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PROGNOSIS OF ADVERSE OUTCOMES AFTER MYOCARDIAL INFARCTION BASED ON LEVEL OF HEART FATTY ACID BINDING PROTEIN

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Abstract. *Heart-type Fatty Acid Binding Protein (H-FABP) is a cytoplasmic protein. It`s released 30 minutes after onset of ischemia and enhances transportation of fatty acids from cardiomyocytes.*

***Aim**: to examine the prognostic value of biochemical and clinical markers and their sum in relation to the development of adverse outcomes in six months follow up after acute myocardial infarction (AMI).*

***Methods and results**. 189 patients with AMI were examined. They were divided into two groups: 1 - NSTEMI n=36 (9%); 2 - STEMI n=153 (81%), male 138 (73%). H-FABP was determined in blood plasma with ELISA, level of H-FABP was measured using normal value up to 1 ng/ml. During a 6-month follow-up 17 patients (9%) died. About 60 clinical and biochemical markers were analyzed using sequential Wald-Genkin's procedure. The curves of sensitivity and specificity were made using method of ROC-analysis and the threshold values were chosen for each parameter. H-FABP had sufficient level of sensitivity 85.7%, but insufficient specificity (49,2%), and such markers as age, heart failure class (Killip) and glucose level had insufficient sensitivity (50,0%; 66,7%; 43,7%) according to prognosis of death case. Each parameter was estimated in scores in relation to the cut-off value and the scale for measurement of prognostic coefficient (PC) using Gubler's method was proposed. Positive value of PC is associated with adverse outcomes in patients with AMI.*

***Conclusions**: The mathematical model including the sum of markers – H-FABP level, age, glucose level, heart failure class (Killip) allows to prognose adverse outcomes after AMI with sensitivity 88% and specificity 78%.*

Key words: *H-FABP, acute myocardial infarction, prognosis*

There are some biochemical markers, which appear to be predictors of adverse outcomes in patients with acute myocardial infarction (AMI). Heart fatty acid binding protein (H-FABP) is the most widely studied from all this family. H-FABP is a little cytoplasmic protein, which is secreted by tissues with active metabolism of fatty

acids, in cardiomyocytes and hepatocytes (Viswanathan et al., 2012). Its prior function is to induce the intracellular transport of fatty acids. Combination of low molecular mass (15 kDa) and cytoplasmic location means that H-FABP secretion starts 30 minutes after ischemic episode. Peak of H-FABP concentration can be seen approximately in 6-8 hours after symptoms' appearance and returns to normal state in 24-30 hours, that's why it can be considered as biomarker of infarction and reinfarction after some days.

Carrol C., et al., 2013, made systemic examination and meta-analysis of H-FABP tests to classify the early sensitivity and specificity of its quantitative and qualitative analysis. There was a trial for understanding, if H-FABP could be used as a standard among with troponins. The authors analyzed 8 researches of quantitative analysis of H-FABP and 9 – of qualitative analysis. Sensitivity and specificity were 81% (95%; CI: 50% - 95%) and 80% (CI: 26% - 98%) accordingly to quantitative analysis 68% (CI: 11% - 97%) and 92% (CI: 20% - 100%) accordingly to qualitative. The researchers reported that combination of H-FABP and troponins T increased the sensitivity from 42–75% to 76–97% but decreased specificity from 94–100% to 65–93%. H-FABP has moderate sensitivity and specificity for myocardial infarction, but the combination can increase early sensitivity [5].

H-FABP also can identify the defect of myocardium in patients who had their heart operated. The high concentration of H-FABP in plasma correlates with some co-morbidities, such as heart failure, chronic kidney disease, diabetes mellitus and appears to be a factor of risk for post-operational acute renal failure (ARF). Oezkur M., et al., 2014 studied the association between level of H-FABP in plasma before operative treatment with frequency of ARF after operation. Positive correlation was registrated and as a result it was concluded that H-FABP can be used as a biomarker of ARF after operations [21].

1. Mechanism of working of H-FABP, its value in heart diseases, ischemia consequences allows to think that it would have a high prognostic significance for adverse outcomes in patients after myocardial infarction, that's why it is the subject of this study.

Purpose of our work: to evaluate new markers and their combinations with other clinical and biochemical markers and making a mathematical model for prognosis in patients with AMI.

Methods and results: The study included 189 patients with AMI: NSTEMI - 36 patients (9%), STEMI – 153 (81%), 138 (73%) males, who were 72±7,5 years old, and 27% females who were 65±6,9 years old. Patients had routine clinical and biochemical examination. Average level of H-FABP in the 1st group was 3,49±0,91 ng/ml, in the 2nd – 5,63±0,57 ng/ml ($p \leq 0,0561$).

The most effective threshold for dividing into intervals can be the value of markers at a point where the sum of sensitivity and specificity of this current marker in relation to result is maximized. ROC-analysis allows revealing this point (characteristic curve). Optimal dividing point was chosen by using ROC-analysis, made with «MedCalc». The effectiveness of prognosis (its sensitivity and specificity) can be increased by estimation of its results on different intervals of researched markers' change. The simplest case requires the markers' change diapason to be divided in two intervals.

Comparing the groups of patients who survived and those who died by analyzing of nearly 60 clinical-biochemical markers, the 4 most important markers were choosing for making a model, which can predict a lethal result in 6 months follow up after AMI: age >74 years old, glucose level >7,68 mmol/l, heart failure by Killip classification more than 2 class and level of H-FABP >1,23 ng/ml. H-FABP level was determmined using ELISA. Plasma level of H-FABP lower than 1 ng/ml, was considered as normal. It appeared, that age, glucose level and class of heart failure (Killip) had insufficient level of sensitivity (AUC 50; 66,7; 43,7% accordingly), and level of H-FABP was characterized by insufficient level of specificity (49,2%), but a high level of sensivity — 85,7%. That's why there was an attempt to determine their sum and to make a mathematical model, which allows to establish if AMI prognosis is unfavorable.

For the next step, diagnostic coefficients (DC) for each interval of markers' change were counted using Gubler formula:

$$DC = 100 \log (PA / PB),$$

Where, PA — frequency (probability) of examined values to be included into current diapason of marker in state A (lethal); PB — same for state B (survived).

The working of algorithm of classification is next: for each patient prognostic coefficients (points) are defined by all of the markers, which are included in the model depending if they are within according diapason. Then, these points are summed and summary prognostic coefficient, which characterizes the patients' prognosis, is found. If patients have positive values of PC, they dispense into group of high risk of adverse outcomes.

Tabl. 1

Risk of death in different values of PC

PC values	Risk of death
PC>0	High
PC<0	Low

Positive values of prognostic coefficients sum mean high probability of disease with lethal result for a patient. Negative values of sum of prognostic coefficients mean high probability of positive prognosis.

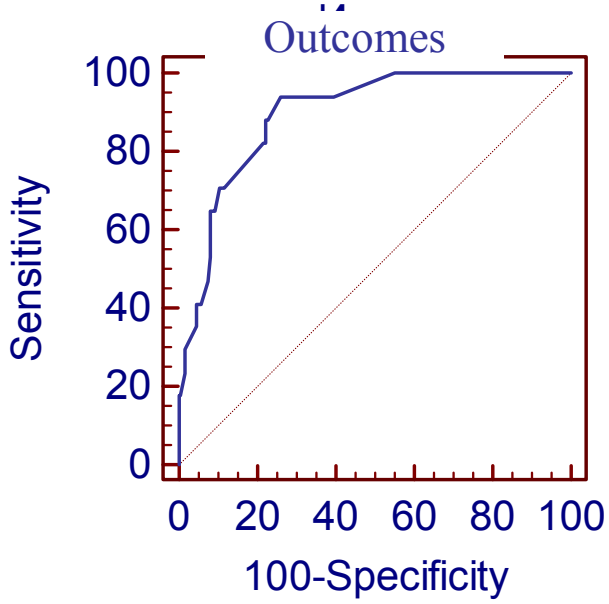
The measured value of PC as independent integral coefficient and prognostic capabilities can be evaluated. Shape of ROC curve for PC and the area under it suggests that the effectiveness for prognosis is high.

Tabl. 2

Prognostic characteristics of certain markers and prognostic model

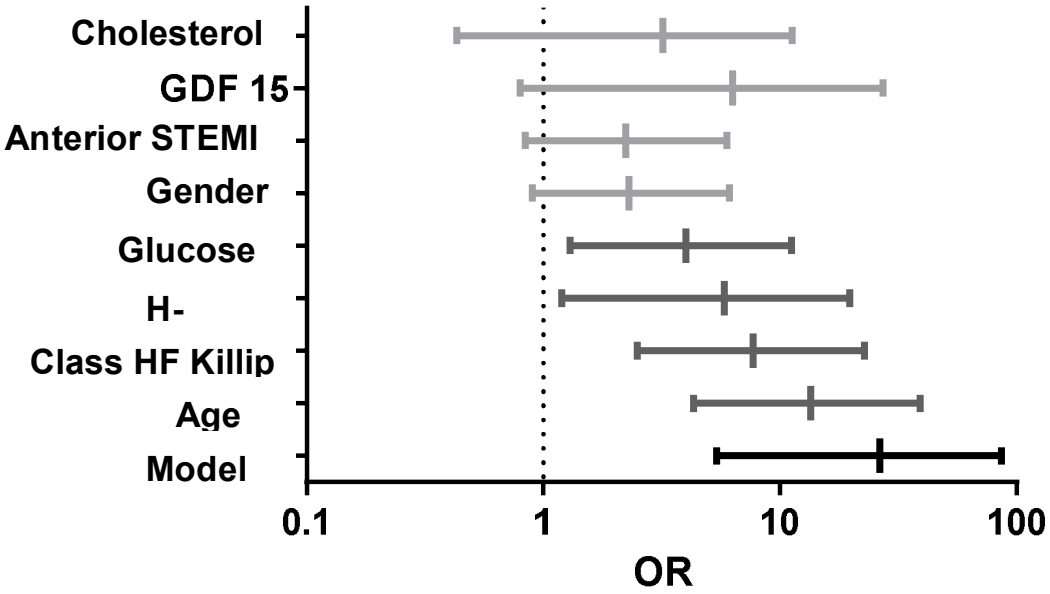
Marker	Se	Sp	AUC	p (AUC)	OR (±95% CI)
H-FABP	85,7	49,2	0,70	0,001	5,8 (1,2-19,7)
Glucose	66,7	66,7	0,68	0,01	4,0 (1,3-11,2)
Age	50,0	93,0	0,76	<0,0001	13,5 (4,3-39,1)
HF by Killip	43,7	90,8	0,70	0,05	7,7 (2,5-22,8)
Model	88,2	77,9	0,90	<0,0001	26,5 (5,4-86,4)

Notes: Se – Sensitivity; Sp – Specificity; AUC – Area under ROC curve; P – (AUC) level of meaning of difference of AUC from value of 0.5; OR (±95% CI) – Odds ratio with lower and higher limits of 95% confidence interval.



Picture 1. ROC-curve of prognostic model.

Influence of individual markers and model on prognosis of adverse outcomes after AMI is shown on picture 2.



Picture 2. Influence of individual markers and model on prognosis of lethal result

Discussion. Kilcullen et al., 2007, observed patients after AMI within 1 year follow up. They are reported that increased level of H-FABP had predictive value of

lethal rezult after AMI and can identify patients with high risk regardless of troponin concentration. Patients who had negative value of H-FABP and troponin, mortality in 6 months was 0%, so they had low risk. Patients who had positive H-FABP and negative troponin, had significantly higher risk of fatal events after 1 year compared to patients with negative H-FABP [16].

After 6 years of follow up, patients in troponin-negative and H-FABP positive group had highest mortality rate (Pearson et al., 2010).

Viswanathan et al., in 2012 investigated that H-FABP`s level higher than 6,48 ng/ml – independent predictor of death or myocardial infarction. Additionally, this research group measured highly sensitive troponin I in cohort and showed that prognostic value of increased H-FABP is additional to troponin in patients with acute coronary syndrome (ACS) with low or moderate risk. Also they reported that H-FABP is a marker of ischemia even without necrosis.

O'Donoghue et al., 2006, observed patients with AMI during10 months for revealing possible major cardiac events, including death from every reason, non-fatal myocardial infarction, new or aggravation of existing heart failure and composite end points. In addition recurrent ischemia which requires hospitalization or urgent revascularization was included. Patients with increased level of H-FABP while being hospitalized (approximately 41±20 hours after the chest pains) had significantly higher level of adverse events after 10 months of observation compared to level of H-FABP which was not defined. Increase of level of H-FABP was associated with death, myocardial infarction and heart failure up to 10 month of follow up in a group of troponin-negative patients (≤1,5 ng/ml), and troponin-positive patients (>1,5 ng/ml). Even when the lowest level of troponin I was used (≤0,1 ng/ml), H-FABP was associated with risk of death, myocardial infarction or heart failure. Increased levels of H-FABP were associated with increased risk of myocardial infarction and recurrent ischemia up to 30 days, especially in patients with unstable angina, whose diagnose was based on negative troponin I test [20].

Our team has made an effort to increase prognostic power of highly sensitive marker – H-FABP and to overcome relatively low specificity in predicting lethal

result with analysing of other clinical and biochemical markers. The research was limited to relatively small amount of patients.

Conclusions. The prognostic mathematical model, which includes a sum of markers – H-FABP level, glucose level, heart failure class by Killip allows to predict lethal results in patients with AMI with sensitivity of 88,2% and specificity 77,9% .

References.

1. Body R., Carley S., McDowell G. et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay // J Am Coll Cardiol. -2011. –Vol.58, Suppl.13. –P.1332-1339.
2. Body R., Dixon D., Burrows G. et al. Economic evaluation of a heart fatty acid binding protein based protocol for rapid chest pain assessment // 14th International Conference on Emergency Medicine. Acad Emerg Med. -2012. –Vol.19, Suppl.6. –P.746-747.
3. Body R., McDowell G., Carley S., et al. A FABP-ulous ‘rule out’ strategy? Heart fatty acid binding protein and troponin for rapid exclusion of acute myocardial infarction //Resuscitation. -2011. –Vol.82, Suppl.8. –P.1041-1046
4. Carless D.R., Wnęk M., Knox C. et al. Clinical and analytical evaluation of an immunoturbidimetric heart-type fatty acid-binding protein assay // Scand J Clin Lab Invest. -2013. –Vol.73, Suppl.1. –P.48-53.
5. Carroll C., Al Khalaf M, Stevens J.W., et al. Heart-type Fatty Acid Binding Protein as an Early Marker for Myocardial Infarction. Systematic Review and Meta-Analysis // Emerg Med J. -2013. -Vol.30, Suppl.4. -P.280-286.
6. Collinson P.O., Premachandram S., Hashemi K. Prospective audit of incidence of prognostically important myocardial damage in patients discharged from emergency department. // BMJ. -2000. –Vol.320, Suppl.7251. –P,1702-1705.
7. Daly M.J., McCann C.J., Owens C.G. et al. Heart fatty acid-binding protein in combination with the 80-lead body surface potential map improves early detection of acute myocardial infarction in patients who are cardiac troponin T-negative at presentation // J Electrocardiol. -2011 –Vol.44, Suppl.4. –P.432-438.
8. Dellas C., Puls M., Lankeit M., et al. Elevated heart-type fatty acid-binding protein levels on admission predict an adverse outcome in normotensivepatients with acute pulmonary embolism // J Am Coll Cardiol. -2010. –Vol.55, Suppl.19. –P.2150-2157.
9. Ekelund U., Forberg J.L. New methods for improved evaluation of patients with suspected acute coronary syndrome in the emergencydepartment // Emerg Med J. -2007 –Vol.24. Suppl.12. –P.811-814.
10. Goodacre S., Cross E., Arnold J. et al. The health care burden of acute chest pain // Heart. -2005. –Vol.91. –P.229-230
11. Hamm C.W. et al ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting

without persistent ST-segment elevation of the European Society of Cardiology (ESC) // Eur. Heart J. -2011. –Vol.32, Suppl.23. –P.2999-3054.
12. Hammarsten O., Fu M.L., Sigurjonsdottir R., et al. Troponin T percentiles from a random population sample, emergency room patients and patients with myocardialinfarction // Clin Chem. -2012. –Vol.58, Suppl.3. –P.:628-637.
13. Hollander J.E. Highly sensitive troponins the answer or just more questions? // J Am Coll Cardiol. -2009. –Vol.54, Suppl.13. –P.1173-1175.
14. Inoue K., Suwa S., Ohta H., et al. Heart fatty acid-binding protein offers similar diagnostic performance to high-sensitivity troponin T in emergencyroom patients presenting with chest pain // Circ J. -2011. -Vol.75, Suppl.12. –P.2813-2820.
15. Kilcullen N., Morrell C., Thistlethwaite S.J. et al. Heart-type fatty acid-binding protein predicts long-term mortality and re-infarction in consecutive patients withsuspected acute coronary syndrome who are troponin-negative. // J Am Coll Cardiol. -2010. –Vol.55, Suppl.23. –P.2590-2598.
16. Kilcullen N., Viswanathan K., Das R. et al. Heart-type fatty acid-binding protein predicts long-term mortality after acute coronary syndrome and identifies high-risk patients across the range of troponin values // J. Am. Coll. Cardiol. -2007. –Vol.50, Suppl.21. –P.2061-2067.
17. McCann C.J., Glover B.M., Menown I.B., et al. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T //Eur Heart J. -2008. –Vol. 29, Suppl.23. –P.2843-2850.
18. McMahon C.G., Lamont J.V., Curtin E., et al. Diagnostic accuracy of heart-type fatty acid-binding protein for the early diagnosis of acute myocardial infarction // Am J Emerg Med. -2012. –Vol.30< Suppl.2. –P.267-274.
19. Muehlschlegel J.D., Perry T.E., Liu K.Y., et al. Heart-type fatty acid binding protein is an independent predictor of death and ventricular dysfunction after coronary artery bypass graft surgery // Anesth Analg. -2010. –Vol.111, Suppl.. –P.1101-1109.
20. O'Donoghue M., de Lemos J.A., Morrow D.A., et al. Prognostic utility of Heart-type fatty acid-binding protein in patients with acute coronary syndromes // Circulation. -2006. –Vol.114, Suppl.6. –P.550-557.
21. Oezkur M., Gorski A., Peltz J. Preoperative serum h-FABP concentration is associated with postoperative incidence of acute kidney injury in patients undergoing cardiac surgery // BMC Cardiovascular Disorders. -2014. -Vol.14. -P.117.
22. Pearson I.R., Hall A.S., Gale C.P. et al. In Acute Coronary Syndromes, Heart-type Fatty Acid Binding Protein is a More Accurate Predictor of Long Term Prognosis than Troponin // Circulation. -2010; -Vol.122:A11374
23. Pope J.H., Aufderheide T.P., Ruthazer R., et al. Missed diagnoses of acute cardiac ischemia in the emergency department. // N Engl J Med. -2000. –Vol.342, Suppl.16. –P.1163-1170.
24. Puls M., Dellas C., Lankeit M., et al. Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism // Eur Heart J. -2007. –Vol.28, Suppl.2. –P.224-229.
25. Reichlin T., Hochholzer W., Bassetti S. et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays // N Engl J Med. -2009. –Vol.361, Suppl.9. –P.858-867

26. Thygesen K. et al. Third universal definition of myocardial infarction // Eur Heart J. -2012. –Vol.33, Suppl.20. –P.2551-2567.
Viswanathan K., Alistar S.H., Barth J.H. An Evidence-Based Approach to the Assessment of Heart-Type Fatty Acid Binding Protein in Acute Coronary Syndrome // Clin.Biochem.Rev. -2012 -Vol. 33, Syppl.1. -P.3–11.

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Прогноз для розвитку несприятливих подій після перенесеного інфаркту міокарда на підставі рівня серцевого білку зв'язуючого жирні кислоти

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Резюме. Серцевий білок, що зв'язує жирні кислоти (СБСЖК) - цитоплазматический протеїн, який вивільняється протягом 30 хвилин після виникнення ішемії і підсилює транспорт жирних кислот з кардіоміоцитів.
Мета: прогнозування летального результату після перенесеного гострого інфаркту міокарда (ГІМ) на підставі аналізу біохімічних і клінічних маркерів і їх суми.
Матеріали і методи. Обстежено 189 пацієнтів з гострим інфарктом міокарду. Хворих з ГКС поділили на 2 групи: 1- інфаркт міокарду без зубця Q (n=36); 2 - інфаркт міокарда с зубцем Q (n=153), чоловіки 138 (73%). Визначали білок, зв'язуючий вільні жирні кислоти (БЗВЖК) в сироватці крови імуноферментним методом, нормальними значеннями рахували його концентрацію до 1 нг/мл. Протягом 6 місяців періоду спостереження 17 пацієнтів (9%) померли. Були побудовані криві чутливості та специфічності методом ROC аналізу та обрані порогові значення для кожного параметру. Виявлено, що БЗВЖК мав достатній рівень чутливості 85,7%, але недостатню специфічність (49,2%), а показники - вік, клас серцевої недостатності за Killip та рівень глюкози мають недостатню чутливість (50,0%; 66,7%; 43,7%) відповідно для прогнозу летального результату. Бальна оцінка була проведена для кожного параметру відносно порогового значення та запропонована шкала для розрахунку прогностичного коефіцієнту (ПК) за методом Гублера. Позитивне значення ПК асоціюється з летальнім результатом у хворих на ГІМ.
Висновок: математична модель з урахуванням суми ознак - рівня БЗВЖК, віку, рівня глюкози, серцевої недостатності за класифікацією Killip дозволяє прогнозувати летальний результат у хворих на ГІМ з чутливістю 88,2% і специфічністю 77,9%
Ключові слова: БЗВЖК, гострий інфаркт міокарда, прогноз

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Прогноз для развития неблагоприятных событий после перенесенного инфаркта миокарда на основании уровня сердечного белка связывающего жирные кислоты

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Резюме. Сердечный белок, связывающий жирные кислоты (СБСЖК) - цитоплазматический протеин, который высвобождается в течение 30 минут после возникновения ишемии и усиливает транспорт жирных кислот из кардиомиоцитов.

Цель: прогнозирование летального исхода после перенесенного острого инфаркта миокарда (ОИМ) на основании анализа биохимических и клинических маркеров и их суммы.

Материалы и методы. Обследовано 189 пациентов с острым инфарктом миокарда. Больных с ОКС разделили на 2 группы: 1 - инфаркт миокарда без зубца Q (n = 36); 2 - инфаркт миокарда с зубцом Q (n = 153), мужчины 138 (73%). Определяли белок, связывающий свободные жирные кислоты (БССЖК) в сыворотке крови иммуноферментным методом, нормальными значениями считали его концентрацию до 1 нг / мл. В течение 6 месяцев периода наблюдения 17 пациентов (9%) умерли. Были построены кривые чувствительности и специфичности методом ROC анализа и выбраны пороговые значения для каждого параметра. Выявлено, что БССЖК имел достаточный уровень чувствительности 85,7%, но недостаточную специфичность (49,2%), а показатели - возраст, класс сердечной недостаточности по Killip и уровень глюкозы имеют недостаточную чувствительность (50,0%; 66,7%; 43,7%) соответственно для прогноза летального исхода. Балльная оценка была проведена для каждого параметра относительно порогового значения и предложена шкала для расчета прогностического коэффициента (ПК) по методу Гублера. Положительное значение ПК ассоциируется с летальным исходом у больных ОИМ.

Вывод: математическая модель с учетом суммы признаков - уровня БССЖК, возраста, уровня глюкозы, сердечной недостаточности по классификации Killip позволяет прогнозировать летальный исход у больных ОИМ с чувствительностью 88,2% и специфичностью 77,9%

Ключевые слова: БССЖК, острый инфаркт миокарда, прогноз

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