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PREDICTION OF THE DEVELOPMENT OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE

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Purpose. To identify prognostic factors for the development of renal dysfunction (RD) and to develop a method for assessing and predicting RD in patients with chronic heart failure (CHF).

Methods. A total of 101 patients with functional class I-III (FC) CHF (according to the classification of the New York Heart Association) were examined. Also, the patients were divided, depending on the glomerular filtration rate, determined by the calculation method according to the CKD-EPI formula (eGFR), into two groups: patients with eGFR≥90 ml / min (n = 20), with eGFR <90 ml / min (n = 81). All patients were determined: creatinine (Cr), eGFR according to the CKD-EPI formula, albumin / creatinine (Al / Cr) level (mg / mmol) in morning urine, specific gravity in morning urine portion (SG); studied renal blood flow according to Doppler sonography at the level of the common left and right renal arteries. To assess the significance of signs for determining and predicting RD in CHF, we used a method based on Wald's sequential statistical analysis with the development of differential diagnostic tables, determination of diagnostic coefficients (DC) and information content (J) of each sign in groups of patients with CHF, depending on the level eGFR, determination of diagnostic thresholds (amount of DC).

Results. As a result of the developed differential diagnostic tables, the most informative signs were identified that determine the unfavorable prognosis of RD in patients with CHF: creatinine above 80 μmol / l, eGFR less than 90 ml / min, Al / Cr ratio in morning urine more than 3.4 mg / mmol, urine specific gravity SG less than 1015, resistance index (RI) at the level of the right and left renal arteries more than 0.7. The sum of DCs of these signs, depending on the severity of symptoms, determines the risk of developing RD: a very high risk in the range from +15 to +32, high risk - from +8 to +14, moderate risk - from +7 to +3, favorable course of CHF - from 0 to +2 points.

Conclusion. Signs of an unfavorable prognosis for the development of RD in patients with CHF were determined: creatinine above 80 μmol / l, eGFR less than 90 ml / min, Al / Cr ratio in morning urine more than 3.4 mg / mmol, urine SG less than 1015, RI at the renal level arteries more than 0.7.

Key words: chronic heart failure, prognosis, renal dysfunction, glomerular filtration rate.

INTRODUCTION

Chronic heart failure (CHF) is one of the most common and progressive diseases of the cardiovascular system, the social significance of which is determined by the high mortality rate and the frequent cause of hospitalization of patients [3,5]. According to the results of a number of studies, renal dysfunction (RD) occurs in 45–63.6% of patients with CHF and is an independent negative prognostic factor for the development of LV systolic and diastolic dysfunction, cardiovascular death, and worsening clinical outcomes [12]. It was found that in patients with CHF, the presence of renal dysfunction is a predictor of an unfavorable clinical outcome, the prevalence of which in CHF is from 25% to 60%.

A decrease in the glomerular filtration rate (GFR) is an independent risk factor for CVD, the cause of the accelerated development of pathological changes in the cardiovascular system and is considered as a marker of an unfavorable prognosis of CVD [16].

A decrease in GFR is considered as a marker of a poor prognosis in the CVD population: with GFR <60 ml / min / 1.73 m^2, the risk of mortality increases by 2.1 times; with a reduced systolic LV function, the risk of death in patients with renal failure (RF) 3.8 times [14].

At present, the mutual negative influence of heart and renal dysfunction has been proven, expressed in the progression of RD in various CVDs, the relationship between RD and CVD is consistent and two-way. The central

link in the cardiorenal relationship is the RAAS, SAS, endothelium-dependent factors and their antagonists - natriuretic peptides and the kallikrein/kinin system. Along with other etiological and pathogenetic mechanisms, the RAAS determines the key features of the clinical course of CHF and RD, the development of cardiac and renal failure. In this regard, an urgent problem is the primary prevention and prognosis of RD in patients with chronic heart failure [8].

A comprehensive assessment of the functional state of the kidneys in patients with cardiovascular diseases with the determination of creatinine, eGFR, albuminuria and the development of early prognostic criteria will make it possible to determine DP at an early stage of its development [13].

The aim of the study was to identify prognostic factors for the development of renal dysfunction (RD) and to develop a method for assessing and predicting RD in patients with chronic heart failure (CHF).

Material and methods. A total of 101 patients with coronary heart disease with functional class I-III (FC) CHF were examined (patients were randomized into groups according to FC CHF according to the classification of the New York Heart Association according to the 6-minute walk test (6MWT) and according to the by the Scale of clinical state of CHF patients. Also, patients were distributed depending on the glomerular filtration rate (GFR), determined by the calculation method according to the formula CKD-EPI (eGFR) (modified MDRD formula, 2011) [14]: Group 1 - patients with eGFR ≥90 ml / min (20 patients), Group 2 - patients with eGFR <90 ml / min (81 patients). The control group consisted of 20 healthy individuals of comparable age, without cardiovascular and renal pathology. The clinical characteristics of the patients are presented in **Table 1.**

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

Indicator	**Total patients**	**Men**	**Women**	**I FC CHF**	**II FC CHF**	**III FC CHF**	**HD**	**PICS**
n (number of patients)	102	65	37	42	40	20	95	43

Note: HD - Hypertonic disease, PICS - postinfarction cardiosclerosis

All patients, along with general clinical research methods, were assessed: assessment by the clinical status scale, control of blood pressure (BP) and heart rate, echocardiography (EchoCG), 6MWT, the level of serum creatinine (Cr) was determined. In order to assess albuminuria, the level of albumin / creatinine (Al / Cr) of urine (mg / mmol) in the morning urine was determined, while the degree of increase in Al / Cr was determined at values <3.4 mg / mmol - the norm (optimal), at values of 3,4-33.9 mg / mmol - a high degree, at values of more than 33.9 mg / mmol - a very high degree of albuminuria, and also for the purpose of assessing the concentration function of the renals - the specific gravity in the morning portion of urine (SG) [2,9,14]. Renal blood flow was studied according to Doppler sonography of the renal arteries at the level of the common left and right renal arteries using the SONOACEX6 ultrasound apparatus (South Korea) by color Doppler mapping, as well as pulsed-wave Doppler and energy mapping with a 3.5 MHz sector probe at a scanning angle of no more than 60 °. The following indicators were used: peak systolic blood flow velocity (Vs), maximum end diastolic blood flow velocity (Vd), resistance index (RI) and pulsation index (PI), RI and PI - characterize the state of peripheral resistance in the vascular basin [6,10].

To assess the significance of signs for the determination and prediction of renal dysfunction in CHF, a method based on the theory of pattern recognition with a probabilistic approach was used [8]. In the probabilistic approach, algorithms were applied based on Bayes' formula (inverse probability theorem, or hypothesis theorem) and Wald's method of sequential statistical analysis [11]. The development of differential diagnostic tables included three stages: the first was the study of the probability of a symptom with normal renal function and kidney disease in patients with CHF, the calculation of diagnostic coefficients and the determination of the informative value of each sign. The second stage was the compilation of diagnostic tables, which included only signs that had a high informative value (more than or equal to 0.5) with a discrepancy on the basis for the compared states of at least 10%. The third stage is the choice of diagnostic thresholds (the sum of diagnostic coefficients), which made it possible to make the correct diagnostic decision.

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

DC = 10 × lgP1 / P2, where DC is the diagnostic coefficient; P1 - the relative frequency of the sign the first verified state, expressed in fractions of one; P2 - the relative frequency of the sign in the second verified state, expressed in fractions of one, lg - the decimal logarithm.

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

J = 0.5 × DC × (P1 - P2), where J is the information content of the diagnostic coefficient; DC - diagnostic coefficient; P1 - the relative frequency of the sign in the first verified state, expressed in fractions of one; P2 - the relative frequency of the sign in the second verified state, expressed in fractions of one.

The assessment of the sensitivity, specificity and prognostic significance of detecting each sign for predicting the course of CHF was carried out on the basis of the corresponding formulas and the matrix presented in **Table 2.**

Table 2. Model of the matrix for determining the diagnostic sensitivity and specificity of signs of RD in patients with CHF

Sign		**Availability of DK**	
		GFR < 90	GFR > 90
available		a	b
not available		c	d

Sensitivity (Se) - the likelihood of detecting the risk of developing RD in patients with CHF when a symptom is detected, was determined as:

Se = a / (a + c) × 100%. Specificity (Sp) - the probability of the absence of the sign in healthy individuals, was determined as Sp = d / (b + d) × 100%.

The predictive value of identifying the sign (PV +) for predicting the risk of developing RD in patients with CHF was calculated using the formula: PV + = a / (a + b).

Statistical analysis of the data obtained was carried out using the MS Excel 7.0 spreadsheet editor and the STATISTICA 6.0 statistical program. Quantitative data at the preliminary stage of statistical analysis were assessed for normality of distribution using the Shapiro-Wilk test. We used the methods of variational parametric and nonparametric statistics with the calculation of the arithmetic mean of the studied indicator (M), standard deviation (SD), standard error of the mean (m), the statistical significance of the measurements obtained when comparing the mean values was determined by the Student's test (t) with the calculation of the error probability (p), the level of significance $p < 0.05$ was taken as statistically significant changes.

Research results.

In the groups of patients with eGFR <90 ml / min and eGFR ≥90 ml / min, the main indicators of renal function were determined: serum Cr level, eGFR, renal blood flow parameters, albuminuria level (Al / Cr), specific gravity in the morning urine portion (SG), the data of these indicators are presented in **Table 3.** These indicators were selected by us as diagnostic criteria for assessing the prognosis of the development of RD in patients with CHF and their prognostic significance was assessed in the groups of patients with eGFR <90 ml / min and eGFR≥90 ml / min [2,4].

Table 3. Diagnostic criteria for RD in patients with CHF groups 1 and 2 (M ± SD)

Indicator	**Control**	**Group 1 (eGFR <90 ml / min)**	**Group 2 (eGFR≥90 ml / min)**
Cr, μmol / l	53,8±12,4	87,2±11,4	67,1±10,9
eGFR, ml / min	126,5±5,5	73,9±12,2	98,5±5,73
Al / Cr in morning urine (mg / mmol)	-	27,3±9,7	2,8±4,4
SG urine	1026,5±4,9	1015,2±9,9	1025,5±4,9
Vs at the level of the right / left renal arteries, cm / sec	59,0±11,2 / 58,8±10,1	53,84±9,08 / 52,77±9,51	52,4±6,2 / 52,25±6,5
Vd at the level of the right / left renal arteries, cm /	21,4±5,6 / 20,5±4,8	15,98±3,88 / 15,8±3,38	16,3±2,89 / 16,4±2,6

sec			
RI at the level of the right / left renal arteries	0,63±0,016 / 0,64±0,01	0,751±0,042 / 0,752±0,056	0,688±0,047 / 0,677±0,066
PI at the level of the right / left renal arteries	1,0±0,08 / 1,01±0,08	1,477±0,229 / 1,465±0,256	1,256±0,175 / 1,28±0,18

In order to assess the risk of developing RD and predicting its development in patients with CHF, we have developed a model, which is a set of individual signs and collected in the so-called diagnostic table to identify the probability of an error-free prognosis of the disease. To do this, we carried out a number of calculations when compiling a diagnostic table and are presented in **Table 4.** The first column of Table 4 presents a list of signs used to compile a diagnostic table, the second and third columns represent the frequency of occurrence of a symptom among patients, respectively, depending on the presence of RD, in the fourth column the value of the DC is indicated, and in the fifth column the informative value J of the attribute, calculated according to the above formulas.

Table 4. Diagnostic table for predicting and assessing renal dysfunction in patients with CHF

Sign	P1	P2	DC of the sign	J of the sign
Creatinine more than 80 μmol / L	0,73	0,19	5,85	1,58
eGFR less than 90 ml / min	1,0	0	40	20
Al / Cr in morning urine more than 3.4 mg / mmol	0,58	0,05	10,64	2,82
SG in morning urine less than 1015	0,23	0,05	6,628	0,596
Vs at the level of the right / left renal arteries less than 56 cm / sec	0,86	0,81	0,26	0,007
Vd at the level of the right / left renal arteries less than 20 cm / sec	0,93	0,89	0,19	0,004
RI at the level of renal arteries more than 0.7	0,77	0,47	2,144	0,322
PI at the level of renal arteries more than 1.2	0,95	0,86	0,432	0,019

Note: P1 is the relative frequency of the sign in the first verified state with eGFR <90 ml / min, expressed in fractions of one; P2 is the relative frequency of the sign in the second verified state with eGFR> 90 ml / min, expressed in fractions of one; DC - diagnostic coefficient of the sign; J – sign informativeness.

From the 4 signs presented in the table, those are selected whose DC has high information content, i.e. equal to or greater than 0.5. For each sign, depending on the severity of symptoms (the degree of violation of each indicator was determined), the gradation in points was determined within the maximum values determined in the range of DC values, taking into account the informative value of the sign, these data are presented in **table 5**:

Table 5. Signs that determine the progression of RD in patients with CHF with their severity

Sign	DC of the sign	Maximum DC in points	Degree of manifestation of the sign	Points depending on the severity of the sign
Creatinine, μmol / l	5,85	3	< 80	0
			81-100	+1
			101-120	+2
			121 and higher	+3
eGFR, ml / min	40	20	> 90	0
			90-60	+5
			59-45	+10
			44-30	+15
			<30	+20
Al / Cr in morning urine, mg / mmol	10,64	5	<3,4	0
			3,4-33,9	2,5

			>33,9	5
SG in morning urine	6,628	3	More then 1020	0
			1020-1015	1
			Less then 1015	2
			Less then 1010	3
RI at the level of the right and left renal arteries	2,144	1	Less then 0,7	0
			More then 0,7	1

Based on the data obtained, a mathematical model was developed for assessing the development of RD, while the diagnostic thresholds were calculated as the sum of the DC of the selected signs, calculated in points in the case of the maximum and minimum values reduced to an algebraic denominator, which determines the risk of developing RD and a favorable course in CHF patients. Thus, based on the amount of DC of these signs, a conclusion is made and the risk of developing RD is determined: very high risk of RD: +15 - +32, high risk of RD: +8 - +14, moderate risk of +7 - +3, favorable course of CHF without RD - 0- +2 points. In practice, when examining a patient, the presence of the signs indicated in the table is checked, after which the algebraic sum of the DC scores for these signs is calculated and the risk of developing RD and CKD is assessed by the sum of the points. The threshold absolute value of the total DC, equal to +20 - +32, is recommended by the used method 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 consistency with medical thinking.

The values of the sensitivity, specificity and prognostic significance of signs for predicting the development of RD in patients with CHF are shown in **Table. 6**

Table 6. Sensitivity, specificity and predictive value of signs for predicting CHF taking into account RD

Sign	Diagnostic coefficient (DC) of the sign	Maximum DC in points according to the sign	Sensitivity (Se)	Specificity (Sp)	Prognostic value
Creatinine more than 80 μmol / L	5,85	1,58	0,128	0,927	0,787
Creatinine less than 80 μmol / L	-5,28	1,69			
eGFR less than 90 ml / min	40	20	0,847	0,078	0,667
eGFR more than 90 ml / min	-40	20			
Al / Cr in morning urine more than 3.4 mg / mmol	7,22	1,697	0,693	0,102	0,81
Al / Cr in morning urine less than 3.4 mg / mmol	-3,26	0,766			
SG in morning urine less than 1015	3,20	0,192	0,599	0,626	0,943
SG in morning urine more than 1015	-0,629	0,038			
RI at the level of the right and left renal arteries more than 0.7	2,14	0,322	1	0	0,87
RI at the level of the right and left renal arteries more than 0.7	-2,93	0,381			

As you can see from the table. 6, the most sensitive signs for predicting and assessing RD in CHF patients are: the presence of GFR less than 90 ml / min (Se = 0.85), RI at the level of the right and left renal arteries more than 0.7 (Se = 1). The most specific sign was creatinine over 80 μmol / L (Sp = 0.93). Prognostically significant for predicting and assessing RD in patients with CHF were - creatinine above 80 μmol / L, eGFR less than 90 ml / min, Al / Cr ratio in morning urine more than 3.4 mg / mmol, urine SG less than 1015, RI per the level of the right and left renal arteries is more than 0.7.

Discussion. Today, it is well known that many risk factors (RFs) associated with the development of CHF and chronic kidney disease (CKD) are also cardiovascular RFs [8]. There have been many previous studies investigating the relationship between changes in the heart and renals. A number of large studies are devoted to the high importance of timely diagnosis of chronic renal disease in CHF [7]. Previous studies have verified the factors contributing to the progression of CHF, represented by microalbuminuria (MAU), a decrease in GFR. In the work of N.S. Vrublevskaya developed an accessible algorithm for determining the prognosis of the course of CHF with the addition of renal dysfunction, which consists in assessing the individual risk by the sum of diagnostic coefficients for clinical (macrohematuria, oliguria, nocturia, decreased GFR) and laboratory (MAU, increased urea, creatinine, erythrocyturia) manifestations of CKD [1].

In our work, we have developed an accessible algorithm for predicting the risk and assessing renal dysfunction in patients with CHF, which consists in assessing the individual risk based on the sum of the diagnostic coefficients of signs of impaired renal function (serum Cr level, eGFR, renal blood flow parameters, Al / Cr level, specific gravity in the morning urine SG).

The high prevalence of CKD among patients with CHF is the basis for a reasoned development of a system for early detection of renal pathology [10]. For practical reasons, it is important for the clinician to identify the profile of patients who are predicted to have an unfavorable course of CHF with the development of renal failure [7,15]. In this regard, in order to assess individual risk stratification and optimize the system for early diagnosis of renal dysfunction in patients with CHF, we present a model, which is a set of individual signs and collected in the so-called diagnostic table to assess the development of RD in patients with CHF. For this purpose, in patients with CHF, by determining the informative value of a number of indicators of the functional state of the renals (the level of Cr in the blood serum, eGFR, RI at the level of the renal arteries, the level of albuminuria Al / Cr, the specific gravity in the morning portion of urine SG), a method has been developed for the mathematical determination of the risk and assessment of RD in patients with CHF. This method is simple to perform, available and is recommended for widespread use in practical medicine to predict RD in patients with CHF.

Conclusion. Thus, we identified the informative and defining unfavorable prognosis of DP in CHF patients: creatinine above 80 μmol / L, eGFR less than 90 ml / min, Al / Cr ratio in morning urine more than 3.4 mg / mmol, urine specific gravity SG less than 1015, RI at the level of the right and left renal arteries more than 0.7; a mathematical model was developed for assessing the development of RD, diagnostic thresholds were calculated as the sum of the DC of these signs in the case of the maximum and minimum values reduced to an algebraic denominator, which determines the risk of developing RD in patients with CHF: from +15 to +32 points - a very high risk of RD, from +8 to +14 points - high risk of RD, from +7 to +3 points - moderate risk, from 0 to +2 points - favorable course of CHF without RD.

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

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