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Model of Two-Years Forecasting of the Anti-Existent Patients with Acute Decompensation of Heart Failure on the Background of the Intermediate Fraction of Left Ventricle

Objective	Build a prognostic model using clinical, laboratory, and instrumental data to predict mortality in patients with midrange left ventricular ejection fraction (mrLVEF) within two years after hospitalization for acute decompensated heart failure (ADHF).
Materials and Methods	The study included 121 patients hospitalized for ADHF with mrLVEF ranging from 40% to 49.9% (91 males and 30 females, mean age 64.6±14.8 years). The independent sample used to validate the statistical model included 71 patients with ADHF and mrLVEF with a mean age of 65.59±12.12 years. Sex distribution of the independent sample was 51 males (70.8% of the independent sample), 20 females (27.8% of the total independent sample). In-hospital mortality of patients included in the study was 4.2%, and long-term mortality was 36.8%. We developed a tool to assess the risk of two-year mortality using classification trees.
Results	The root node is the red blood cell distribution width–coefficient of variation (RDW-CV); its diagnostic value in this model was 13.3%. The second-level nodes are glomerular filtration rate (GFR), with a cutoff level of 35 mL/min/1.73 m2, and chronic kidney disease (CKD). The third-level nodes are sex, the anterior-posterior dimension of the left atrium, with the cutoff level >47 mm, and low red blood cell count <4.22x1012/L. The estimated sensitivity of the model is 71.4%; estimated specificity is 85.7%.
Conclusion	This model can be used to assess long-term mortality risk and identify groups of patients with mrLVEF who require closer monitoring.

Keywords	Midrange left ventricular ejection fraction; prognostic model; classification tree; acute decompensated heart failure
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The concept of heart failure with midrange ejection fraction (HFmrEF) of the left ventricle was introduced into Russian clinical practice following the National Congress of Heart Failure in December 2016 [1, 2]. It comprises a left ventricular ejection fraction (LVEF) ranging from 40% to 49.9% [3]. Several studies have shown that patients with HFmrEF may not always have signs and symptoms typical of reduced or preserved left ventricular ejection fraction, and in some cases, symptoms are somewhere in between [4]. A distinctive feature of this category of patients is a clinical picture similar to that of patients with preserved LVEF, combined with a prognosis similar to that of patients with reduced LVEF [5].

Our objective was to build a prognostic model using clinical, laboratory, and instrumental data to predict mortality in patients with HFmrEF within two years of initial hospitalization for acute decompensated heart failure (ADHF).

Materials and Methods

The study included 121 patients with LVEF ranging from 40% to 49.9%. Sex distribution of the study sample was 91 males and 30 females. The mean age of patients was 64.6±14.8 years. The independent sample used to validate the statistical model comprised 71 patients with HFmrEF, with a mean age of 65.59±12.12 years. The sex distribution of the independent sample was 51 males (70.8%) and 20 females (27.8%). In-hospital mortality was 4.2%, while long-term (two-year) mortality was 36.8%. All patients were treated under the ADHF treatment protocol, comprising angiotensin-converting enzyme inhibitors, metoprolol succinate/bisoprolol, mineralocorticoid-recep-

tor antagonists, and loop diuretics. The etiological factors of HFmrEF were coronary artery disease (CAD) in 100% of patients; 46.5% had myocardial infarction and 5.6% had a history of myocarditis. Among the comorbidities, hypertension was the most frequent pathology (92.1%,) followed by chronic kidney disease (CKD) (57.1%), diabetes mellitus (DM) (42.3%), and chronic obstructive pulmonary disease (COPD) (28.6%).

Diagnosis of ADHF was based on the typical clinical picture (at least two of the following signs: shortness of breath in New York Heart Association (NYHA) functional class (FC) III–IV, clinical or radiographic pulmonary congestion, peripheral edema, increased jugular pressure, liver enlargement, ascites). We developed a tool to assess the risk of two-year mortality with mathematical modeling approach using classification trees. We created a prognostic model of two-year mortality in patients after the first-time hospitalization using hazard ratio (HR), the chi-squared test, the standardized Pearson correlation coefficient, and the Cramer-von Mises test. We also used a multivariate analysis method with decision trees.

Results

All admitted patients had high FC CHF according to the assessment of reported history of walking distance or a number of flights of stairs climbed.

The theoretical analysis included the comprehensive assessment of death risk factors for two years from first hospitalization. Parameters not meeting the criteria of reliability and validity were eliminated. The final model was based on the parameters shown in Table 1.

Interestingly, GFR was highly correlated (0.965) on the Chaddock scale, as was the anterior-posterior dimension of the left atrium (LA) (0.894) and red blood cell count (RBC) (0.858); the red blood cell distribution width – coefficient of variation (RDW-CV) (0.562) and sex (0.618) showed medium correlation, and history of CKD (0.460) had moderate correlation. Results were evaluated by the Cramer-von Mises test, with similar results (shown in Table 1). Present CKD had moderate correlation (0.344). In the chi-squared test, all parameters of the statistical model were significant: CKD $p<0.05$, LA dimension $p<0.05$, and all other parameters $p<0.01$. Analysis of hazard ratios showed that glomeruler filtration rate (GFR) 40–60 mL/min/1.73 m^2 increased the mortality risk 14.5-fold, with a confidence interval (CI) of 5.6–37.3, and the history of CKD doubled the mortality risk [1.2–3.4]. The integrated prognostic model for mortality is shown in Figure 1.

As Figure 1 shows, the root node is the red blood cell distribution width-variation coefficient (RDW-CV); its diagnostic value in this model was 13.3%. Second-level nodes are GFR with a cutoff level of 40 mL/min/1.73 m^2 and a history of CKD. Third-level nodes are sex, the anterior-posterior dimension of LA (cutoff level >47 mm), and RBC count (cutoff level 4.22 x 1012/L).

As seen in this model, male patients with RDW-CV <13.3% and GFR >30 mL/min/1.73 m^2 are at lower risk of death than female patients with the same parameters (HR for RDW-CV in the subgroups of deceased and surviving patients is 2.32 [1.7; 3.2], and HR for GFR is 14.5 [5.6; 37.3]).

At the same time, the mortality risk increased manyfold to reach 100% in patients with GFR <30 mL/min/1.73 m^2 and the same level of RDW-CV. When patients with a history of CKD (HR 2 [1.2; 3.4]) had RDW-CV >13.3%, mortality risk depended on the anterior-posterior dimension of LA (HR not applicable). The larger dimensions were associated with a mortality risk of 84.2%; at the same time, the mortality risk was not high in patients with LA <47 mm. The RBC cutoff level of 4.22x1012/L is a significant factor in patients with RDW-CV >13.3% and without a history of CKD. The mortality risk in patients with RBC count <4.22x1012/L was 87.5%, and decreased to 11.1% in patients whose RBC exceeded this value.

Table 1. Validation of model parameters and correlation with long-term mortality (24 months)

Parameter	HR	CI	Chi-squared test	Cramer-von Mises test	Standardized Pearson's coefficient
RDW-CV	2.32	[1.7; 3.2]	24.4**	0.433	0.562
GFR	14.5	[5.6; 37.3]	101.0**	0.933	0.965
CKD	2	[1.2; 3.4]	7.6*	0.344	0.460
Sex	N/A	N/A	36.1**	0.486	0.618
LA	N/A	N/A	13.3*	0.816	0.894
RBC	9	[2; 34]	24.4**	0.763	0.858

* $p<0.05$; ** $p<0.01$. HR, hazard ratio; CI, confidence interval; RDW-CV, red blood cell distribution width-variation coefficient; GFR, glomerular filtration rate; CKD, chronic kidney disease; LA, anterior-posterior dimension of the left atrium; N/A, not applicable.

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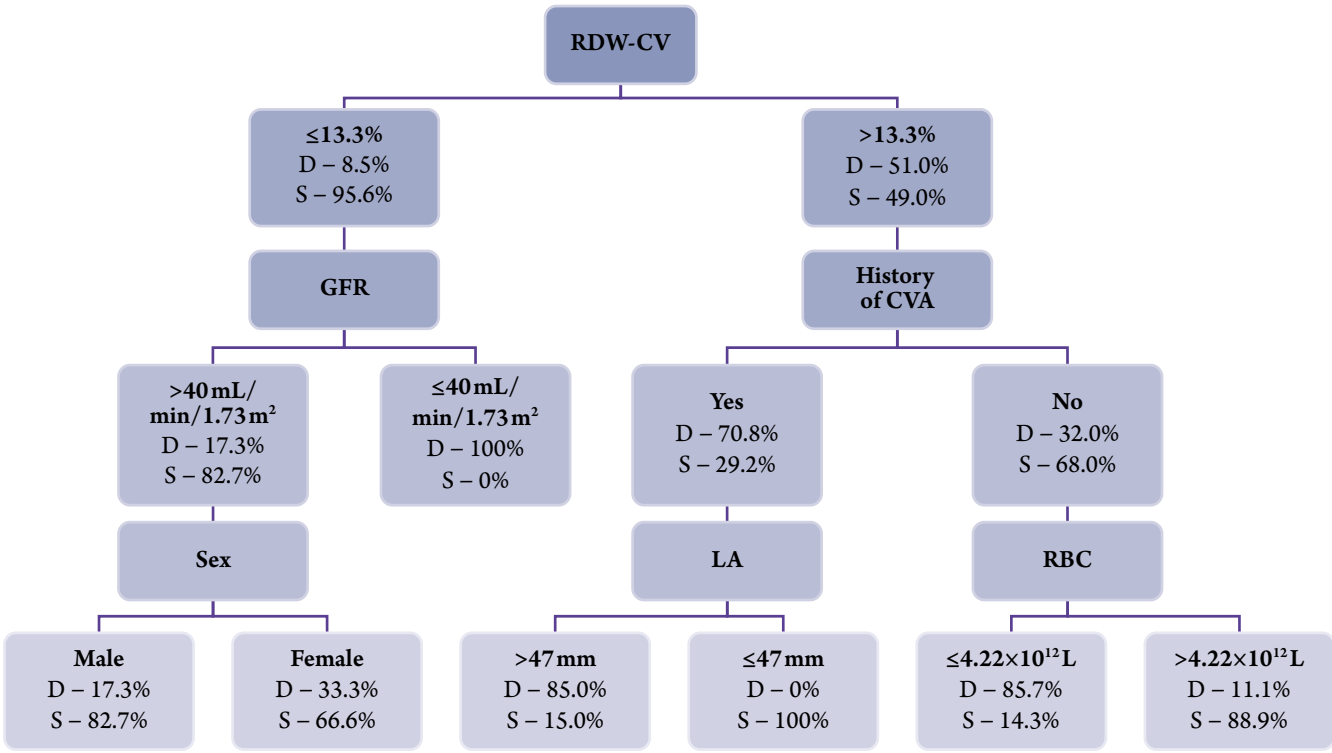
Figure 1. Integrated prognostic model for estimating two-year mortality in patients with acute decompensated heart failure with midrange left ventricular ejection fraction



D – deceased patients; S – surviving patients; GFR – glomeruler filtration rate; CVA – cerebrovascular accident; LA – anterior-posterior dimension of the left atrium; RBC – red blood cell count.

Example 1. Male patients with ADHF and midrange LVEF (mrLVEF), GFR 85 mL/min/1.73 m², RDW-CV 16.4%, no history of CKD, anterior-posterior dimension of LA 44 mm, and RBC count 4,62x1012/L. According to the model, RDW-CV is diagnostically significant: in this case, its value exceeds the cutoff level of 13.3% (right side of the model). Since the patient has no history of CKD, the next relevant factor is RBC count, which also exceeds the diagnostic cutoff value of 4.22x1012/L. Thus, stimated mortality risk according to the classification tree is 11.1%.

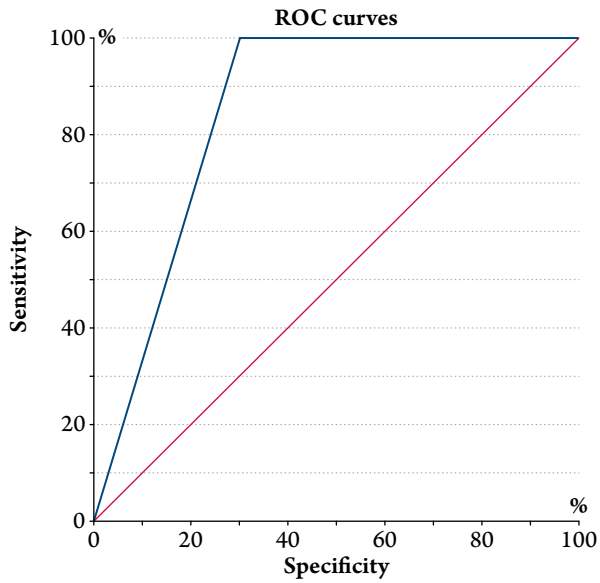
Example 2. Female patients with ADHF and mrLVEF, GFR 51 mL/min/1.73 m², RDW-CV 12.1%, no history of CKD, anterior-posterior dimension of LA 45 mm, and RBC count 4.53x1012/L.

According to the model, RDW-CV is diagnostically significant: in this case, its value is less than 13.3% (left side of the model). Since this patient has a history of GFR >35 mL/min/1.73 m², the next relevant factor is sex. The estimated risk of mortality according to the classification tree is 33.3%.

This multifactorial model was verified using ROC analysis (Figure 2).

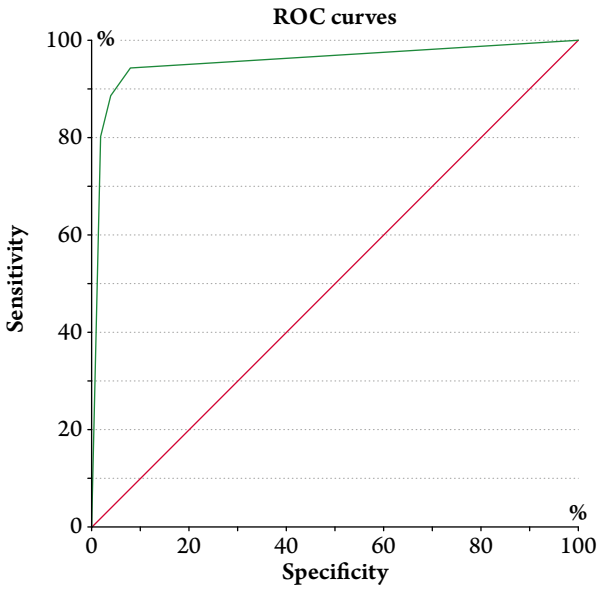
The model has been tested in the independent sample of patients with ADHF and mrLVEF with the following results: true-positive – 37; true-negative – 45, false-positive – 5, and false-negative – 4 patients. This test was also performed using ROC analysis (Figure 3).

Figure 2. ROC curve used to validate the prognostic model



The estimated sensitivity of the model is 71.4%, specificity – 85.7%. The area under the curve is 0.849, which corresponds to "very good" on the expert scale for AUC values.

Figure 3. ROC curve used to validate the prognostic model in the independent sample



The estimated sensitivity of the model is 88.1%, with an estimated specificity of 91.8%. The area under the curve is 0.965, which corresponds to "very good" on the expert scale for AUC values.
The validity of the model is 89.2%.

Discussion

The prognosis of adverse outcomes, mortality in particular, in patients with CHF and mrLVEF must acknowledge that additional risk factors include conditions resulting from structural and functional changes to other other than the heart [4–9].

There is very little information in the literature on using mathematical modeling for prognosis in patients with CHF and midrange LVEF. The available data show that LVEF and CHF FC have a low prognostic value [8–13]. In the Seattle Heart Failure Model, among the most significant in the univariate analysis are the following parameters: age, male sex, present CAD, low body mass index, LVEF, blood pressure, blood sodium levels, cholesterol, hemoglobin, and CHF of NYHA FC III–IV, leukocytosis, high blood levels of creatinine and uric acid, administration of allopurinol and co-administration of thiazide and loop diuretics; all increased the risk of mortality [14]. A comparison of the effectiveness of the Seattle model versus SurVivAl (NEVA-75) in the Russian population found that the Seattle model overestimates the survival rate by 4% to 19% [15].

Our model, based on analysis of the Russian population, shows the prognostic algorithm for mortality within two years after initial hospitalization.

Conclusion

1. Based on analysis of the Russian population, this mathematical model allows determination of mortality risk in patients with CHF and mrLVEF within two years after first hospitalization.
2. The most significant factors for high mortality risk are red blood cell distribution width-variation coefficient, glomerular filtration rate, chronic kidney disease, anterior-posterior dimension of the left atrium, and red blood cell count.

No conflict of interest is reported.

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