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INDIVIDUAL PROGNOSIS OF COMPLICATIONS IN THE PRESENCE OF CHRONIC HEART FAILURE

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Neurohumoral theory of chronic heart failure (CHF) development, approved by most scientists, does not completely explain mechanisms of its decompensation. Standard treatment is not always effective, thus, search for pathogenetic and prognostic factors, which influence the course of CHF, remains a current issue. However, individual prognosis of CHF course in clinical practice is not performed at present, since its distinct criteria have not been specified. Thus, it became the expediency and rationale of our research, the aim of which was to assess individual risk of occurrence of complications in patients with CHF, considering a combined influence of several factors. A complete clinical examination of 110 patients (74.5 % males, 25.5 % females) with CHF has been performed. The method of logistic regression was used for determination of combined influence of analyzed factors on CHF prognosis; adequacy and reliability of the difference of the obtained model were investigated by Wald's criteria and chi-square test. On elaboration of the prognosis method of individual risk of the development of cardiac insufficiency, among other factors that, according to literature data, influence the development of the disease, we have singled out three factors, which have a reliable ($P < 0.05$) association with CHF: BMI, total cholesterol and amount of lymphocytes. Elaborated computer program, which can calculate the prognosis of CHF complications. This file opens in the program "Microsoft Excel" calculates individual risk and graphically demonstrates the degree of risk. Conducted correlation analysis of individual risk of CHF complications showed that its likelihood is accompanied by development of systolic dysfunction, hypertrophy of the left ventricle with dilatation, anemic and detoxification syndromes, impairment of liver and kidney functions with the reduction of leptin in the blood, which has important regulative functions. Thus, based on conducted logistic, correlation and prognostic analyses, individual risk of the development of CHF complications increases under conditions of combined factors, such as weight loss, decrease in total cholesterol level and reduction of the content of peripheral blood lymphocytes. Application of elaborated computer program allows a doctor to calculate individual risk and visualize it.

Key words: chronic heart failure, individual prognosis, body mass index, total cholesterol, amount of lymphocytes, logistic regression.

Introduction. Chronic heart failure (CHF) is rather widespread worldwide. Its incidence ranges within 0.4–2.5 %, constituting 38 million people in the world. [1]. Annually over 915000 new cases are diagnosed [9]. Although, survival of patients with CHF has currently improved, mortality rate still remains very high: over 30 % of individuals die within 5 years since the diagnosis has been made [9]. Neurohumoral theory of CHF development, approved by most scientists, does not completely explain mechanisms of its decompensation. Standard treatment is not always effective, thus, search for pathogenetic and prognostic factors, which influence the course of CHF, remains a current issue. Obesity is considered one of such factors; it is a noninfectious pandemic of present days: in 2014, approximately 1.9 billion adults in the world were overweight and over 600 million individuals suffered from obesity [12, 18]. In Ukraine, 30 % of the population has excess body weight and obesity [2]. Thus, scientists have reached the consensus concerning the role of obesity in the occurrence and course of many diseases (diabetes, cancer, cardiovascular diseases, etc.); however, the phenomenon "paradox of obesity" was recorded after certain investigations [5]. It implies that a better prognosis was observed in patients with excess body weight and cardiovascular diseases than in persons with normal body weight [7]. There was the suggestion about U-like association between mortality and body mass index (BMI) in the presence of CHF [19].

However, individual prognosis of CHF course in clinical practice is not performed at present, since its distinct criteria have not been specified. Thus, it became the expediency and rationale of our research, the **aim** of which was to assess individual

risk of occurrence of complications in patients with CHF, considering a combined influence of several factors.

Materials and methods. A complete clinical examination of 110 patients (74.5 % males, 25.5 % females) with CHF has been performed. The basic diagnosis and functional class (FC) of CHF were specified based on the decree of the Ministry of Health of Ukraine № 436 dated 03.07.2006. The main cause (90 %) of CHF was ischemic heart disease, in 7.8 % – dilatation cardiomyopathy, in 2.7 % – chronic rheumatic heart disease. Among the forms of IHD, angina pectoris was most frequently revealed (69.1 %), 43.4 % survived myocardial infarction. Permanent form of atria fibrillation was observed in 29.1 % individuals, in 20.9 % – diabetes mellitus. In addition to standard examination, there was performed determination of IMT, N-terminal brain fraction of natriuretic propeptide by qualitative method (CITO TEST NT-proBNP, Farmasco), endogenous intoxication based on the level of middle molecules (MM_{254}) by spectrophotography method in ultraviolet part of the spectrum by Gabrielyan et. al. (1985), leptin by enzyme-binding immunosorbent assay with reagents "DRG Leptin ELISA" (Germany). Structural and functional parameters of the heart were determined on apparatus Aloka SSD-500 (Japan) by the standard technique.

Statistical processing was performed by the methods of variation statistics "Statistica 6.0" (USA), correlation analysis – by Kendall method. Prognosis of CHF severity and analysis of survival was carried out by the Kaplan – Meier estimator: cumulative fraction of survival was evaluated in 24 months of monitoring with estimation of reliability by Wilcoxon signed-rank test and Cox's *F*-test. Cases of repeated hospitalization due to CHF decompensation or a patient's death were regarded as an event. The method of logistic regression was used for determination of combined influence of analyzed factors on CHF prognosis; adequacy and reliability of the difference of the obtained model were investigated by Wald's criteria and chi-square test. Individual risk may assume meaning from 0 (impossible event) to 100 % (the event always occurs).

Probability of individual risk (*R*) of CHF progression, depending on chosen factors, has been calculated by the formula (1):

$$R = \frac{1}{1 + e^{-z}} \cdot 100\ \% \qquad (1)$$

where e = 2.72... – basis of natural logarithms, *Z* – value, calculated by the formula (2): $Z = K + \beta\beta_1 x_1 + \beta\beta_2 x_2 + ... \beta\beta_n x_n$, where *K* – constant β_0, $\beta\beta_i$ – coefficients in each factor, x_i – meaning of factors.

Results and discussion. On elaboration of the prognosis method of individual risk of the development of cardiac insufficiency, among other factors that, according to literature data, influence the development of the disease, we have singled out three factors, which have a reliable ($P < 0{,}05$) association with CHF: BMI, total cholesterol and amount of lymphocytes.

The results of logistic regression of the studied prognostic factors are given in table. Inserting the results, obtained by the method of logistic regression into the formula (2), we may obtain meaning Z : $Z = 5.804 - 0.104 \cdot IMT - 0.052 \cdot Lymph - 0.013 \cdot Ch$, where Lymph – lymphocytes (%), Ch – cholesterol (mg/dL). Adequacy and reliability of the obtained model by Wald's criteria and chi-square test showed that our model is reliable with possible error less 0.1 % ($P = 0.001$).

Results of estimation of the influence of reliably proved risk factors of CHF progression by the method of logistic regression

№	Factors	Coefficients of regression (i)	
		meaning	P
	Constant β_0	5.804	0.001
1	BMI	–0.104	0.024
2	Lymphocytes, %	–0.052	0.035
3	Cholesterol, mg/dL	–0.013	0.015

For practical use of a prognostic model, we divided individual risks into three stages: low ($R < 25$ %), average ($R = 25–54.9$ %) and high ($R \geq 55$ %) and elaborated computer program, which can calculate the prognosis of CHF complications. This file opens in the program "Microsoft Excel", and after insertion of cholesterol, lymphocyte amounts and BMI, it calculates individual risk and graphically demonstrates the degree of risk (for example, in fig. 1 – high). At the same time, there is possibility to model an individual risk under conditions of other combinations of analyzed factors and to determine the priority of changes and visually persuade a patient in the need for aid. Determination of individual risk of the examined patients with CHF by this program showed that 37.2 % had the low risk, 40 % – average, and 22.8 % – high risk.

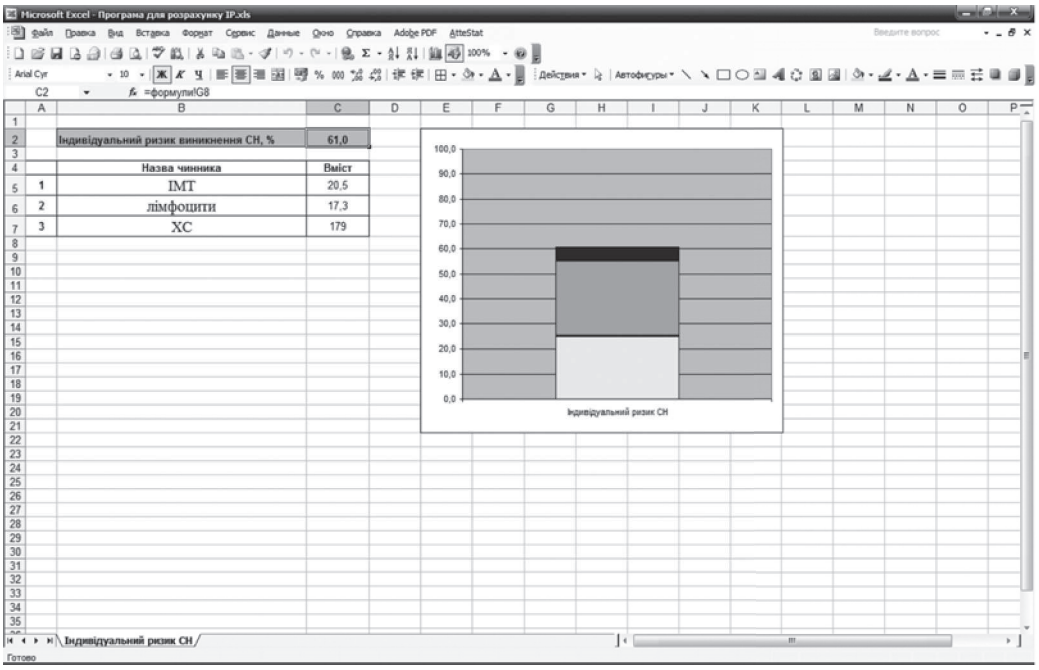

Fig. 1. Program for calculation of individual risk of CHF complications of patient X

Conducted correlation analysis of individual risk of CHF complications showed that its likelihood is accompanied by an increase in CHF severity (FC CHF $\tau = 0.31$, $P = 0.0007$ and left ventricular ejection fraction $\tau = –0.24$; $P = 0.02$), impairment of kidney function (creatinine $\tau = 0.22$; $P = 0.01$; urea $\tau = 0.22$; $P = 0.03$) and liver (de Rittis index $\tau = 0.32$; $P = 0.0003$), appearance of anemic syndrome (hemoglobin $\tau = –0.23$; $P = 0.01$; erythrocytes $\tau = –0.23$; $P = 0.01$), decrease in the thickness of interventricular septum ($\tau = –0.27$; $P = 0.01$) and increase in the index mass of the left ventricular myocardium ($\tau = 0.43$; $P = 0.0005$), reduction of leptin in the blood ($\tau = –0.34$; $P = 0.02$) and increased probability of endogenous intoxication syndrome (MM_{254}, $\tau = 0.26$; $P = 0.03$). Thus, a high individual risk of CHF complications, detected with the program based only on BMI parameters, lymphocytes and cholesterol, is distinctly associated with the development of systolic dysfunction, hypertrophy of the left ventricle with dilatation, anemic and detoxification syndromes, impairment of liver and kidney functions with the reduction of leptin in the blood, which has important regulative functions.

Having analyzed survival of patients and cases of repeated hospitalization depending on the level of individual risk, we revealed that cumulative proportion of survival of patients with low risk was 85.7 %, average risk – 56.5 %, high risk – 38.46 % (Cox's F-test $P_{1–2} = 0.009$, Wilcoxon signed-rank test $P_{1–2} = 0.02$; Cox's *F*-test $P_{1–3} = 0.003$, Wilcoxon signed-rank test $P_{1–3} = 0.01$; Cox's *F*-test $P_{2–3} = 0.17$, Wilcoxon signed-rank test $P_{2–3} = 0.4$) (fig. 2).

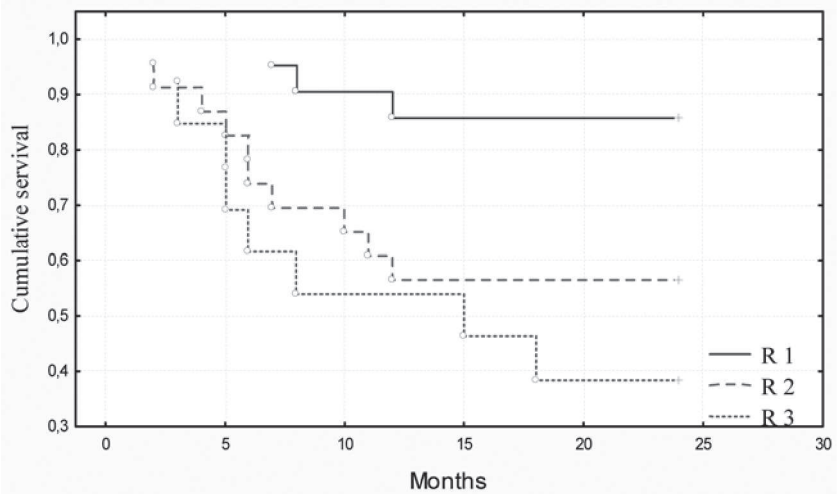

Fig. 2. Cumulative proportion of survival of patients with low (R1), average (R2) and high (R3) individual risks

Thus, based on conducted logistic, correlation and prognostic analyses, individual risk of the development of CHF complications increases under conditions of combined factors, such as weight loss, decrease in total cholesterol level and reduction of the content of peripheral blood lymphocytes. The first reports that low cholesterol level is closely associated with the increase in mortality of patients with CHF appeared at the end of the 20th century and were later confirmed by other investigations, where high cholesterol level was accompanied by the decrease in mortality [14].

Our investigation also confirms previously described reports about negative prognostic meaning of low lymphocyte level, which was associated with increased incidence of rapid CHF appearance, rapid coronary death and ventricular arrhythmias, as well as non-cardiovascular deaths both in patients with heart pathology [16] and in healthy individuals [13]. It can be explained by the fact that low amount of lymphocytes may be a marker of immune suppression and malnutrition [17], or, more likely, a marker of unsatisfactory adaptation and formation of stress reaction [4] with the discharge of endogenous mineral corticoids that increases CHF risk or causes its progression due to sodium retention [11].

Revealed increase in individual risk of the development of CHF complications under conditions of low BMI may also be explained by sacropenia, manifested by decrease in muscle mass [15]. Severe CHF is known to be often accompanied by the development of heart cachexia, subclinical manifestations of which, characterized by impairment of correlation between catabolism and anabolism processes, are present even before a significant loss of body mass [6]. It was described that cachexia is associated with worse CHF, lower functional capability and worse life quality [10]. Worse prognosis of survival is for patients with both low body mass and obesity (U-like dependence), and better prognosis was in patients with normal and excess body mass [3].

In addition to three crucial prognostic factors, severity of endogenous intoxication syndrome also had a significant effect on CHF course, which is proved by revealed correlations (BMI with MM_{254} $\tau = -0.2$; $P = 0.01$ and R with MM_{254} $\tau = 0.26$; $P = 0.03$). Levels of blood lipids are also closely associated with endotoxicosis intensity, since circulating lipoproteins with significant amount of cholesterol and triglycerides are natural non-specific inhibitors of endotoxicosis, they bind and destruct bacterial lipopolysaccharides [8]. This may explain the phenomenon of correlation between low cholesterol level and mortality increase among patients with CHF.

Conclusions. 1. Individual risk of the development of CHF complications increases under conditions of low body weight with decreased cholesterol level and blood lymphocytes, which determines the strategy of therapeutic tactics – normalization of body mass and correction of lipid metabolism. 2. Application of elaborated computer program allows a doctor to calculate individual risk and visualize it.

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ІНДИВІДУАЛЬНЕ ПРОГНОЗУВАННЯ УСКЛАДНЕНЬ ПРИ ХРОНІЧНІЙ СЕРЦЕВІЙ НЕДОСТАТНОСТІ

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Визнана більшістю науковців нейрогуморальна теорія розвитку хронічної серцевої недостатності (ХСН) не повністю пояснює механізми її декомпенсації, стандартне лікування не завжди сприяє отриманню бажаних результатів, тому актуальним залишається пошук патогенетичних та прогностичних факторів, що впливають на перебіг ХСН. Проте індивідуальне прогнозування перебігу ХСН у клінічній практиці дотепер не проводиться, оскільки чіткі його критерії не визначено, що зумовило актуальність і доцільність проведеного нами дослідження, мета якого – визначення індивідуального ризику виникнення ускладнень у хворих з ХСН, враховуючи поєднаний вплив декількох чинників. Проведено повне клінічне обстеження 110 пацієнтів з ХСН (74,5 % чоловіків, 25,5 % жінок). Для визначення поєднаного впливу аналізованих факторів на прогноз ХСН застосовано метод логістичної регресії, адекватність та достовірність різниці отриманої моделі досліджували за критеріями Вальда і ксі-квадрата. При розробці способу прогнозування індивідуального ризику розвитку серцевої недостатності нами, крім факторів, що, за даними літератури, впливають на розвиток цього захворювання, виділено три чинники, які мають достовірний ($P < 0,05$) взаємозв'язок з ХСН: індекс маси тіла (ІМТ), загальний холестерин та кількість лімфоцитів. Опрацювано комп'ютерну програму, за якою можна розраховувати прогноз ускладнень ХСН. Це файл, що відкривається у програмі «Microsoft Excel», після введення значень вмісту холестерину, лімфоцитів та ІМТ розраховує індивідуальний ризик та графічно зображує ступінь ризику. Проведений кореляційний аналіз індивідуального ризику ускладнень ХСН показав, що високий індивідуальний ризик ускладнень ХСН чітко асоціюється з розвитком систолічної дисфункції, гіпертрофією лівого шлуночка з дилатацією, анемічним та інтоксикаційним синдромами, погіршенням функцій печінки і нирок із зменшенням рівня лептину крові, який має важливі регулювальні функції. Таким чином, за проведеними логістичним, кореляційним та прогностичним аналізами, індивідуальний ризик розвитку ускладнень ХСН збільшується при поєднанні таких факторів, як зменшення маси тіла, зниження рівня загального холестерину та зменшення кількості лімфоцитів периферичної крові. Використання розробленої комп'ютерної програми дозволяє лікареві розрахувати індивідуальний ризик та унаочнити його.

Ключові слова: хронічна серцева недостатність; індивідуальний прогноз; маса тіла; рівень загального холестерину; кількість лімфоцитів; логістична регресія.

ИНДИВИДУАЛЬНОЕ ПРОГНОЗИРОВАНИЕ ОСЛОЖНЕНИЙ ПРИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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Признанная большинством учёных нейрогуморальная теория развития хронической сердечной недостаточности (ХСН) полностью не объясняет механизмов её декомпенсации, стандартное лечение не всегда способствует получению желаемых результатов, поэтому актуальным остаётся поиск патогенетических и прогностических факторов, влияющих на течение ХСН. Однако индивидуальное прогнозирование течения ХСН в клинической практике до сих пор не проводится, поскольку чёткие критерии его не определены, что обусловило актуальность и целесообразность нашего исследования, цель которого – определение индивидуального риска возникновения осложнений у больных с ХСН, учитывая сочетанное влияние нескольких факторов. Проведено полное клиническое обследование 110 пациентов с ХСН (74,5 % мужчин, 25,5 % женщин). Для определения сочетанного воздействия анализируемых факторов на прогноз ХСН применён метод логистической регрессии, адекватность и достоверность разницы полученной модели исследовали по критериям Вальда и кси-квадрат. При разработке способа прогнозирования индивидуального риска развития сердечной недостаточности нами, кроме ряда факторов, что, по данным литературы, влияют на развитие этого заболевания, было выделено три фактора, имеющих достоверную ($P < 0,05$) взаимосвязь с ХСН: индекс масси тела (ИМТ), общий холестерин и количество лимфоцитов. Разработана компьютерная программа, с помощью которой возможно рассчитывать прогноз осложнений ХСН. Это файл, который открывается в программе «Microsoft Excel», после ввода значений содержания холестерина, лимфоцитов и ИМТ рассчитывает индивидуальный риск и графически изображает степень риска. Проведённый корреляционный анализ индивидуального риска осложнений ХСН по-

казал, что высокий индивидуальный риск осложнений ХСН чётко ассоциируется с развитием систолической дисфункции, гипертрофией левого желудочка с дилатацией, анемическим и интоксикационным синдромами, ухудшением функции печени и почек с уменьшением уровня лептина крови, который имеет важные регулирующие функции. Таким образом, по проведённым логистическим, корреляционным и прогностическим анализам индивидуальный риск развития осложнений ХСН увеличивается при сочетании таких факторов, как уменьшение массы тела, снижение уровня общего холестерина и уменьшение количества лимфоцитов периферической крови. Использование разработанной компьютерной программы позволяет врачу рассчитать индивидуальный риск и наглядно его показать.

Ключевые слова: хроническая сердечная недостаточность; индивидуальный прогноз; масса тела; уровень общего холестерина; количество лимфоцитов; логистическая регрессия.