNDC5", "Human FABP 4" (Elabscience, USA) and "Human CTRP 3" (Aviscera Bioscience Inc, Santa Clara, USA) following the manufacturers' instructions. Fasting capillary blood glucose level was measured by glucoseoxidase method. Insulin resistance (IR) was measured using the homeostatic model of insulin resistance assessment (HOMA-IR). Mean values and reference ranges were defined as follows: 23.58 (19.76-26.82) pg/ml for adropin, 5.97 (2.74-8.69) ng/ml for irisin, 5.02 (3.14-8.98) ng/ml for FABP 4 and 325.97 (274.59-399.96) ng/ml for CTRP 3.

Optimal weight was estimated using ***body mass index*** (BMI) which was calculated as weight in kilograms divided by height in meters squared. The study determined a scale of Thrombolysis in Myocardial Infarction (TIMI) flow grade before intervention.

Statistical data were processed using the licensed software package "IBM SPPS Statistics (version 27.0", 2020, license No. L-CZAA-BKKMKE). The main calculated statistical parameters were as follows: mean (M) and standard deviation (SD). Nominal variables were expressed as number and percentage. The difference was considered significant at a level of $p<0.05$. Generalized linear mixed models (GLMM) were applied in the study to predict AHF development [14]. This type of statistical models provides high flexibility in the construction and new hypotheses testing, as correlations are found at the level of mean values of variables, their dispersions and covariances. The GLMM linear predictor combines fixed (β) and random (υ) effects as:

$$\eta = X\beta + Z_{\upsilon} ,$$

where, η – is the linear predictor of GLMM; β – represents fixed effects and υ - random effects included in the model, whereas X and Z are the matrix of fixed and random effects sought in the model, respectively.

Here, the study predictor variables are given as follows:

$$y = \eta + \varepsilon ,$$

where y – is the study predictor variable; ε – is the residual vector.

Then, the expected GLMM values are:

$$E(y|\eta) = g^{-1}(X\beta + Z_{\upsilon}) = g^{-1}(\eta) ,$$

the relationship between the study variables and the predictor is sought using GLMM as:

$$(y|\eta)\sim(g^{-1}(\eta),R)$$

The above value means that the distribution of study value *y* is determined by the prediction η with the mean value of $g^{-1}(\eta)$ and the variation R. The entire GLMM procedure was implemented as a corresponding function of the IBM SPSS Statistical package.

RESULTS AND DISCUSSION

The main clinical characteristics of AMI patients are shown in Table 1. In our study, the majority of AMI patients were male (83.6%), and 68.25% of AMI patients were overweight. The concentrations of adropin, irisin, CTRP3 in AMI patients were reduced by 32.27%, 67.67%, 24.29%, respectively, on day 1-2. The content of FABP4 on day 1-2 was found to be increased more than 2-fold compared to its mean value. The vast majority of AMI patients had Killip classes I and IV AHF, coronary artery occlusion by the TIMI grade. AMI patients had dyslipidemia and hypertension. On admission, blood pressure ≥140/90 mm Hg was in 43.38% of patients, ≥180/110 mm Hg – in 10% of patients. AHF episodes were shown to end with recovery of patients during the follow-up.

Table 1

Baseline clinical characteristics

Characteristics	Value: n, %, M±SD
Age, years	**58.85±7.83**
Sex (male)	**158 (83.59)**
Sex (female)	**31 (16.40)**
Weight, kg,	**83.15±13.06**
Height, cm	**172.88±7.71**
BMI, kg/m^2	**27.76±4.11**
Overweight	**68 (35.97)**
Obesity	**61 (32.27)**
Arterial hypertension	**189 (100)**
Medical history of myocardial infarction	**15 (7.93)**
Killip class prior to admission: I	**152 (80.42)**
II	**11 (5.82)**
III	**12 (6.34)**
IV	**14 (7.40)**
Systolic BP, mm Hg	**138.56±28.17**
Diastolic BP, mm Hg	**83.24±15.84**
Total cholesterol, mmol/L	**5.33±1.24**
Triglyceride, mmol/L	**1.79±0.97**
LDL, mmol/L	**3.36±1.11**
VLDL, mmol/L	**0.82±0.45**
HDL, mmol/L	**1.22±0.39**
AC	**3.65±1.47**
Platelets, ×10^9/L	**237.18±63.69**
Glucose, mmol/L	**6.77±2.47**

Table 1 continued

Characteristics	Value: n, %, M±SD
Insulin, μlU/mL	**19.97±12.63**
HOMA-IR	**8.26±4.60**
Troponin I, ng/mL	**2.58±2.86**
TIMI flow grade before intervention **0**	**108 (57.1)**
1	**31 (16.4)**
2	**24 (12.7)**
3	**26 (13.8)**
Irisin, ng/mL	**1.93±0.68**
Adropin, pg/mL	**15.97±5.57**
FABP4, ng/mL	**10.89±3.18**
CTRP3, ng/mL	**246.79±52.86**

Notes: BP – blood pressure, BMI – body mass index; FABP 4 – fatty acid binding protein 4; CTRP 3 – C1q/TNF-binding protein 3; HOMA-IR – homeostasis model assessment of insulin resistance; AC – atherogenic coefficient; LDL – low density lipoproteins; VLDL – very low density lipoproteins; HDL – high density lipoproteins; TIMI – thrombolysis in myocardial infarction.

Killip class I, II, III, IV AHF was used as the study predictor variable. In that case, it was *y* for GLMM. A total of 118 indicators were measured in AMI patients on day 1-2. The first stage involved determination of statistically significant correlations between *y* and the measured parameters. This significantly reduced the number of possible variables in the GLMM, listed in Table 2.

Table 2

Indicators selected for GLMM

Indicator, units of measurement	Statistical significance	Correlation with *y*
HOMA-IR	**p<0.01**	**0.234**
Insulin, μlU/mL	**p<0.05**	**0.147**
Adropin, pg/mL	**p=0.05**	**0.103**
Irisin, ng/mL	**p<0.01**	**0.201**
FABP4, ng/mL	**p<0.05**	**0.144**
CTRP3, ng/mL	**p=0.05**	**-0.002**
Systolic BP, mm Hg	**p<0.01**	**-0.401**
Diastolic BP, mm Hg	**p<0.01**	**-0.356**
TIMI Grade Flow	**p<0.05**	**-0.135**
Platelets, $\times 10^9$/L	**p<0.01**	**0.187**
Total cholesterol, mmol/L	**p=0.05**	**-0.083**
AC	**p<0.05**	**-0.164**

Notes: BP – blood pressure; FABP 4 – fatty acid binding protein 4; CTRP 3 – C1q/TNF-binding protein 3; AC – atherogenic coefficient; HOMA-IR – homeostasis model assessment of insulin resistance; TIMI - thrombolysis in myocardial infarction.

All correlations were statistically significant but minimal. The next stage was to sequentially consider all the options from Table 1 for including and excluding selected variables in the number of fixed

and random effects of the model. The criteria for selecting a high-performance and statistically validated model were as follows: information (Akaike and Bayesian) criteria, overall statistical significance of the model and its variables (in our case $p<0.05$).

Thus, we tested all possible hypotheses and combinations of variables, until we found the best statistically significant model in terms of accuracy of *y* prediction and all its independent variables: fixed effects from Table 3 and random effects from Table 4.

Table 3

Indicators of fixed GLMM effects

Indicator	Statistical significance, p	Coefficient in GLMM, *X*
One-factor indicators		
HOMA-IR	**p=0.019**	**0.116**
Systolic BP	**p<0.001**	**-0.150**
Two-factor indicators (combined impact of two-factor indicators)		
Systolic and diastolic BP	**p=0.001**	**$6.7\ 10^{-4}$**
Three-factor indicators (combined impact of three-factor indicators)		
Adropin, irisin and CTRP3	**p=0.042**	**$8.8\ 10^{-5}$**

Notes: BP – blood pressure; CTRP 3 – C1q/TNF-binding protein 3; HOMA-IR – homeostasis model assessment of insulin resistance; AC – atherogenic coefficient; TIMI – thrombolysis in myocardial infarction.

Fixed (main) effects of the model were presented by two one-factor, one two-factor and one three-factor indicators (Table 3), and random effects – by four one-factor indicators (Table 4). The overall accuracy of the model comprised 89.4% (Fig.).

According to Abd El-Mottaleb N. et al. [5], AMI patients with AHF were found to have a significantly low concentration of irisin compared with that in controls. Decreased irisin concentration in AMI patients resulted in increased secretion of proinflammatory factors due to activation of signaling pathways, such as mitogen-activated protein kinase and extracellular signal-regulating kinase 1/2, and thus impairing healing.

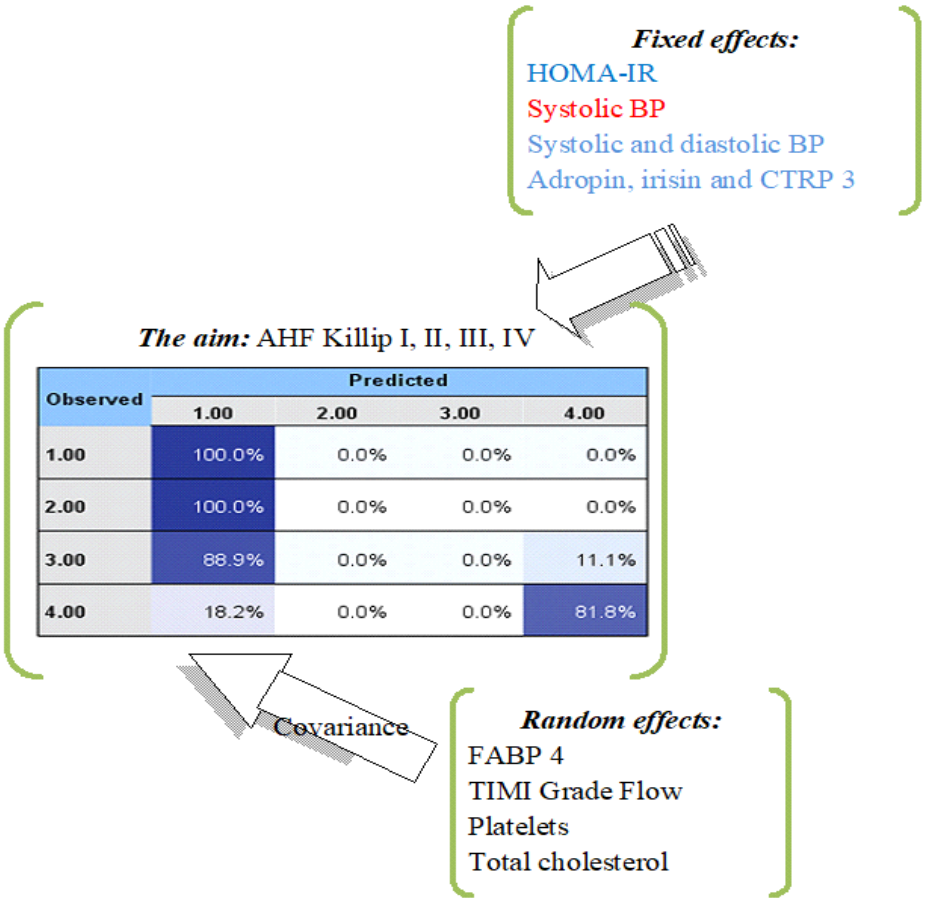
Table 4

Indicators of random GLMM effects
(only statistically significant effects with p<0.05 are included)

Indicator	Covariation
One-factor indicators	
FABP4	**0.003**
TIMI Grade Flow	**0.571**
Platelets	**0.001**
Total cholesterol	**0.006**

Shen S. and coauthors [11] found that irisin in serum was associated with an increased AHF mortality risk (OR: 1,287 [1,079-1,537]). Ertem A.G. et al. [6] showed that AMI patients had lower levels of adropin compared to patients without coronary artery disease. It was noted that adropin level was

lower in patients with severe coronary artery disease than in patients with moderate coronary artery disease degree. Obokata M. et al. [8] demonstrated that FABP 4 levels peaked on admission or just after PCI and then gradually declined over time in AMI patients. According to Yildirim A. et al. [7], low levels of CTRP3 were observed in patients with heart failure and reduced ejection fraction. Si Y. et al. [13] reported decreased CTRP 3 levels in ischemic heart disease.



Notes. Positive effect; negative effect.

Design of AHF prediction model in AMI patients

The study revealed low concentrations of energy homeostasis indicators, adropin and irisin, in STEMI patients on day 1-2. There was an imbalance in adipokine metabolism in AMI evident as an increase in FABP 4 and a decrease in the concentration of CTRP 3 on day 1-2. High prognostic performance of the constructed model was indicated, namely: the accuracy of predicting the absence of Killip class I AHF was 100%, and the accuracy of Killip class II AHF prediction was 0%, i.e. the model was not sensitive to that level of complications. The prediction accuracy for Killip class III AHF was 11%, i.e. the model was low-sensitive to complications of that level, and the prediction accuracy for Killip class IV AHF was 82%, indicating a very high degree of the model sensitivity to that level of complications.

CONCLUSIONS

1. The study has shown low concentrations of adropin, irisin, C1q/TNF-binding protein 3 and high levels of fatty acid binding protein 4 in patients with acute myocardial infarction indicating an imbalance in both energy homeostasis and the adipokine system.

2. The constructed statistical model predicts probability of Killip class IV acute heart failure development with high accuracy of 82% after day 1 follow-up in patients with acute myocardial infarction.

3. Qualitative assessment of the coefficients with fixed factors of generalized linear mixed model has shown that high systolic blood pressure on day 1 was the strong negative prognostic factor, and all other factors, such as the combined effect of adropin, irisin, C1q/TNF-binding protein 3, insulin resistance index and the combined effect of systolic and diastolic blood pressure were the positive prognostic factors, and the overall model accuracy comprised 89.4%.

Funding. This research received no external funding.

Conflict of interests. The authors declare no conflict of interest.

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Стаття надійшла до редакції
06.07.2021