

## Decision rule for stratification of patients with chronic heart failure of functional class II and III

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### ABSTRACT

**The aim of the study** was focused on the development of a decision rule for classifying patients as functional class (FC) II or III of chronic heart failure (CHF) by discriminant analysis with inflammatory markers.

**Materials and methods.** The study included CHF patients ( $n = 61$ ) of both sexes. According to symptom severity, they were assigned to FC II ( $n = 20$ ) and III ( $n = 41$ ). In addition to conventional clinical and biochemical parameters to evaluate a patient's state, parameters characterizing inflammation (IL-6, soluble IL-6 receptor, sgp130) were used. Statistically significant differences were revealed with the use of Mann-Whitney U test, Student's t-test, Pearson's  $\chi^2$  test and Fisher's exact test. Discriminant analysis was employed to formulate the decision rule. Receiver Operating Characteristic (ROC) analysis was used to evaluate the quality of the developed diagnostic test. The results were considered statistically significant at  $p < 0.05$ .

**Results.** Discriminant analysis included significantly different variables (age, brain natriuretic peptide, sgp130, CHF etiology, ischemic heart disease) and additional clinically important variables (diastolic and systolic arterial blood pressure (BP), IL-6). The decision rule for assigning patients to different CHF FC was developed. The optimum cut-off value was found with the use of the ROC curve with a sensitivity of 75.6% and specificity of 85%.

**Conclusion.** The decision rule for assigning CHF patients to FC II or III was developed using discriminant analysis. In addition to conventional clinical parameters, the model included the ones reflecting inflammatory processes (IL-6 and sgp130). ROC analysis revealed high quality of the model.

**Key words:** chronic heart failure, interleukin 6, sgp130, decision rule, discriminant analysis.

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## Решающее правило для стратификации больных хронической сердечной недостаточностью II и III функционального класса

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### РЕЗЮМЕ

**Цель.** Разработать решающее правило отнесения пациентов ко II и III функциональным классам (ФК) хронической сердечной недостаточности (ХСН) методом дискриминантного анализа с включением маркеров воспаления.

**Материалы и методы.** Исследование включало 61 пациента обоего пола с ХСН. В зависимости от выраженности симптомов ХСН пациенты были отнесены ко II ( $n = 20$ ) и III ( $n = 41$ ) ФК. В работе помимо общепринятых клинических и биохимических показателей, оценивающих состояние пациентов, дополнительно исследовались параметры, отражающие течение воспалительного процесса (IL-6, растворимый рецептор IL-6, sgp130). Для выявления статистически значимо различающихся переменных в группах использовали  $U$ -критерий Манна – Уитни,  $t$ -критерий Стьюдента,  $\chi^2$  Пирсона, точный критерий Фишера. Для построения решающего правила применялся метод дискриминантного анализа. Для оценки качества разработанного диагностического теста использовали ROC-анализ. Статистически значимыми считались результаты при уровне значимости  $p < 0,05$ .

**Результаты.** В дискриминантный анализ были включены выявленные при сравнении групп II и III ФК ХСН значимо различающиеся переменные – возраст, мозговой натрийуретический пептид, sgp130, этиология ХСН, ишемическая болезнь сердца, а также дополнительные переменные, имеющие существенное значение в клинике (артериальное давление (АД) систолическое, АД диастолическое, IL-6). На основании данных показателей было построено решающее правило для отнесения пациентов к различным функциональным классам ХСН. При оценке качества полученного решающего правила было найдено оптимальное значение точки отсечения с использованием ROC-кривой, которой соответствует чувствительность – 75,6%, специфичность – 85%.

**Заключение.** С помощью метода дискриминантного анализа разработано решающее правило разделения больных на II и III ФК ХСН. Наряду с общепринятыми клиническими показателями ХСН в модель включены новые параметры, отражающие степень воспалительного процесса (IL-6 и sgp130). ROC-анализ выявил очень хорошее качество полученной модели.

**Ключевые слова:** хроническая сердечная недостаточность, интерлейкин 6, sgp130, решающее правило, дискриминантный анализ.

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## INTRODUCTION

Chronic heart failure (CHF) remains a current problem of cardiology, being an unfavorable, progressing cardiovascular disease all over the world. Epidemiological studies demonstrate a constant increase in CHF incidence in Western Europe and the USA, particularly in the aging population [1–3]. Epidemiological studies performed in the Russian Federation indicate a similar increase in CHF incidence [4]. The number of patients with more severe forms of the disease increases considerably. Therefore, identification of the early stages of CHF is an important strategy in the treatment of patients with CHF. Effectiveness of treatment is strongly associated with the choice of a therapeutic scheme based on evaluation of the disease symptoms. Severity of CHF symptoms is characterized according to NYHA functional classification [1]. However, evaluation of the CHF severity and identifying patients' functional class often cause difficulties in medical practice. Decision rules have been widely used for assigning patients to the

appropriate functional class. Greater number of clinical parameters reflecting patient's condition allows for better stratification and minimizes errors in classification according to the functional class (FC). In addition to clinical parameters, biochemical markers that reflect organic damage to the heart and hemodynamic load increase have been used in CHF diagnostics [5]. However, the indicators of inflammatory processes that intensify with CHF progression have not received sufficient attention.

The aim of the study was to develop the decision rule that includes inflammatory markers (IL-6 and sgp130) for assigning CHF patients to FC II or III.

## MATERIALS AND METHODS

Parameters characterizing the state of 61 patients aged 31–83 years suffering from functional class II–III chronic heart failure [New York Heart Association (NYHA)] with decreased left ventricular ejection fraction are given in Table 1.

Table 1

Baseline characteristics of patients			
Parameter	II FC ( <i>n</i> = 20)	III FC ( <i>n</i> = 41)	<i>p</i>
Age, y/o, <i>Me</i> ( $Q_1$ – $Q_3$ )	50.5 (42.75–58.25)	62 (53–67)	0.003
Men / Women, abs. (%)	19/1 (95/5)	35/6 (85/15)	0.409
Etiology of CHF (IHD, HT, DCM), abs. (%)	5/6/9 (25/30/45)	24/13/4 (58.5/31.7/9.8)	0.004
LVEF, (%), <i>Me</i> ( $Q_1$ – $Q_3$ )	27.5 (25–31.75)	30 (23.5–35)	0.595
BP systolic, mmHg, <i>Me</i> ( $Q_1$ – $Q_3$ )	120 (105.25–140)	120 (110–140)	0.871
BP diastolic, mmHg, <i>Me</i> ( $Q_1$ – $Q_3$ )	80 (70–88.75)	80 (70–85)	0.374
Heart rate, beats / min, <i>Me</i> ( $Q_1$ – $Q_3$ )	70 (68.50–92.75)	85 (70–96)	0.725
Degree of mitral regurgitation (1, 2, 3), abs. (%)	4/11/5 (20/55/25)	5/20/16 (12.2/48.8/39)	0.490
Congestion Ro, abs. (%)	15 (75)	36 (87.8)	0.205
Hypertension, abs. (%)	12 (60)	34 (83)	0.064
IHD, abs. (%)	5 (25)	25 (61)	0.008
NT-proBNP (pg/ml), <i>Me</i> ( $Q_1$ – $Q_3$ )	395.5 (224.5–825)	793 (408.5–1746.5)	0.009
Creatinine (μmol/l), <i>Me</i> ( $Q_1$ – $Q_3$ )	88 (74–130)	101 (72.5–112.25)	0.432
IL-6, pg/ml, <i>Me</i> ( $Q_1$ – $Q_3$ )	3.48 (2.34–6.66)	3.95 (2.57–8.35)	0.249
pIL-6P, pg/ml, <i>Me</i> ( $Q_1$ – $Q_3$ )	36.25 (32.46–3.26)	40.48 (35.22–48.77)	0.167
Sgp130, pg/ml, <i>Me</i> ( $Q_1$ – $Q_3$ )	333 (309.5–359.5)	415 (355–469)	0.001

Note. Data are presented as median (25th percentile–75th percentile) or absolute number (%). LVEF – left ventricular ejection fraction; Congestion Ro – congestion in the lungs according to X-ray; IHD – ischemic heart disease; HT – hypertension; DCM – dilated cardiomyopathy; NT-proBNP – N-terminal pro-brain natriuretic peptide; IL-6 – Interleukin 6; sIL-6R – soluble Interleukin-6 receptor.

Diagnostics and FC assignment were performed according to up-to-date national recommendations. In order to meet the research

purpose, CHF etiology was defined as a major disease that, according to the researchers' opinion and clinical examination, was a main cause

of the heart failure symptom complex. Patients with an acute cardiovascular event within preceding 30-day period, acute and chronic inflammatory diseases requiring specific anti-inflammatory therapy and potentially influencing test parameters, pronounced renal and/or hepatic functional disorders, malignant tumors, or with other chronic diseases of internal organs, or with left ventricular outflow tract obstruction were excluded from the study. All patients who participated in the study signed an informed consent.

Statistical analysis was done with IBMSPSS Statistics 23. Statistically significant differences between quantitative variables for two independent samples with distribution other than normal were revealed with Mann – Whitney *U*-test. Pearson’s  $\chi^2$  test and Fischer’s exact tests were used to reveal statistically significant differences between qualitative variables in two groups. Discriminant analysis was employed to establish the decision rule for assigning patients to the appropriate FC. The quality of diagnostic test was evaluated by ROC analysis. The results were regarded as statistically significant at  $p < 0.05$ .

**RESULTS AND DISCUSSION**

In order to develop the decision rule, test variables were compared and the following statistically significant variables in patients with CHF of FC II and III were revealed: age, N-terminal pro-brain natriuretic peptide (NT-proBNP), sgp130, etiology of CHF and IHD (Table 1). Clinically important parameters (systolic and diastolic BP, IL-6) were also included in the discriminant analysis.

CHF classification according to FC (NYHA) is based on the severity of clinical manifestations. BP parameters are used in clinical practice to choose pharmacotherapy and control its effectiveness. In addition, BP deviations represent the risk of decompensation of a patient’s condition [5]. Therefore, such variables as diastolic and systolic BP were included in the discriminant analysis.

IL-6 is another variable that was selected as a clinically important one. IL-6 is currently regarded as a major cytokine participating in immune response and inflammatory reaction. High level of IL-6 correlates with more severe CHF

and high mortality [6–9]. Pro-inflammatory effects of IL-6 are realized via trans-signaling pathway which is inhibited by plasma sgp130. It was reported that increase and decrease in sgp130 are related to the severity of inflammation [10–12]. This parameter was also included in the development of the decision rule.

The following linear discriminant functions (LDF) were obtained:

$$Z_1 = 0,907 * X_1 + 27,645 * X_2 + 33,546 * X_3 - 0,001 * X_4 + 0,102 * X_5 + 0,285 * X_6 + 0,464 * X_7 + 0,002 * X_8 - 115,749 \tag{1.1}$$

Для группы больных, относящихся ко II ФК ХСН ЛДФ:

$$Z_2 = 0,828 * X_1 + 28,609 * X_2 + 33,643 * X_3 - 0,001 * X_4 + 0,088 * X_5 + 0,245 * X_6 + 0,558 * X_7 - 0,011 * X_8 - 109,853 \tag{1.2}$$

for patients with FC II CHF, where  $X_1$  – age;  $X_2$  – CHF etiology;  $X_3$  – IHD;  $X_4$  – NT-proBNP;  $X_5$  – sgp130;  $X_6$  – systolic BP;  $X_7$  – diastolic BP;  $X_8$  – IL-6.  $Z_1$  is the first discriminant function and  $Z_2$  is the second discriminant function.

The quality of the discriminant function was assessed with the help of the learning sample and cross-validation (Tables 2, 3). The first method is based on inclusion of each patient from the learning sample in the decision rule. Percentages of correct and incorrect classifications were calculated. Cross-validation implies that each patient is alternately excluded from the sample. An excluded patient was classified with the help of the obtained decision rule and returned to the learning sample.

Table 2

Coefficients of linear discriminant functions (LDF) for patients with CHF of FC II and III			
Variable		FC	
Used in LDF	Explanation	II	III
$X_1$	Age	0.828	0.907
$X_2$	Etiology of CHF	28.609	27.645
$X_3$	IHD	33.643	33.546
$X_4$	NT-proBNP	0.001	0.001
$X_5$	sgp130	0.088	0.102
$X_6$	BP systolic	0.245	0.285
$X_7$	BP diastolic	0.558	0.464

Table 2 (continued)

Variable		FC	
Used in LDF	Explanation	II	III
$X_8$	IL-6	0.011	0.002
C	Constant	-109.853	-115.749

Note. LDF – linear discriminant functions; CHF – chronic heart failure; IHD – ischemic heart disease; NT-proBNP – N-terminal pro-brain natriuretic peptide; BP – blood pressure; IL-6 – interleukin 6.

Table 3

Classification results for the learning sample method				
Parameter	FC	Predicted Group Membership		Total
		II	III	
Count	II	15	5	20
	III	9	32	41
Count, %	II	75.0	25.0	100
	III	22.0	78.0	100

Note. 77% of original grouped cases were classified correctly; FC – functional class.

Table 4

Cross-validated classification results				
Parameter	FC	Predicted Group Membership		Total
		II	III	
Count	II	14	6	20
	III	11	30	41
Count, %	II	70.0	30.0	100
	III	26.8	73.2	100

Note. 72.1% of cross-validated grouped cases were classified correctly; FC – functional class.

The decision rule was based on the following principle: predictor variables of a patient were inserted into functions  $Z_1$  and  $Z_2$  (1.1 and 1.2). The calculated  $Z_1$  and  $Z_2$  values were compared and if  $Z_1 \geq Z_2$ , the patient was assigned to FC III, if  $Z_1 < Z_2$ , the patient was assigned to FC II.

It should be noted that sensitivity and specificity were used to evaluate reliability of the diagnostic test.

Since this study had no objective of classifying patients as sick or healthy, patients with CHF FC III were regarded as sick and those with FC II as healthy. Thus, when using the learning sample, sensitivity of the given model was  $Se = (32/(32+9))*100\% = 78\%$  and speci-

ficity  $Sp = (15/(15+5))*100\% = 75\%$ . When employing cross-validation, sensitivity was  $Se = (30/(30+11))*100\% = 73.2\%$  and specificity was  $Sp = (14/(14+6))*100\% = 70\%$ .

The ROC-curve reflecting the correlation between correct and incorrect assignments (Fig.1) was constructed to evaluate the quality of the model [13]. A new variable  $Z = Z_1 - Z_2$  was created for this purpose.

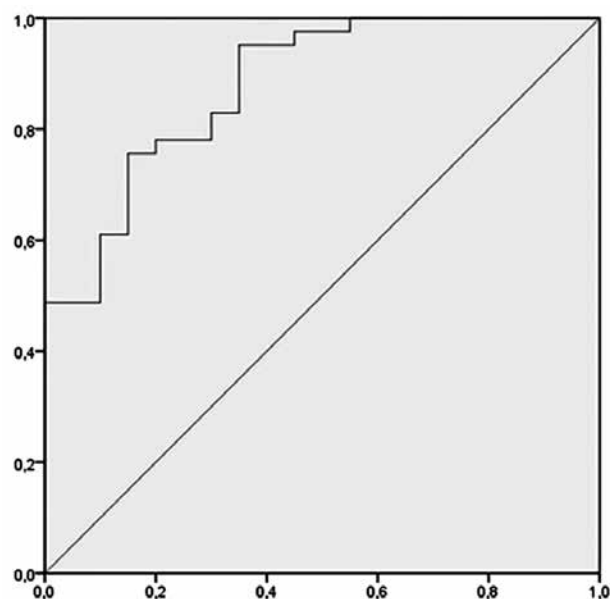


Fig. 1. ROC-curve to evaluate the quality of the developed model for assigning CHF patients to II or III FC

An ideal model is a model with 100% sensitivity and specificity. Since this is difficult to achieve in reality, a cut-off value is used, i.e., the most adequate point to cut off one diagnosed group from the other.

The maximum sensitivity and specificity were chosen to determine the cut-off point. Cut-off = 0.07438 corresponds to sensitivity 0.756 (75.6%) and specificity 0.85 (85%). Thus, if  $Z \geq 0.07438$ , the patient should be assigned to FC III,  $Z < 0.07438$ , the patient is assigned FC II.

In addition, the quality of a model can be evaluated by the square under a ROC-curve (AUC): the greater the square, the higher the model quality. In this study,  $AUC = 0.879 \pm 0.045$ , which indicates excellent quality (0.8–0.9) of the model [13].

## CONCLUSION

A comparison of CHF patients of FC II and III was performed so as to develop the decision rule for the assignment of patients to the appropriate FC. The following statistically significant variables were revealed: age, NT-proBNP, sgp130, CHF etiology and IHD. In addition to these parameters, clinically important parameters (systolic and diastolic BP, IL-6) were included in the decision rule. The obtained results allowed for the development of the decision rule for assigning CHF patients to FC II or III. Evaluation of the model by the square under the ROC-curve demonstrated excellent quality (0.8–0.9) of the model. Additional parameters reflecting severity of the inflammatory process (IL-6 and agp130) were used along with conventional clinical parameters.

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## Authors contribution

Samoilova E.V. – conception and design, analysis and interpretation of data, critical revision for important intellectual content. Fatova M.A. – analysis and interpretation of data, statistical data processing, graphical representation of data. Mindzaev D.R. – selection and examination of patients, database creation, statistical data processing. Zhitareva I.V. – conception and design, critical revision for important intellectual content. Nasonova S.N. – selection and examination of patients, treatment of patients. Zhirov I.V. – substantiation of the manuscript, critical revision for important intellectual content. Tereschenko S.N. – substantiation of the manuscript, critical revision for important intellectual content. Korotaeva A.A. – substantiation of the manuscript, critical revision for important intellectual content.

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