https://doi.org/10.35336/VA-2023-2-05

CLINICAL CHARACTERISTICS AND FACTORS ASSOCIATED WITH DEATH FROM ACUTE DECOMPENSATED HEART FAILURE

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Aim. To assess the diagnostic significance of clinical indicators and left ventricle ejection fraction (LV EF) for predicting the probability of death from acute decompensated heart failure (ADHF) in patients with chronic heart failure with a reduced LV EF (HFrEF) within one year after implantation of cardioverter defibrillator (ICD).

Methods. The study included 384 patients with heart failure NYHA 3-4 functional class with LV EF ≤ 35%, undergoing ICD implantation for the purpose of primary prevention of sudden cardiac death. After ICD implantation the patients included in the study were prospectively observed during one year (visits to the clinic after 3, 6, 12 months). The primary end point - a case of ADHF was registered.

Results. In a one-year observation, the primary endpoint was recorded in 38 patients (10 per cent). Single factor logistic regression analysis showed 5 factors with the greatest predictive potential ($p<0.1$), related to the occurrence of the investigated endpoint. These included: history of arterial hypertension (AH) and obesity, LV EF based on the biplane Simpson's method, LV EF ≤ 28% and systolic blood pressure. Based on the results of the multi-factor regression analysis, a predictive model was developed, which included three factors with the highest levels of statistical significance: the presence of AH, obesity and LV EF ≤ 28%. The diagnostic efficiency of the model was 69.5% (sensitivity 78.9%; specificity 68.5%).

Conclusion. The results of the research indicate that the main predictor of one-year mortality due to ADHF in the studied cohort of HFrEF patients with NYHA class 3-4 is LV EF ≤ 28%. The presence in the history of AH and obesity was associated with the best prognosis for life.

Key words: chronic heart failure; acute decompensated heart failure; clinical predictors; implantable cardioverter-defibrillator; left ventricle ejection fraction; sudden cardiac death

Conflict of Interests: none.
Funding: none.
Received: 03.08.2022 **Revision Received:** 22.01.2023 **Accepted:** 14.02.2023
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For citation: Ilov NN, Boytsov SA, Palnikova OV, Terentyeva MG, Nechepurenko AA. Clinical characteristics and factors associated with death from acute decompensated heart failure. *Journal of Arrhythmology.* 2023;30(2): 35-43. https://doi.org/10.35336/VA-2023-2-05.

Chronic heart failure (CHF) is a cardiovascular disease outcome associated with high morbidity and mortality [1]. The causes of death in patients with CHF are acute decompensation of heart failure (ADHF) and emerging life-threatening ventricular tachyarrhythmias which lead to sudden cardiac death (SCD) in the absence of emergency care [2].

Implantable cardioverter defibrillators (ICDs) are a first-line treatment for the SCD prevention in CHF patients with reduced left ventricular ejection fraction (HFrEF) [3]. The available data indicate imperfect criteria used for selection of patients for this type of treatment [4]. According to the current recommendations, an absolute contraindication for ICD implantation for the primary prevention of SCD is life expectancy less than one year [3, 5]. Terminal CHF is often manifested by prolonged state of myocardial electrical instability as one of the variants of cardiovascular death. In this situation, ICD shocks prove to be ineffective and can cause serious physical and psychological disorders, which requires consideration of its deactivation in case of a previously implanted device [6]. For this reason, the high risk of death due to ADHF reduces the potential effect of implantation of an expensive device.

Existing data suggest using ischemic origin of CHF, manifestation of malnutrition, changes in blood biomarker concentrations as clinical predictors of ADHF. The absence of verified risk factors, indicating a poor short-term prognosis for life, makes such a choice a task lying outside the regulatory documents, with the solution left to the intuition and clinical experience of the treating physician.

Aim: to evaluate the diagnostic significance of clinical parameters and value of the left ventricular ejection fraction (LVEF) in predicting the probability of death due to ADHF in HFrEF patients one year after ICD implantation.

METHODS

Selection of patients

This study was performed in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by the local ethical committee of the Federal State Budgetary Educational Institution of Higher Professional Education, Astrakhan State Medical University, Ministry of Health Care of Russia (Protocol № 3 of the LEC meeting dated 30.12.2021), submitted to the public register clinicaltrials.gov (NCT05539898).

The patients were recruited during the period from 2013 to 2021. The study included patients with CHF functional class NYHA 3-4 and LV EF ≤ 35% despite optimal medical therapy within at least three months, who were planned to undergo ICD implantation for the primary SCD prevention. The majority of patients with CHF functional class 4, in the absence of indications for cardiac resynchronization therapy, were on the waiting list for heart transplantation.

Patients with hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia and verified hereditary channelopathies were excluded from the study. The exclusion criterion was also the presence of indications for cardiac surgery (revascularization, heart valve surgery).

After inclusion/exclusion screening, 384 patients were included in the study (Fig. 1). After ICD implantation the patients included in the study were prospectively followed up for one year by the cardiologists of the center where the implantation was performed (visits to the clinic after 3, 6, 12 months). In case of cardiac decompensation the patient had unscheduled contact with the study physician, therapy correction and clinical status assessment were performed together with cardiologists at the place of residence. Information about the occurrence of the endpoint was obtained from medical records and by interviewing the relatives.

Endpoints of the study

The primary endpoint was death due to ADHF. In addition, the time from study enrollment to the occurrence of the primary endpoint was analyzed.

Statistical analysis

Materials of research were subjected to statistical processing using methods of parametric and nonparametric analysis. Accumulation, correction, systematization of the initial information and visualization of the results were carried out in spreadsheets Microsoft Office Excel 2010. Statistical analysis was performed using IBM SPSS Statistics 23. Quantitative indicators were described and compared taking into account the distribution, which was assessed for normality using the Kolmogorov-Smirnov criterion. If a normal distribution was confirmed, the data were described using the arithmetic mean (M) and standard deviation (SD), and compared using Student's t-test. If the distribution was not normal, median (Me), lower and upper quartiles (Q1-Q3) values were indicated, and measures were compared by Mann-Whitney test. Comparisons of measures measured on a nominal scale were made using Pearson's χ criterion2 . We used the odds ratio (OR) as a quantitative measure of effect when comparing relative measures. A factor was considered to be significant if the confidence interval was outside the no-effect boundary, taken as 1. Relationships between variables were analyzed using Spearman correlation analysis. The critical level of significance for testing statistical hypotheses was taken to be 0.05.

Construction of a multifactorial prognostic model to determine the probability of cardiovascular death in the studied patients on the basis of the studied parameters was performed using binary logistic regression method. The selection of independent variables was performed by stepwise inverse selection using Waldowski statistics as the exclusion criterion. Statistical significance of the resulting model was determined using the χ^2 criterion. The measure of certainty, indicating the part of variance that

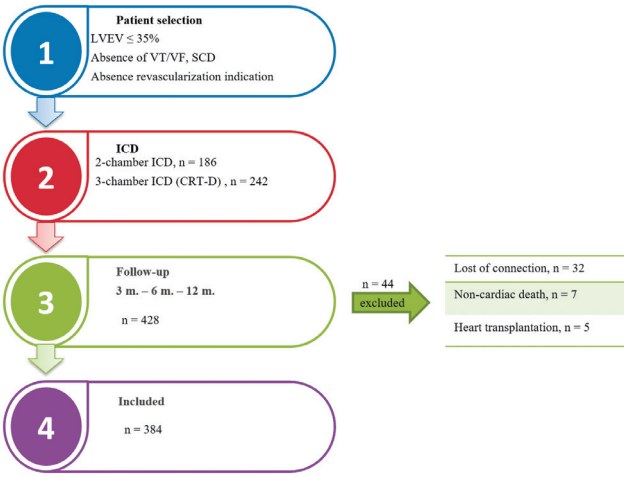
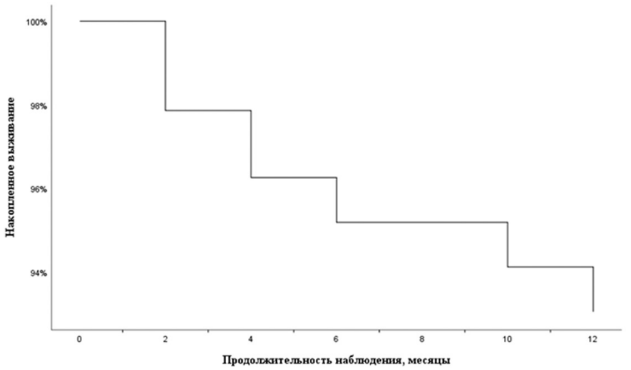


Figure 1. Flow chart reflecting the study design. Note: LVEF - left ventricular ejection fraction; VT - ventricular tachycardia; VF - ventricular fibrillation; SCD - sudden cardiac death; ICD - implantable cardioverter-defibrillator; CRT-D - implantable cardioverter-defibrillator with cardiac resynchronization therapy.



	0 мес.	2 мес.	4 мес.	6 мес.	8 мес.	10 мес.	12 мес.
Число пациентов, подвергшихся риску, n (%)	384 (100)	376 (98)	370 (96)	366 (95)	366 (95)	362 (94)	358 (93)
Число терминальных случаев, n (%)	8 (2)	6 (2)	4 (1)	0	4 (1)	4 (1)	12 (3)
Число выживших, n (%)	378 (98)	370 (96)	366 (95)	366 (95)	362 (94)	358 (93)	346 (90)

Figure 2. Kaplan-Meier curve and survival table (primary endpoint registration).

Table 1.

Clinical and demographic characteristics of the patients included in the study

Clinical Indicator	Total (n=384)	Survivors (n=346)	Deceased (n=38)	P[&]
Age, years	56 (51-62)	56 (51-62)	55 (50-58)	0.262
Male gender, n (%)	324 (84)	290 (84)	34 (89)	0.741
Body mass index, kg/m^2	28.7 (25.6-32.5)	28.8 (25.7-32.7)	28.4 (23.8-29.9)	0.224
Coronary heart disease, n (%)	180 (47)	162 (47)	18 (47)	0.963
Postinfarction cardiosclerosis, n (%)	134 (35)	120 (35)	14 (37)	0.852
Nonischemic cardiomyopathy, n (%)	204 (53)	184 (53)	20 (53)	0.912
CHF NYHA class III, n (%)	343 (89)	311 (90)	32 (84)	0.28
CHF NYHA class IV, n (%)	41 (11)	35 (10)	6 (16)	0.17
History of arterial hypertension, n (%)	216 (56)	204 (59)	12 (32)	0.028
Diabetes mellitus, n (%)	72 (19)	62 (18)	10 (26)	0.361
Obesity at the time of study inclusion, n (%)	148 (39)	138 (40)	10 (26)	0.161
History of obesity*, n (%)	146 (38)	140 (40)	6 (16)	0.045
Brain stroke, n (%)	28 (7)	22 (6)	6 (16)	0.154
Chronic kidney disease, n (%)	192 (50)	174 (50)	18 (47)	0.631
Anemia, n (%)	26 (7)	26 (8)	0	0.372
Paroxysmal / persistent AF, n (%)	102 (27)	94 (27)	8 (21)	0.791
Persistent FP, n (%)	24 (6)	18 (5)	6 (16)	0.984
Unstable ventricular tachyarrhythmias, n (%)	24 (6)	18 (5)	6 (16)	0.102
Systolic blood pressure, mm Hg.	120 (110-130)	120 (110-130)	110 (100-130)	0.061
Diastolic blood pressure, mm Hg.	80 (70-80)	80 (70-80)	70 (60-88)	0.441
Heart rate, bpm.	78 (68-90)	78 (69-90)	80 (67-90)	0.933
Left ventricular ejection fraction Simpson, %	29 (25-34)	30 (27-34)	23 (19-26)	0.0001
Surgical interventions on the heart:				
Revascularization, n (%)[#]	156 (41)	142 (41)	14 (37)	0.812
Heart valve surgery, n (%)	76 (20)	66 (19)	10 (26)	0.541
LV plasty, n (%)	34 (9)	28 (8)	6 (16)	0.392
Medication therapy received				
ß-adrenoblockers, n (%)	133 (100)	346 (100)	38 (100)	0.993
ACE inhibitor/ARA II, n (%)	90 (68)	230 (69)	25 (67)	0.851
ARNI, n (%)	43 (32)	107 (31)	13 (33)	0.831
Mineralocorticoid antagonists, n (%)	119 (89)	304 (88)	34 (90)	0.154
Loop diuretics, n (%)	129 (97)	332 (96)	37 (98)	0.912
SGLT-2, n (%)	30 (8)	27 (8)	3 (8)	0.381
Sotalol**, n (%)	21 (16)	42 (12)	8 (20)	0.191
Amiodarone, n (%)	43 (32)	121 (35)	11 (29)	0.152
Implanted ICD				
CRT-D, n (%)	218 (57)	198 (57)	20 (53)	0.393
Two-chamber ICD, n (%)	166 (43)	148 (43)	18 (47)	0.411

Note: Data are presented as the absolute number of patients (%) or as Me (Q1-Q3), unless otherwise indicated; [&] - significance of differences between survivors and deceased; CHF - chronic heart failure; * - the variable «history of obesity» did not include patients whose obesity was first identified at the time of study inclusion; AF - atrial fibrillation; [#] - coronary bypass or percutaneous coronary intervention; ACEs - angiotensin-converting enzyme inhibitors; ARA II - angiotensin II receptor antagonists; ARNI - angiotensin receptor and neprolysin inhibitors, and SGLT-2 - sodium-glucose transport protein 2 inhibitors; ** - sotalol was administered when amiodarone was contraindicated; ICD - implantable cardioverter-defibrillator; CRT-D - cardiac resynchronization therapy device with ICD function.

can be explained by logistic regression, was R^2 coefficient of determination. To assess the predictive significance of the model and to find the threshold value of the obtained function at the cut-off point, ROC analysis with calculation of the area under the curve (AUC) was performed.

RESULTS

The revealed differences in systolic blood pressure (SBP) had significance level close to statistically significant (p=0.06). All patients included in the study had target BP values and received drug therapy according to the national guidelines for CHF treatment, including drugs with hypotensive effect. For this reason, the researchers could not assess the presence of AH at the time of inclusion in the study. The odds of dying due to cardiac decompensation in patients with a history of AH were 3.1 times lower than in study patients with no history of AH (OR=0.32; 95% CI: 0.12-0.89). The correlation between the risk of the primary endpoint and a history of AH, as assessed by the Mantel-Cox log-rank test, was statistically significant (p=0.019).

Patients with history of obesity 3.5 times were more likely to during one year of follow-up, but the odds differences were not statistically significant (OR=0.28; 95% CI: 0.08-1.008). There were no patients with body mass deficiency (BMI < 18.5 kg/m^2) among the studied patients.

In the survivor group, LV EF was significantly higher than in the deceased patients (30 (27-34)% vs. 23 (19-26)%, p=0.0001). The diagnostic significance of LVEF in predicting the probability of one-year mortality was assessed using ROC-curves. The area under the ROC curve corresponding to the relationship between the probability of one-year cardiovascular mortality and LVEF was 0.83±0.043 with 95% CI:0.75-0.92. The optimal cut-off value for this index was chosen. LVEF values ≤28% were predictive of cardiovascular death in the next year with a sensitivity of 89% and specificity of 30%. LVEF ≤28% was found to increase the risk of one-year mortality 8-fold (OR=8.4; 95% CI: 2.4-30; p=0.0001).

Single-factor logistic regression identified 5 factors with the highest prognostic potential (p<0.1) associated with the occurrence of the studied end point. These included anamnestic data on AH and obesity, LVEF value, LVEF ≤ 28%, and CAD value (Table 2). A correlation matrix was constructed to eliminate possible multicollinearity. It was found that LVEF had a high correlation relationship with another factor, LVEF ≤ 28% (r=0.7; p<0.01), and for this reason was excluded from the multivariate analysis.

Using binary logistic regression method, a prognostic model was developed to determine the probability of death due to ADHF in CHF patients based on the investigated clinical parameters.

As a result, the following equation (1) was obtained:

$p = 1/(1+e^{-z})*100\%$

$z = -2.77 - 0.77*X_{AH} - 0.97*X_{Obesity} + 1.86*X_{LVEF\leq 28\%}$ (1)

where p is the probability of occurrence of cardiovascular death, X_{AH} is the presence of a history of AH, $X_{Obesity}$ is the presence of a history of obesity, $X_{LVEF\leq 28\%}$ is the presence of LVEF ≤ 28%, e is a mathematical constant approximately equal to 2.71828.

Table 2.

Relationship between the studied factors and the primary endpoint

Factors	Single-factor analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age	0.97	0.93-1.02	0.29			
Male gender	0.61	0.13-2.81	0.53			
Body Mass Index	0.93	0.84-1.02	0.13			
Coronary heart disease	0.99	0.38-2.56	0.98			
Postinfarction cardiosclerosis	1.08	0.4-2.88	0.88			
History of arterial hypertension	0.32	0.12-0.89	0.029	0.49	0.15-1.57	0.23
Diabetes mellitus	1.64	0.55-4.91	0.37			
A history of obesity	0.28	0.08-1.008	0.051	0.44	0.11-1.74	0.24
Brain stroke	2.68	0.68-10.6	0.16			
Chronic kidney disease	0.76	0.29-1.97	0.57			
Anemia	0.001	0.001-2.1	0.99			
Paroxysmal / persistent AF	0.69	0.22-2.18	0.52			
Permanent AF	3.29	0.81-13.4	0.096			
Unstable ventricular tachyarrhythmias	3.31	0.81-13.5	0.095			
Systolic blood pressure	0.97	0.94-1.001	0.055			
Diastolic blood pressure	0.98	0.94-1.03	0.38			
Heart rate	1.0	0.97-1.04	0.99			
Left ventricular ejection fraction Simpson	0.796	0.72-0.89	0.0001			
Left ventricular ejection fraction Simpson ≤ 28%	8.04	2.26-28.66	0.0001	6.43	1.76-23.44	0.005

Note: OR - odds ratio; CI - confidence interval; AF - atrial fibrillation.

Based on the values of the regression coefficients, the variables XAH and XObesity included in the equation are inversely related, and the variable $X_{LVEF\leq 28\%}$ is directly related to the probability of the primary end point under study.

The obtained regression model is statistically significant (p=0.0001). Based on the value of coefficient of determination, model (1) takes into account 20.6% of factors determining the probability of death due to ADHF in CHF patients. The area under the ROC curve corresponding to the relationship between the prognosis of the primary end point and the value of the regression function was 0.722 ± 0.056 with 95% CI:0.612-0.831.

The threshold value of function (1) at the cut-off point was 0.111. Values equal to or greater than this value corresponded to the prognosis of death due to ADHF within the next year. The sensitivity and specificity of the method were 84.2% and 39.9%, respectively. After adjusting the classification threshold based on the results of ROC-curve analysis, the diagnostic efficiency of the prognostic model was 69.5% (sensitivity 78.9% specificity 68.5%).

As part of the sensitivity analysis, an additional regression analysis was performed, in which the variable "the history of obesity" was included instead of the variable "obesity at the time of study inclusion." Given the same classification threshold (0.111), the results were comparable both with respect to the variable itself (OR=0.63; 95% CI: 0.21-1.91; p=0.411) and with respect to the diagnostic performance of the resulting model (R2=0.189; sensitivity 78.9%; specificity 69%; p=0.0001).

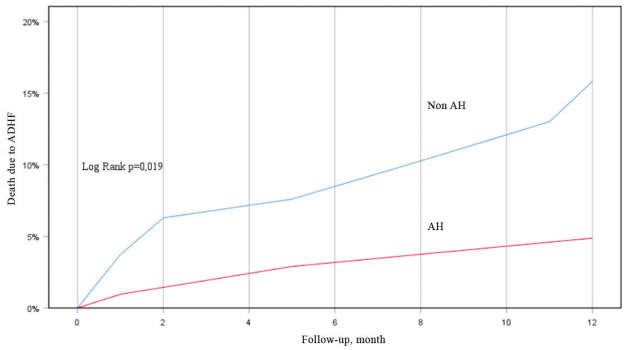


Figure 3. Kaplan-Meier curve showing the relationship between a history of AH and the cumulative risk of death due to ASDHF in the cohort of studied patients.

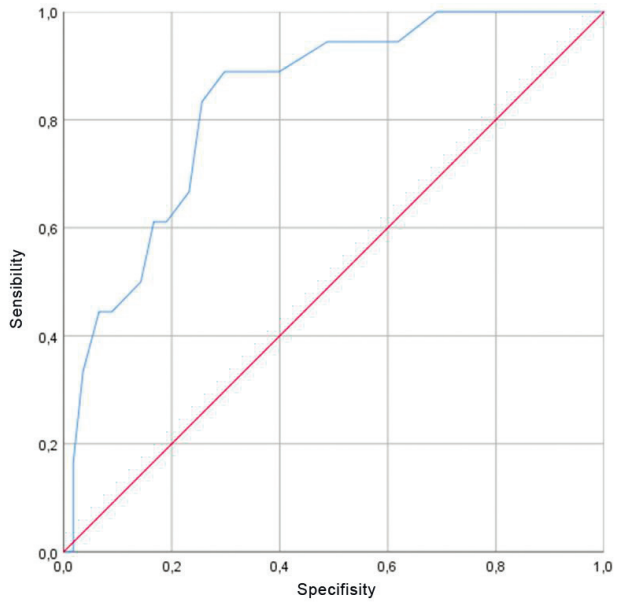


Figure 4. ROC-curve showing the relationship between the probability of one-year cardiovascular mortality and left ventricular ejection fraction.

DISCUSSION

The study was one of the first Russian clinical studies to investigate mortality due to ADHF in CHF patients prospectively followed up for one year after ICD implantation for primary SCD prevention. About 10% of the studied patients died during the first year of follow-up due to ADHF development. In case of timely prediction of such an outcome, the feasibility of ICD implantation could have been questioned. This means that other patients on the waiting list would have received life-saving ICD electrotherapy.

The considered problem, along with a possibility of deactivation of ICD electrotherapy, certainly presents a difficult question for discussion both for patients and medical workers. The received results can become a subject for discussion of experts participating in development of clinical recommendations on management of patients with HFrEF. The use in practice of the obtained model requires external validation.

The study was aimed at identifying clinical factors associated with one-year mortality due to decompensation of CHF. Similar work on design was carried out by a group of researchers from Turkey, who on a cohort consisting of 1107 patients with HFrEF demonstrated that patients who died within a year were older (p=0.002), more often had diabetes mellitus (p=0.004), chronic kidney disease (p=0.02), atrial fibrillation (p<0.001) and CHF NYHA class > 2 (p<0.001) [10]. The important result of this work correlating with our findings was the association of one-year cardiovascular mortality with decreased LVEF (p=0.007), LV end-diastolic dimension (p=0.04) and severe tricuspid regurgitation (p=0.02). It is worth noting that the predominant part of the patients in this study had indications for secondary prevention of SCD (64%), larger values of LVEF and milder course of CHF (NYHA 1 - 80%), which may explain the differences with our results.

The study developed a prognostic model, which included three factors with maximum levels of statistical significance: history of AH and obesity, and LVEF. We showed that history of AH was associated with a threefold lower risk of one-year CVD mortality (OR=0.32; 95% CI: 0.12-0.89), and patients who died during the follow-up period had lower BP values: 120 (110-130) mm Hg versus 110 (100-130) mm Hg, p=0.06. It is known that AH is a recognized risk factor linearly related to adverse cardiovascular events; it is known that the primary prevention of the occurrence and worsening of CHF is to reduce BP to the target values [11]. On the other hand, there is an opinion that low BP may indicate the progression of LV contractile dysfunction and act as a predictor of ADHF [12]. However, it is probably important to distinguish between low BP associated with patient's severe state and BP decrease against the background of the ongoing therapy. It is also important that low BP is a factor significantly limiting

the prescription and use of all major classes of drugs for the treatment of HFrEF.

The ambiguity of clinical interpretation of BP in different categories of CHF patients was vividly illustrated by S.Ather et al. [13]. Having compared mortality in the groups of patients with moderate (3263 patients) and severe systolic dysfunction (2906 patients), the authors found that at 30% ≤ LV EF < 50% the dependence between SBP and cardiovascular mortality has U-shaped form with minimal mortality at SBP=130-140 mm Hg. An interesting finding was the revealed linear correlation between SBP and cardiovascular mortality in LV EF <30% group: at SBP >140 mm Hg, the probability of mortality was minimal, and at SBP <120 mm Hg - increased [13]. The large Russian epidemiological study EPOHA-D-CHF showed similar regularity with regard to hospital prognosis for patients with ADHF: when SBP decreased less than 120 mm Hg, the risk of hospital mortality increased, while increasing of SBP for each 10 mm Hg was associated with 13-16% reduction of the risk of death [14].

The close association between the SPB level and cardiovascular morbidity and mortality is probably explained by cardiac physiology. The systolic blood pressure is determined by cardiac output and systemic vascular resistance. In preserved LV contractility, peripheral vasoconstriction is the leading determinant of elevated SBP. In CHF patients, low SBP indicates decreased cardiac output; for this reason, elevated SBP is associated with decreased mortality due to ADHF [15].

Apparently, our results should be interpreted from the same perspective, according to which the risk of one-year mortality increased 8-fold (95% CI: 2.3-28.7; p=0.0001) for LV EF ≤ 28%. This fact can emphasize the importance of LV EF value when selecting candidates for ICD implantation, to make not only a positive decision, but also to determine the cohort of patients for whom such a decision may be inappropriate.

The relationship identified in this study between a history of obesity and the likelihood of death due to ADHF may fit within the "obesity paradox" described in the literature [16]. In a meta-analysis of clinical trials including 28209 patients with CHF, A.Oreopoulos et al. showed that compared to patients with normal body mass index, CHF patients with excess body weight or obesity had lower rates of cardiovascular and total mortality at follow-up for an average of 2.7 years [17]. Such cardioprotective effects are attributed to the endocrine activity of adipose tissue, manifested by inhibition of systemic inflammation and slowing of atherosclerosis, changes in the concentration of adiponectin and other biologically active agents [18]. There is also an opposite position, according to which the "obesity paradox" described in a number of cardiovascular diseases is a consequence of methodological errors made during the planning and conduct of studies [19]. It is worth emphasizing that we were not able to find differences between the study groups in body mass index, including its value ≥30 kg/m^2.

The opposite effect of previously validated risk factors on clinical endpoints is often seen as a manifestation of reverse epidemiology [20]. The results of this study should be viewed both from this perspective and take into account the potential presence of confounders, which form false correlations.

Limitations of the study

The limitations of the study include the single-center nature and lack of analysis of the effect of cardiac resynchronization therapy on the endpoint registration, impossibility of using physical and biophysical methods of obesity diagnosis. A possible limitation of the study is the lack of analysis of other available clinical markers of adverse prognosis (respiratory rate, SBP in orthostasis, etc.). The results obtained should be evaluated from the position of possible inclusion of colliders and confounding factors in the models, which may explain the presence of a "false paradox". The developed model has not undergone external validation, which limits its application in practice.

CONCLUSION

The results of the study demonstrated that the main predictor of one-year mortality due to ADHF in the studied cohort of CHF patients is LV FV ≤ 28%. A history of AH and obesity were associated with a better prognosis for life. These data along with other recognized factors can help to develop decision-making algorithms regarding interventional treatment, including ICD implantation in patients with CHF NYHA class III-IV.

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