# Mathematical forecasting of adverse course of chronic heart failure in patients with ischemic heart disease.

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## Abstract

**Aim: To identifies prognostic factors and develops a method for the mathematical evaluation of the unfavourable course of CHF.**

**Material and methods: A total of 120 patients with IHD with I, II and III FC of CHF were examined. All patients underwent Echocardiography with assessment of end-diastolic and end-systolic volumes and LV sizes (ESS, ESV and EDS, EDV), left ventricular ejection fraction (EFLV), LV myocardial mass index (LVMMI), systolic and diastolic sphericity index (SIs and SId); In the dopplerography of brachiocephalic arteries (BCA) and renal arteries, the intima-media thickness (IMT) at the level of the common carotid artery (CCA), the resistive and pulsatile index (RI and PI) at the level of the right and left renal arteries, characterizing the state of peripheral resistance in the renal arteries.**

**Results: The level of serum creatinine (Cr), the calculated glomerular filtration rate (cGFR) calculated by formula on MDRD (Modification of Diet in Renal Disease Study) in ml/min/1.73 $m^2$, urinary enzyme level: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), while the total index of the fermentation was estimated to be more than 6.0.**

**Conclusion: The final list of signs determining the progression of CHF is cGFR less than 60 ml/min/1.73 $m^2$, EF LV less than 50%, EDV more than 137 ml, ESS more than 43 mm, IMT on CCA more than 1.1 mm, SId more than 0.72.**

**Keywords**: Chronic heart failure, Prognosis, Renal dysfunction.

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## Introduction

Cardiovascular diseases have now consolidated a leading position in the structure of morbidity and mortality, and their share in Uzbekistan is 59.3% in the structure of total mortality [1]. The prevalence of chronic heart failure (CHF) continues to increase steadily. CHF is the outcome of the so-called cardiovascular continuum and is one of the main problems of clinical cardiology [2-4]. This determined the relevance of the study aimed at identifying reliable signs of unfavorable course and progression of CHF, as well as the possibility of mathematical calculation and assessment of the prognosis of patients with CHF.

In literature the way of the forecast of emergence of CHF at patients with ischemic heart disease, with determination of arterial pressure and the chosen indicators radiological, echocardiographic, veloergometric, anamnestic is known, including the elements of social and hygienic and psychological researches which are mainly reflecting morpho functional aspects of hemodynamics and calculate predictive indicator on mathematical formula. After calculation of mathematical formula judge possibility of development of chronic heart failure or absence of that forecast ("Way of the forecast of developing of chronic heart failure at patients with ischemic heart disease» the patent Russian Federation number: 2444982, A 61 V, publ. 20.03.2012y.).

However, the way is not rather exact and informative, as only on the provided indicators it is impossible to predict fully risk of development of heart failure. In way, there is no subjectivity of assessment and dependence of quality of the received information on qualification of the researcher, in view of use mathematically of exact indicators. He leads to receiving unambiguous and definitely treated quantitative and the main thing of integrative criterion of assessment of availability or lack of this form of coronary disease of heart and it objectify medical diagnosis.

The closest on technical essence is "The way of forecasting of progressing of chronic heart failure" by method of echocardiography (EchoCG) at patients CHF reveal cicatricial changes, signs of hypertrophy of myocardium of left ventricle, pulmonary hypertensia, and also define functional class CHF. Considering these parameters, anemia, irregular therapy, appropriate to the revealed risk factors gradation and establish their numerical values. Determine high or low probability of progressing of CHF by original mathematical formula. The way provides opportunity to predict approach of progressing of CHF and gives the chance of definition of risk degree (the item Russian Federation number: 2444981, A 61 V, publ. 20.03.2012y.).

Shortcomings of this way are absence of instructions on sensitivity and specificity of method, by drawing up mathematical model only separate parameters, anemia and functional class CHF are considered according to echocardiography, and thus is not rather exact and informative.

Problem of the offered method is simplification and increase of accuracy when forecasting progressing of chronic heart failure taking into account assessment of function of kidneys. The mathematical assessment of the forecast and development of CHF taking into account as LV structural and geometrical parameters, parameters of vascular remodeling, and functional condition of kidneys was not carried out earlier and therefore it is represented actual.

## The Aim of the Study

The aim of the study was to identify prognostic factors and develop a method for the mathematical evaluation of the unfavorable course of CHF.

## Material and Methods

A total of 120 patients with IHD with I, II and III FC of CHF were randomized (patients were randomized to CHF groups according to the classification of the New York Cardiology Association according to the test of six-minute walking (TSMW) and the Clinical Patient Assessment Scale (CPAS). The clinical characteristics of patients are presented in Table 1.

Apparently from Table 1, have made CHF I FC of 120 patients of 37 patients, 43 – CHF II FC, 40 patients with CHF III FC, from them 113 patients had the arterial hypertension (AH), 54 patients have had the myocardial infarction (MI) in the past, 10 patients had atrial fibrillation, 7 patients have ventricular and supraventricular extra-systole.

All patients were evaluated along with general clinical methods of evaluation: EchoCG with assessment of end-diastolic and end-systolic volumes and LV sizes (ESS, ESV and EDS, EDV), left ventricular ejection fraction (EFLV), LV myocardial mass index (LVMMI), systolic and diastolic sphericity index (SIs and SId); In the dopplerography of brachiocephalic arteries (BCA) and renal arteries, the intima-media thickness (IMT) at the level of the common carotid artery (CCA), the resistive and pulsatile index (RI and PI) at the level of the right and left renal arteries, characterizing the state of peripheral resistance in the renal arteries; The level of serum creatinine (Cr), the calculated glomerular filtration rate (cGFR) calculated by formula on MDRD (Modification of Diet in Renal Disease Study) in ml/min/1.73 $m^2$, urinary enzyme level: Alanine aminotranspherase (ALT), aspartate aminotranspherase (AST), alkaline phosphatase (AP), while the total index of the fermentation was estimated to be more than 6.0.

***Table 1.*** *Clinical characteristics of patients included in the study protocol.*

| Indicator | n (%) |
|---|---|
| Total number of patients | 120 |
| Men | 75 (63%) |
| Women | 45 (37%) |
| CHF I FC | 37 (30.8%) |
| CHF II FC | 43 (35.8%) |
| CHF III FC | 40 (33.3%) |
| Arterial hypertension | 113 (94.2)% |
| Post-infarction cardiosclerosis | 54 (45%) |
| Atrial fibrillation | 10 (8.3%) |
| Ventricular extrasystole | 6 (5%) |
| Supraventricular extrasystole | 1 (0.3%) |

The study of blood flow of the common carotid artery and renal arteries was performed by ultrasonic methods using the SONOACEX6 (Korea) ultrasound scanner by color Doppler mapping, as well as pulse-wave Doppler and energy mapping with a 3.5 MHz sector sensor with a scanning angle of no more than 60°.

To assess the significance of parameters in predicting the course of CHF, taking into account the kidney function, a method based on the theory of pattern recognition with a probabilistic approach was used. In the probabilistic approach, algorithms based on the Bayes formula (the inverse probability theorem or the hypothesis theorem) and Wald's methods of sequential statistical analysis were applied [5]. To optimize the diagnostics, we used the method of inhomogeneous sequential procedure, developed by Genkin and Gubler for use in biology and medicine [6]. The development of differential diagnostic tables included three stages: the first - the study of the likelihood of a symptom in CHF depending on the degree of severity, the calculation of diagnostic coefficients (DC) and the definition of the informativeness of each feature. The second stage is the compilation of diagnostic tables, including features that have high information content (more than or equal to 0.5). The third stage is the selection of diagnostic thresholds (the sum of the diagnostic coefficients), which made it possible to make the correct diagnostic decision.

In accordance with Wald's method, the calculation of the diagnostic coefficients (DC) of each of the signs was carried out according to the formula:

$$DK = 10 \times lgP1 / P2,$$

where DK is the diagnostic coefficient; P1 is the relative frequency of the characteristic in the first verifiable condition, expressed in fractions of unity; P2 is the relative frequency of the characteristic in the second verifiable state, expressed in fractions of unity, lg is the decimal logarithm.

The informativeness of each of the diagnostic coefficients was calculated using the Kullback formula:

$$J = 0.5 \times DK \times (P1 - P2),$$

where J is the informative value of the diagnostic coefficient; DK is the diagnostic coefficient.

Assessment of sensitivity, specificity and prognostic significance of the detection of each trait for predicting the course of CHF was carried out on the basis of the developed solution matrix (Table 2) and the corresponding formulas.

Sensitivity (Se) - The probability of identifying an unfavorable course of CHF in detecting a trait, was determined by:

$Se=a/(a + c) \times 100\%$.

Specificity (Sp) - the probability of absence of a sign in healthy individuals, was defined as:

$Sp=d/(b + d) \times 100\%$.

The prognostic significance of revealing the trait (PS +) for the determination of CHF flow was calculated by the formula: PS +=a/(a + b).

The results of the study were processed using a package of statistical programs Microsoft Excel 7.0.

## Results and Discussion

Pathological changes in LV myocardium as a result of myocardial remodeling were accompanied by thinning of the walls; loss of geometric shape, left ventricle became spherical. To assess the structural and geometric parameters of the LV, the following parameters were determined: ESV, ESS, EDV and EDS of the LV, LVEF, LVMMI, SId and SIs. The main parameters of vascular remodeling were also determined: right and left CCA, RI and PI at the level of the right and left renal arteries, as well as renal function according to $GFR_{MDRD}$ and fermenturia are presented in Table 3.

These indicators were selected by us to assess the prognosis of progression of patients with CHF taking into account the kidney function. For practical reasons, it is important for the clinician to identify the patient profile for which the adverse course of the disease is projected. In this regard, in order to assess the individual risk-stratification of the patient, we present a model that is a set of individual characteristics and collected in a so-called diagnostic table in order to identify the probability of an error-free forecast in order to assess the severity and unfavorable course of the disease. To this end, we performed a number of calculations in the compilation of the diagnostic table and are presented in Table 4.

The first column of Table 4 contains a list of the characteristics used to compile the diagnostic table, the second and third columns represent the incidence of the symptom in the patients, respectively, depending on the severity of the CHF flow, and the fifth column indicates the value of the DC. DC is presented with a negative if the symptom is not characteristic for patients with unfavorable course of CHF or a positive sign if the sign indicates an unfavorable course of CHF.

From the characteristics presented in Table 4, a profile of factors was chosen whose diagnostic coefficient is informative, i.e., equal to or greater than 0.5 and characterize the unfavorable course of CHF. The final list of signs determining the progression of CHF is: GFR less than 60 ml/min/1.73 $m^2$, EF LV less than 50%, EDV more than 137 ml, ESS more than 43 mm, IMT on CCA more than 1.1 mm, SId more than 0.72.

Diagnostic coefficients in the case of both the presence of a characteristic and its absence with an informative character of the sign, a discrepancy in the occurrence of a feature in the two extreme expressions are reflected in Table 5.

The sum of the diagnostic coefficients, based on which the conclusion is made about the progression of CHF, is +22.6, and the sum of the diagnostic coefficients characteristic for making a decision on the favorable course of CHF is -38.0. In practice, when the patient is examined, the presence of the characteristics indicated in the table is checked, after which the algebraic sum of the DC scores of these characteristics is calculated. With a threshold value of DC=+15 or more, an unfavorable course of CHF is predicted. At values of DC=-20 or less (that is, in cases where the number of identified risk factors for an adverse outcome is minimal or absent), a conclusion is made about the stable course of CHF. The threshold absolute value of the total DK, equal to -20 and +15, is recommended by the method used for the level of conclusions with the probability of an error-free forecast with $p<0.05$. The advantages of this method include its simplicity and logical correspondence to medical thinking.

The values of sensitivity, specificity and prognostic significance of the signs for predicting the course of CHF with regard to renal dysfunction are reflected in Table 6.

As can be seen from Table 6, the most sensitive signs for the prediction of CHF in patients were the presence of EF LV less than 50% (Se=1), IMT on CCA more than 1.1 mm (Se=0.96), EDV more than 137 ml (Se=0.95) and ESS more than 43 mm

***Table 2.*** *Matrix layout for determining diagnostic sensitivity and specificity of CHF symptoms.*

| Symptoms | Severity grade of CHF | |
|---|---|---|
| | Progressing CHF | stable CHF |
| Yes | a | b |
| No | c | d |
| Note: Where the progressing CHF belongs - c III-IV FC CHF the accruing decompositions signs. to stable CHF I-II of FC CHF | | |

***Table 3***. *Diagnostic parameters in patients with I-III FC CHF.*

| Indicator | Control | IFC | IIFC | IIIFC |
|---|---|---|---|---|
| EDS. cm | 4.86 ± 0.82 | 5.41 ± 0.35 | 5.75 ± 0.65 | 6.12 ± 0.82 |
| EDV. ml | 98.2 ± 12.7 | 148.1 ± 17.7 | 168.9 ± 27.85 | 198.31 ± 55.2 |
| ESS. cm | 4.0 ± 0.7 | 3.86 ± 0.32 | 4.38 ± 0.44 | 4.96 ± 0.79 |
| ESV. ml | 42.4 ± 5.1 | 63.08 ± 9.3 | 91.7 ± 15.4 | 133.2 ± 36.6 |
| EF LV. % | 56.4 ± 2.11 | 56.8 ± 1.48 | 45.7 ± 0.95 | 36.31 ± 1.65 |
| LVMMI. g/$cm^2$ | 122.1 ± 10.18 | 159.01 ± 22.7 | 173.3 ± 39.0 | 174.8 ± 22.5 |
| SID | 0.537 ± 0.025 | 0.681 ± 0.035 | 0.716 ± 0.05 | 0.757 ± 0.088 |
| SIS | 0.608 ± 0.037 | 0.653 ± 0.04 | 0.735 ± 0.05 | 0.819 ± 0.086 |
| IMT right CCA/left CCA | 0.88 ± 0.02/0.87 ± 0.02 | 0.97 ± 0.03/1.02 ± 0.03 | 1.1 ± 0.04/1.16 ± 0.04 | 1.49 ± 0.09/1.46 ± 0.09 |
| RI on right /left renal artery | 0.67 ± 0.016/0.70 ± 0.01 | 0.74 ± 0.042/0.75 ± 0.056 | 0.75 ± 0.047/0.77 ± 0.066 | 0.77 ± 0.062/0.79 ± 0.078 |
| PIon right /left renal artery | 1.0 ± 0.03/1.01 ± 0.02 | 1.21 ± 0.11/1.25 ± 0.145 | 1.256 ± 0.21/1.28 ± 0.21 | 1.265 ± 0.23/1.3 ± 0.16 |
| ALT. u/l | 2.53 ± 0.071 | 2.89 ± 0.168 | 3.28 ± 0.26 | 4.59 ± 0.17 |
| AST. u/l | 2.69 ± 0.085 | 3.1 ± 0.147 | 3.24 ± 0.325 | 4.1 ± 0.009 |
| AP. u/l | 0.81 ± 0.049 | 1.15 ± 0.101 | 1.53 ± 0.259 | 1.61 ± 0.01 |
| cGFR. ml/min/1.73 $m^2$ | 88.9 ± 15.6 | 76.4 ± 11.1 | 68.4 ± 11.9 | 61.1 ± 9.3 |

***Table 4.*** *Diagnostic table for assessing the adverse course of CHF.*

| Indicators | Frequency of the indicator for I-II FC CHF (P1) | Frequency of the indicator for III FC CHF (P2) | Diagnostic coefficient (DC) of the trait | Informative character of the sign (J) |
|---|---|---|---|---|
| Creatinine more than 90 μmol/l | 0.5 | 0.55 | 0.414 | 0.010 |
| GFR less than 60 ml/min/1.73 $m^2$ | 0.18 | 0.44 | 3.882 | 0.505 |
| GFR less than 90 ml/min/1.73 $m^2$ | 0.84 | 0.9 | 0.3 | 0.009 |
| EF LV less than 50% | 0.45 | 1 | 3.468 | 0.954 |
| EF LV more than 50% | 0.55 | -0 | -0 | -0 |
| EDSmore than 55 mm | 0.537 | 0.85 | 1.990 | 0.311 |
| EDVmore than 137 ml | 0.375 | 0.95 | 4.037 | 1.161 |
| ESSmore than 43 mm | 0.385 | 0.95 | 3.923 | 1.108 |
| LVMMI more than 135 (g/$m^2$) | 0.925 | 0.975 | 0.229 | 0.006 |
| SI d more than 0.72 | 0.287 | 0.6 | 3.195 | 0.5 |
| Total index of the fermenturia more than 6.0 | 0.56 | 0.85 | 1.812 | 0.263 |
| IMT on CCA more than 1.1 mm | 0.37 | 1 | 4.318 | 1.360 |
| RI on right/left renal artery more than 0.7 | 0.77 | 0.81 | 0.22 | 0.004 |
| PIon right /left renal artery more than1.0 | 0.888 | 0.909 | 0.102 | 0.001 |
| Where P1 – is the relative frequency of the characteristic in the first verifiable state, expressed in fractions of unity; P2 - relative frequency of the characteristic in the second verifiable state. expressed in fractions of unity; DC– diagnostic coefficient; J – informative character of the diagnostic coefficient | | | | |

***Table 5.*** *The final list of signs that determine the progression of CHF.*

| Indicator | Characteristic range | Diagnostic coefficient (DC) of the sign | Informative character of the sign (J) |
|---|---|---|---|
| GFR | less than 60 ml/min/1.73 $m^2$ | 3.8818 | 0.504634 |
| | more than 60 ml/min/1.73 $m^2$ | -1.656258 | 0.215314 |
| EF LV | less than 50% | 3.46787 | 0.953666 |
| | more than 50% | 0 | 0 |
| EDV | more than 137 mm | 4.03692 | 1.160615 |
| | less than 137 mm | -10.9691 | 3.153616 |
| ESS | more than 43 mm | 3.92263 | 1.108143 |
| | less than 43 mm | -10.89905 | 3.078982 |
| ИCd | more than 0.72 | 3.19513 | 0.5 |
| | less than 0.72 | -2.507249 | 0.391758 |
| IMT on CCA more than 1.1 mm | Yes | 4.1407 | 1.221505 |
| | No | -11.97281 | 3.531978 |

***Table 6.*** *Sensitivity, specificity and prognostic significance of the signs for predicting the course of CHF.*

| Indicator | Sensitivity (Se) | Specificity(Sp) | Prognostic significance (PS) |
|---|---|---|---|
| GFR less than 60 ml/min/1.73 $m^2$ | 0.44 | 0.82 | 0.71 |
| EF LV less than 50% | 1 | 0.55 | 0.69 |
| EDV more than 137 ml | 0.95 | 0.625 | 0.72 |
| ESS more than 43 mm | 0.95 | 0.615 | 0.71 |
| SIdmore than 0.72 | 0.6 | 0.713 | 0.68 |
| IMT on CCA more than 1.1 mm | 0.96 | 0.63 | 0.722 |

(Se=0.95). The most specific signs were a decrease in GFR less than 60 ml/min/1.73 $m^2$ (Sp=0.82), an increase in the size of the sphericity index in diastole more than 0.72 (Sp=0.71). Prognostically significant for determining the adverse course of CHF were the presence of EF LV decrease of less than 50% (PS=0.71), increase in IMT on CCA more than 1.1 mm (PS=0.72), EDV more than 137 ml (PS=0.72) and ESS more than 43 mm (PS=0.71).

Thus, for the decision put tasks the way of forecasting of progressing of chronic heart failure taking into account dysfunction of kidneys including assessment of sensitivity, specificity, diagnostic value and the predictive importance of separate signs in forecasting of current of CHF taking into account dysfunction of kidneys thus is offered the method with creation of mathematical model of signs is used: The key LV structural and geometrical parameters determined at echocardiography with determination of final and diastolic and end-systolic volumes and LV sizes, fractions of emission of LV, index of mass of myocardium of LV, index of systolic and diastolic sphericity; indicators of vascular remodeling at the level of the general carotid artery and renal arteries; determination of level of serumal creatinine (Kr), settlement GGF on formula MDRD, total index of fermenturiya (alaninaminotranspherase (ALT)+aspartataminotranspherase (nuclear heating plant)+alkaline phosphatase (AF).

Thus, these distinguishing characters allow drawing conclusion on novelty of technical solution. Inventive level of the offered way is defined by that allows to increase the accuracy of diagnosis and to predict the course of chronic heart failure taking into account functional condition of kidneys.

## Relationship of cause and effect

For the purpose of assessment individual risk stratification of the patient we represent the model representing set of separate signs and collected to the so-called, diagnostic table with the purpose to reveal probability of the faultless forecast and assessment of weight of the patient. That gives the chance to carry out the individual forecast of progressing of CHF, and in this case, defines it in group of high risk, need of purpose of more intensive care, allows to increase the accuracy and informational content, i.e., timely to reveal patients with high risk of developing of chronic heart failure and to hold preventive events taking into account functional condition of kidneys.

## Conclusions

1. The offered method of definition of the adverse forecast of CHF can be applicable in broad clinical practice since it is simple in use, allows to reveal timely patients with high risk of developing of chronic heart failure and to hold preventive events taking into account functional condition of kidneys.
2. Prognostically significant criteria for progression and unfavorable prognosis of CHF flow are GFR decrease less than 60 ml/min/1.73 $m^2$, EF LV less than 50%, increase in EDV more than 137 ml, ESS more than 43 mm, IMT on CC level of more than 1.1 mm.
3. The most sensitive signs for the prediction of CHF in patients were the presence of EF LV less than 50%, IMT on CCA more than 1.1 mm, EDV more than 137 ml and ESS more than 43 mm.
4. The most specific signs were a decrease in GFR less than 60 ml/min/1.73 $m^2$, an increase in the size of the sphericity index in diastole more than 0.72.
5. Prognostically significant for determining the adverse course of CHF were the presence of EF LV decrease of less than 50%, increase in IMT on CCA more than 1.1 mm, EDV more than 137 ml and ESS more than 43 mm.

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