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Analysis of mortality in patients with heart failure after decompensation during long-term follow-up in specialized medical care and in real clinical practice

Background — Mortality from chronic heart failure (CHF) remains high and entails serious demographic losses worldwide. The most vulnerable group is patients after acute decompensated HF (ADHF) who have a high risk of unfavorable outcome.

Aim — To analyze risks of all-cause death (ACD), cardiovascular death (CVD), and death from recurrent ADHF in CHF patients during two years following ADHF in long-term follow-up with specialized medical care and in real-life clinical practice.

Materials and methods — The study successively included 942 CHF patients after ADHF. 510 patients continued out-patient treatment in a specialized CHF treatment center (CHFTC) (group 1) and 432 patients refused of the management in the CHFTC and were managed in out-patient clinics at the place of patient's residence (group 2). Causes of death were determined based on inpatient hospital records, postmortem reports, or outpatient medical records. Cases of ACD, CVD, death from ADHF, and a composite index (CVD and death from ADHF) were analyzed. Statistical analysis was performed with the software package Statistica 7.0 for Windows, SPSS, and statistical package R.

Results — Patients of group 2 were older, more frequently had functional class (FC) III CHF and less frequently FC I CHF compared to group 1. Women and patients with preserved left ventricular ejection fraction (LV EF) prevailed in both groups. Results of the Cox proportional hazards model for ACD, CVD, death from ADHF, and the composite mortality index showed that belonging to group 2 was an independent predictor for increased risk of death ($p<0.001$). An increase in CCS score by 1 also increased the risk of death ($p<0.001$). Baseline CHF FC and LV EF did not influence the mortality in any model. Female gender and a higher value of 6-min walk test (6MW) independently decreased the risk of all outcomes except for CVD. An increase in systolic BP by 10 mm Hg reduced risk of all fatal outcomes. At two years of follow-up in groups 2 and 1, ACD was 29.9% and 10.2%, (OR, 3.7; 95% CI: 2.6–5.3; $p <0.001$), CVD was 10.4% and 1.9% (OR, 5.9; 95% CI: 2.8–12.4; $p<0.001$), death from ADHF was 18.1% and 6.0% (OR, 3.5; 95% CI: 2.2–5.5; $p<0.001$), and the composite mortality index was 25.2% and 7.7% (OR, 4.1; 95% CI: 2.7–6.1; $p<0.001$). Analysis of all outcomes by follow-up period (3 and 6 months and 1 and 2 years) showed that the difference between groups 2 and 1 in risks of any fatal outcome was maximal during the first 6 months.

Conclusion — The follow-up in the system of specialized medical care reduces risks of ACD, CVD, and death from ADHF. The first 6 months following discharge from the hospital was a vulnerability period for patients after ADHF. The CCS score impaired the prognosis whereas baseline LV EF and CHF FC did not influence the long-term prognosis after ADHF. Protective factors included female gender and higher values of 6MW and systolic BP.

Keywords — Center for Treatment of Chronic Heart Failure; specialized medical care of patients with heart failure; decompensated chronic heart failure; all-cause mortality; cardiovascular mortality; death from acute decompensated heart failure; survival in chronic heart failure

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Introduction

In the past decade, the global mortality of chronic heart failure (CHF) has remained high and resulted in serious demographic losses [1–9]. The EPOCH study revealed that the risk of total mortality in CHF of any functional class (FC) exceeded more than 10 times the risk of total mortality in the population of respondents without CHF, and the mean life expectancy of patients with FC I–II and FC III–IV CHF is 7.8 and 4.8 years, respectively [10]. In the ESC-HF Pilot study, the annual

total mortality of patients with FC I–II and FC III–IV CHF was 4.8% and 13.5%, respectively [8, 9].

It was largely discussed in relevant literature that CHF survival rates are often worse than those of cancer. For example, several studies reported a low 25–50% survival rate of patients within five years of the CHF diagnosis [11–13].

Mortality rates vary from study to study, depending on the conditions of patient enrollment. In the studies that enrolled patients at the time of hospitalization (with decompensated HF), mortality rates were predictably higher than in relatively stable patients, who were enrolled at outpatient clinics. As an example, in the ESC-HF Pilot study, the total mortality rate one year after the diagnosis of CHF was higher in patients registered after acute decompensated HF (ADHF) and hospitalization (17.4%) compared with in patients with CHF registered in outpatient clinics (7.2%) [8, 9, 14].

Recent publications have generally reported higher survival rates in patients with CHF compared with those published between 2000–2010. However, the authors note that mortality is still high, and the rates of decline are not high enough [1, 15, 16]. Therefore, the development of reduction strategies for demographic and financial losses due to CHF is relevant for many countries, and the adoption of new technologies to reduce mortality in patients with CHF continues to be investigated and largely discussed in the literature [1, 10, 17–21].

Target patient groups have been identified in the Russian Federation for priority interventions that have been put in place to manage cardiovascular risks and mortality rates. One of these groups comprises patients suffering from CHF [22].

The most vulnerable group among patients with CHF are patients after ADHF. They have hypotension, impaired kidney function, and organ damage, which makes it difficult to titrate the CHF background therapy [23]. This is why this category of patients requires careful management and proper titration of background therapy in the period immediately after discharge from the hospital, which will reduce the risk of developing adverse outcomes [24].

The organization of specialized medical care for patients with CHF is growing more urgent in the Russian healthcare system, as despite the good coverage of CHF background therapy in other European countries, no significant reduction in CHF mortality has been demonstrated in recent years [1, 14].

This paper is devoted to the analysis of mortality risks in patients with CHF after ADHF during long-term follow-up at specialized CHF treatment centers and in real-life outpatient clinical practice.

Objective

This paper aims to analyze the risks of total mortality, Cardiovascular Mortality (CVM) and the mortality of repeat ADHF in patients with CHF within two years of ADHF diagnosis during long-term follow-up under the conditions of specialized medical care and real-life clinical practice.

Materials and Methods

A total of 942 patients with CHF of any origin aged 18 years or more were included in the prospective cohort study. All patients were treated for ADHF at the respective city's hospital CHF treatment center, educated at the CHF patient school, and followed up for two years. All patients were divided into two groups depending on their decision to continue outpatient follow-up in the CHF treatment center or local outpatient clinics. Group 1 included 510 patients who continued follow-up in the CHF treatment center, and Group 2 included 432 patients who did not visit the CHF treatment center after discharge. They were followed up in local outpatient clinics. The CHF treatment center operates on principles of seamless outpatient care for patients with CHF after discharge from the hospital, supported by nursing control (monthly structured telephone calls).

Outpatient follow-up of Group 1 patients at the CHF treatment center combined face-to-face and telephone communication with patients. Group 1 patients were consulted as outpatients by a CHF treatment center cardiologist. Visits were scheduled individually depending on the severity of the patient's condition, but at least once every three months if the course of CHF was stable. Additional visits were carried out when necessary if CHF deteriorated. During the outpatient follow-up of patients after ADHF, the CHF background therapy and diuretic treatment were titrated, as well as the treatment of diseases that caused CHF and comorbidity. Patients who missed visits or refused to be followed up were supervised by a CHF treatment center nurse who made structured telephone calls once a month. The structure and operation of the CHF treatment center have been described in detail previously [25, 26].

The group 2 patients were treated in local outpatient clinics and supervised by a nurse from the CHF treatment center using structured telephone calls (once every 1 to 3 months). They did not visit a cardiologist at the CHF treatment center and had no face-to-face contact with CHF treatment center specialists.

Patients of the study groups were analyzed based on demographic and clinical parameters. We used a Mareev modification of the clinical assessment scale (SHOCS)

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[27]. Patients were classified by left ventricular ejection fraction (LVEF) in line with the national guidelines: heart failure with preserved LVEF (HFpEF), mid-range LVEF (HFmrEF), and reduced LVEF (HFrEF) [28].

The baseline clinical parameters are shown in Table 1.

Patients of Group 2 were older and had a higher baseline SHOKS score, shorter 6-minute walk distance and had FC III more often and FC I less often (Table 1). The percentage of severe patients with FC III–IV CHF was higher in Group 2 than in Group 1: 56.9% vs. 47.1% (p=0.002).

Thus, the Group 2 patients were initially more clinically severe compared with Group 1, which was taken into account in the subsequent analysis of clinical outcomes.

Both groups included more female patients than male, and a predominance of patients with HFpEF. Patients in both groups did not differ in the categories of baseline mean levels of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean heart rate and were characterized by a comparably high rate of comorbidities (Table 1).

During the 24-month follow-up period, causes of death in Group 1 and Group 2 were established based on inpatient case records, autopsy data, or conclusions formed in the outpatient medical record. In case of sudden death or death at home, or if no autopsy was performed, the mortality analysis was carried out with the participation of patients' relatives who were interviewed by a CHF treatment center physician. We analyzed the following endpoints: total mortality and CVM, ADHF mortality, cumulative CVM, and ADHF mortality. CVM was identified based on the following causes of death: sudden cardiac death, death due to acute myocardial infarction (MI), and cerebrovascular accident (CVA).

Statistical analysis was performed using the Statistica 7.0 software package for Windows, SPSS, and the R software package [29]. The data are presented as means and standard deviation (M, σ) for parametric distributions of the sample and as median (1st quartile; 3rd quartile) for non-parametric distributions. The Student's t-test was used for data with a normal distribution, and the chi-squared test was used to analyze rate differences.

Table 1. Baseline clinical parameters of patients

Parameter	Group 1, n=510	Group 2, n=432	p*
Age, years	69.7±10.2	71.9±10.8	**0.002**
Male/female, n (%)	217 (42.5) / 293 (57.5)	179 (41.4) / 253 (58.6)	0.7
Duration of hospitalization, bed-days	11.4±3.1	11.3±3.4	0.95
SBP, mm Hg	135.4±24.0	137.3±25.0	0.2
DBP, mm Hg	77.3±12.1	78.7±13.1	0.1
HR, bpm/min	76.3±15.5	78±16.7	0.1
HFpEF / HFmrEF / HFrEF, n (%)	351 (68.8) / 91 (17.9) / 68 (13.3)	316 (73.1) / 76 (17.6) / 40 (9.3)	0.1/0.9/0.05
6MWD, m	299.2±102.1	276.3±94.2	**0.0003**
FC I /II /III /IV CHF, n (%)	71 (13.9) / 199 (39) / 197 (38.6) / 43 (8.5)	31 (7.2) / 155 (35.9) / 203 (47) / 43 (9.9)	**0.0009**/0.3/ **0.009**/0.4
SHOKS, points	3 (Q1=2; Q3=4)	4 (Q1=2; Q3=5)	**<0.001**
History of hypertension, n (%)	482 (94.5)	412 (95.3)	0.5
History of CAD, n (%)	415 (81.4)	356 (82.4)	0.7
History of MI, n (%)	139 (27.3)	112 (25.9)	0.6
History of DM/CI, n (%)	131 (25.7) / 53 (10.4)	103 (23.8) / 34 (7.9)	0.5/0.2
AF, n (%)	254 (49.8)	190 (44.0)	0.07
GFR <60 mL/min/1.73 m^2, n (%)	181 (35.5)	175 (40.5)	0.1
History of CVA, n (%)	45 (8.8)	38 (8.8)	0.98
Anemia, n (%)	87 (17.1)	66 (15.3)	0.5
History of cancer, n (%)	38 (7.5)	28 (6.5)	0.6
Charlson comorbidity index, points	5 (Q1=4; Q3=7)	5 (Q1=4; Q3=7)	0.6

*, significance of differences between Group 1 and Group 2. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; FC, functional class; HFpEF, heart failure with preserved left ventricular ejection fraction; HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; 6MWD, 6-minute walk distance; SHOKS, clinical assessment scale; CAD, coronary artery disease; MI, myocardial infarction: DM, diabetes mellitus; CI, carbohydrate intolerance; AF, atrial fibrillation; GFR, glomerular filtration rate; CVA, cerebrovascular accident.

The Shapiro-Wilk test was used to verify distribution normality. The Mann-Whitney U test was used where the distribution was not normally distributed.

The Cox's proportional hazards model was used to assess the effect of different variables on the endpoints (total mortality, CVM, ADHF mortality, and combined mortality rate). Patient survival rates are presented as Kaplan-Meier curves. The level of statistical significance of the differences was determined using a log-rank test. Differences were considered statistically significant with $p<0.05$.

Results

We developed the multivariate Cox proportional hazards models to analyze the independent effects of such factors as belonging to Group 1, CHF FC, and HF phenotype depending on LVEF. The Cox models also included such parameters as sex, age, an increase in 6MWD in increments of 20 meters, an increase in the SHOKS score by single points, and every 10 mmHg increase in SBP versus the mean values.

The following parameters were used as references: belonging to Group 1, male sex, HFpEF, FC I–II CHF.

The results of the multivariate Cox's proportional hazards models for total mortality, CVM, mortality of ADHF, and cumulative mortality are presented in the relevant forest plots (Figures 1–4).

These multivariate Cox's proportional hazard models showed that, for every endpoint, the risk of total mortality, CVM, mortality of ADHF, and cumulative CVM and ADHF mortality independently increased the assignment of patients along with their age cohort to Group 2.

The female sex was, by contrast, a protective factor, reducing the probability of death of any cause by 38% (the risk of death from ADHF and the risk of cumulative mortality), but did not have a separate effect on CVM (Figures 1–4). The lack of protective effect on the risk of CVM as a result of female sex is probably attributable to the high comorbidity rates among patients.

The stratification based on the initial LVEF (HFpEF, HFmrEF, and HFrEF) did not affect any of the study endpoints (Figure 1–4). Interestingly, the initial stratification by CHF FCs at discharge from the hospital also did not affect any endpoints of mortality in both groups (Figures 1–4). The reason for this could be either that the LVEF and CHF FC could change during the two-year follow-up period in both groups depending on the outpatient treatment, or that the quality of treatment could be a determinant of the prognosis rather than LVEF or baseline FC. The quality of outpatient treatment and other factors were likely to reduce the sensitivity of baseline LVEF and CHF FC regarding the risk of total and ADHF mortality in the long-term follow-up period. Moreover, the parameters expressing the clinical severity of CHF were not correlated with the risk of CVM, which is entirely explicable.

The protective factor against the risks of total mortality, mortality of ADHF, and cumulative mortality was the increase in 6MWD in increments of 20 meters (Figures 1–4). CVM was the endpoint, which was not significantly affected by the baseline values of 6MWD.

The baseline SHOKS score was another parameter that did not influence the risk of CVM. The SHOKS score was sensitive to increases in the risk of total mortality, mortality of ADHF, and the cumulative mortality rate (Figures 1–4).

The protective factor that significantly affected the risks of total mortality, CVM, mortality of ADHF, and the cumulative mortality rate was the increase in BP in increments of 10 mmHg versus the mean values of the corresponding indicators (Figures 1–4).

The Kaplan – Mayer analysis (survival curves) for all the endpoints analyzed is shown in Figure 5.

Thus, we analyzed the total mortality, CVM, and mortality of ADHF for the two-year follow-up period, and the percentages of patients in both groups who had these adverse outcomes are shown in Figure 6. The data showed that the percentages of patients with any adverse outcome were higher in Group 2 than in Group 1.

We performed a mortality analysis for follow-up periods of 3, 6, 12, and 24 months. Total mortality, CVM, mortality of ADHF, and the combined CVM and ADHF mortality were calculated, excluding patients who died of other causes in the specified periods. The data are given in Table 2.

The analysis of total mortality in Group 1 and Group 2 revealed a consistent trend of higher mortality rates as follow up time increased. The comparison of mortality rates in all four follow-up periods showed that total mortality was 3.7–7.8 times higher in Group 2 versus Group 1, depending on the follow-up period. The most significant differences were observed during the first 3 and 6 months of follow-up, which proves once again that the first six months after discharge is a vulnerable period if there is no active titration of the CHF background therapy.

The cardiovascular mortality in any follow-up period was higher in Group – 12.4, 16.6, 10.6, and 5.9 times higher after 3, 6, 12, and 24 months of follow-up, respectively. The differences in CVM rates were more significant than the differences in total mortality. Well-titrated CHF background therapy in Group 1 allowed for

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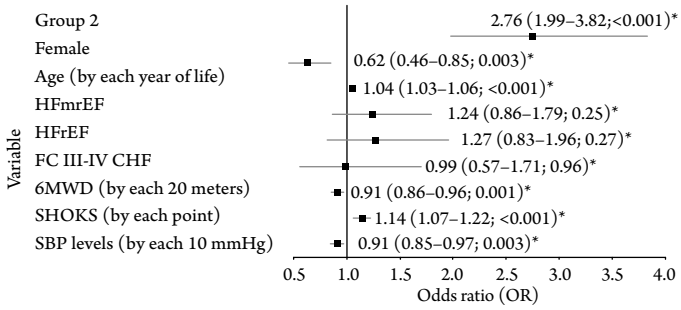
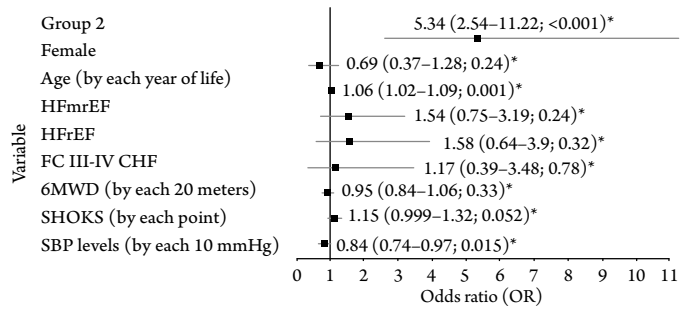
Figure 1. Forest plot of total mortality



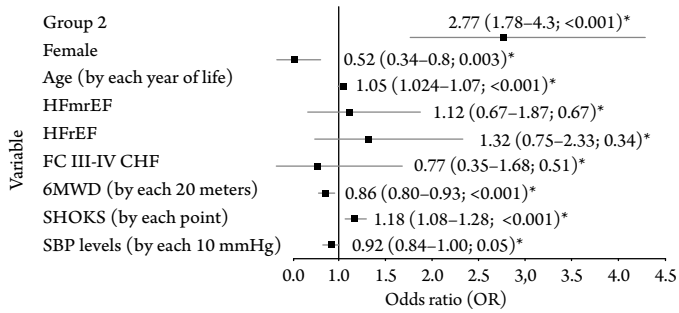
**, 95% CI; p value HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; 6MWD, 6-minute walk distance; SHOKS, clinical assessment scale.*

Figure 2. Forest plot of cardiovascular mortality



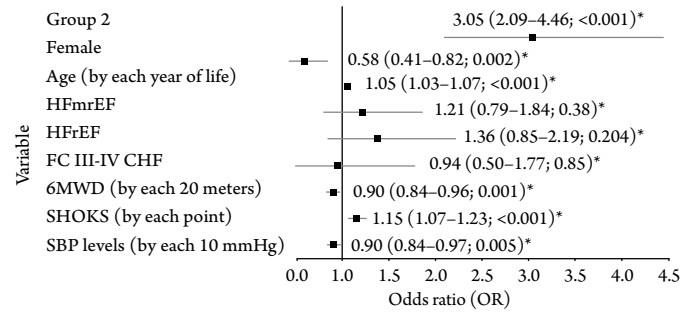
***, 95% CI; p value HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; 6MWD, 6-minute walk distance; SHOKS, clinical assessment scale.*

Figure 3. Forest plot of ADHF mortality



**, 95% CI; p value HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; 6MWD, 6-minute walk distance; SHOKS, clinical assessment scale.*

Figure 4. Forest plot of CVM and ADHF mortality



**, 95% CI; p value HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; 6MWD, 6-minute walk distance; SHOKS, clinical assessment scale.*

a reduction in CVM risk, and patients in Group 1 also received treatments for comorbidities and etiological factors of CHF – primarily hypertension, coronary artery disease, and atrial fibrillation.

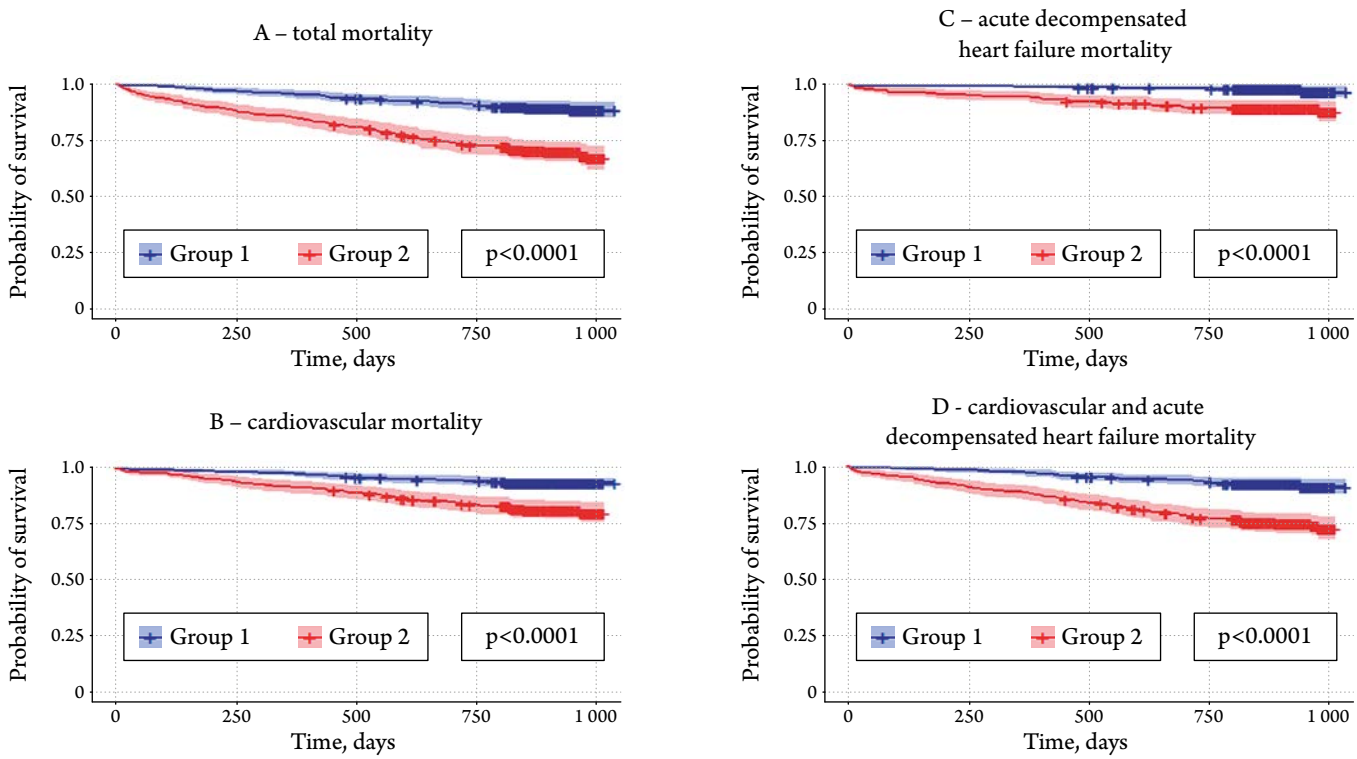
Mortality after three months of follow-up did not differ between the groups, i.e., patients after ADHF had a severe prognosis and a vulnerable period (the first 90 days after discharge from the hospital) in both groups. After six months of follow-up and until the end of the study, the risks of mortality of ADHF were lower in Group 1, which proves the efficacy of the background treatment and diuretic therapy of CHF as well as the general efficacy of interventions in Group 1 for the prevention of ADHF mortality.

Table 2. Analysis of total, cardiovascular, and ADHF mortality, cumulative cardiovascular and ADHF mortality in Group 1 and Group 2 taking into the follow-up period

Endpoints, outcomes	Group	After 3 months	After 6 months	After 12 months	After 24 months
TM, n (%)	Group 1	4 (0.8)	11 (2.2)	21 (4.1)	52 (10.2)
	Group 2	25 (5.8)	41 (9.5)	62 (14.4)	129 (29.9)
	OR; 95% CI; $p_{1/2}$	7.8; 2.7–22.5; **<0.001**	4.8; 2.4–9.4; **<0.001**	3.9; 2.3–6.5; **<0.001**	3.7; 2.6–5.3; **<0.001**
CVM, n (%)	Group 1	1 (0.2)	1 (0.2)	2 (0.4)	9 (1.9)
	Group 2	10 (2.4)	13 (3.2)	16 (4.1)	35 (10.4)
	OR; 95% CI; $p_{1/2}$	12.4; 1.6–97.5; **0.002**	16.6; 2.6–127.4; **0.0003**	10.6; 2.4–46.3; **0.0001**	5.9; 2.8–12.4; **<0.001**
ADHF mortality, n (%)	Group 1	2 (0.4)	5 (1.0)	9 (1.8)	29 (6.0)
	Group 2	6 (1.5)	16 (3.9)	28 (7.0)	67 (18.1)
	OR; 95% CI; $p_{1/2}$	3.7; 0.7–18.6; **0.08**	4.1; 1.5–11.2; **0.003**	4.1; 1.9–8.8; **<0.001**	3.5; 2.2–5.5; **<0.001**
CVM+ADHF mortality, n (%)	Group 1	3 (0.6)	6 (1.2)	11 (2.2)	38 (7.7)
	Group 2	16 (3.8)	29 (6.9)	44 (10.6)	102 (25.2)
	OR; 95% CI; $p_{1/2}$	6.6; 1.9–22.9; **0.0006**	6.2; 2.5–15.0; **<0.001**	5.3; 2.7–10.4; **<0.001**	4.1; 2.7–6.1; **<0.001**

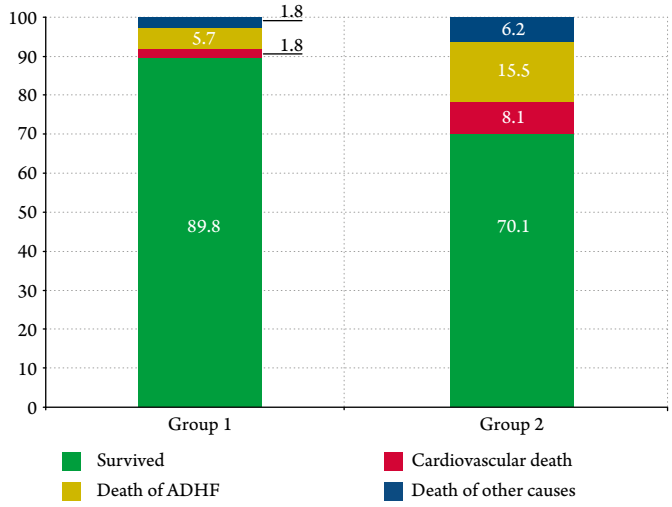
TM, total mortality, CVM, cardiovascular mortality, ADHF, acute decompensated heart failure; OR, odds ratio, CI, confidence interval; p1/2, statistical difference between Group 1 and Group 2.

Figure 5. Endpoint survival curves for Group 1 and Group 2 during the 24-month follow-up period



In Group 2, the combined CVM and ADHF mortality was 6.6, 6.2, 5.3, and 4.1 times higher after 3, 6, 12, and 24 months of follow-up, respectively. This marker expresses the changes in these outcomes over time (separate CVM and separate mortality of ADHF). It shows the presence of a period of particularly high mortality and vulnerability for patients after ADHF within the first six months in the absence of specialized medical care and active titration of the background treatments for CHF along with diuretic therapy.

Figure 6. Structure of survival and mortality in Group 1 and Group 2 during the 24-month follow-up period



Discussion

In this study, patients were distributed between the study groups based on their decision to continue follow-up at the specialized CHF treatment center or local outpatient clinics. Patients who preferred to be followed up at the local outpatient clinics were older and clinically more severe according to CHF FC, 6MWT, and SHOKS score. These differences were likely to influence patient mobility and their choices.

A high rate of comorbidities and somatically severe diseases were observed in both patient groups. In both groups, patients had a similar rate of both active cancer and a history of ADHF and cancer. These factors should also be considered when assessing patient mobility and scheduling specialized care for patients with CHF.

The clinical portrait of a modern outpatient with CHF was discussed many times in the literature, and the CHF of the 21st century has a female face and is characterized by a preserved EF [15, 18, 30]. This study included patients with a history of ADHF – female patients and patients with HFpEF prevailed in both groups.

We analyzed 2-year total mortality after the diagnosis of ADHF, which was 10.2% in the specialized follow-up group and 29.9% in the outpatient clinic group. If the real-life outpatient mortality in this study is compared to the epidemiological data from the EPOCH study for the Nizhny Novgorod Region (24% in 4-year follow-up), it will be evident that survival of patients after ADHF

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without specialized follow-up is at least 2 times lower than the survival of patients with CHF of any FC [31].

Cardiovascular mortality in a 2-year follow-up was 5.9 times higher in the group of local outpatient clinics (10.4%), which confirms the protective effect of titrated background therapy of CHF, resulting in a decrease in cardiovascular endpoints in the specialized care group (1.9%). The analysis of the literature studying CVM in patients with CHF revealed that in the ESC-HF Pilot study, the annual CVM differed between outpatients (3.9%) and hospitalized (11.6%) patients. However, this data should be interpreted with caution because about ⅓ of patients in the ESC-HF Pilot study died of unknown causes [9].

It should be noted that the mortality of ADHF is not analyzed in the literature. Most studies typically estimate hospitalizations as due to aggravation of CHF, which does not provide information concerning the mortality of ADHF [9, 15]. In this study, the risk of ADHF mortality after two years of follow-up was 4.1 times higher in the local outpatient follow-up group, which was associated not only with poor quality of CHF background therapy but also with insufficient use of loop diuretics [32].

The analysis of mortality risks by follow-up periods showed that the first three months were sensitive to the risk of ADHF mortality in both follow-up groups. The analysis of all outcomes (total mortality, CVM, mortality of ADHF, and combined CVM and ADHF mortality) showed that the first six months after discharge are critical for patients after ADHF, especially in the absence of specialized care.

The previously reported «vulnerable» period for patients with ADHF after discharge was 30 to 100 days [33, 34]. We agree with this data, but our findings suggest that significant mortality risks remain for an extended period, specifically the first six months after discharge from the hospital.

The Cox's proportional hazards analysis suggests that follow-up in local non-specialized facilities elevated the risk of death for all outcomes regardless of the patient's age or clinical severity.

Interestingly, a sensitive marker of poor prognosis in the long-term follow-up of patients after ADHF was the Mareev modification of the SHOKS score, which makes this tool necessary in the routine work of a practicing physician who follows up patients with CHF. Unfortunately, the SHOKS score is not common today – it is used only in specialized CHF departments and even then is rarely used repeatedly.

Surprisingly, baseline LVEF and CHF FC did not affect any of the outcomes analyzed with the 2-year follow-up period. This might be because the parameters related to the clinical severity of CHF could have changed during the treatment of CHF in different follow-up conditions both upwards and downwards. It is suggested that patients with severe baseline clinical manifestations might improve clinical status with the help of appropriate treatment and as a result have a more favorable prognosis, whereas patients with mild baseline manifestations could have a worse prognosis in the absence of quality CHF background therapy, which can influence both cardiovascular outcomes and ADHF mortality.

The literature is split on the issue of the effect of LVEF on the prognosis. Several studies reported that the total mortality did not differ in patients with preserved and reduced LVEF [8, 9, 15]. Other studies suggested that the long-term prognosis after an ADHF event was better for patients with HFpEF versus patients with HFmrEF and HFrEF [35].

It should be noted that the baseline LVEF was estimated during ADHF, which could influence the results of the study because it is known that LVEF can change during ADHF and differ from the LVEF of a stable patient.

In our analysis, the mortality risks reduced as the 6MWD increased. This marker was sensitive for all outcomes except for CVM, which is reasonable because it denotes the severity of CHF. However, CHF FC associated with this marker was not sensitive to the prognosis in long-term follow-up after ADHF. Thus, we suggest that CHF FC is not the only marker to be used in the diagnosis of patients with CHF – 6MWD and LVEF should also be utilized so that a practicing physician can correctly assess the prognosis and follow-up data in the treatment of CHF.

In our study, the female sex had a protective effect on the risks of all adverse outcomes analyzed except for CVM. The differences in the mortality rate in CHF depending on sex are contradictory in the literature. Several studies have suggested that sex has no effect on total mortality in patients with CHF [4], and other studies reported improved prognosis in female patients [30, 35–37]. The protective effect of the female sex on mortality in CHF cannot be associated with differences in hormonal status, because the mean age of patients in our study corresponds to the age of late post-menopause. This might be due to national peculiarities in mentality, for example, Russian women are known to be more adherent to the treatment of cardiovascular diseases [38].

Interestingly, the increase in the baseline SBP in increments of 10 mmHg at discharge from the hospital is a protective factor reducing the risk of mortality for all the outcomes analyzed. Previously, the EPOCH-D–CHF study found that the total mortality rate varied depending

on BP at discharge after ADHF and was 46.4% and 22.1% in patients with BP <120 and >120 mmHg, respectively [23, 33].

Hypotension makes it difficult to titrate the background therapy. It significantly worsens the prognosis, which may be associated with hypoperfusion of organs and tissues when blood BP is low [39–41] and the development of organ lesions, as well as deterioration in kidney filtration function in many cases [42].

Thus, the above data show the high mortality rates for patients after ADHF, which requires a special treatment approach at the outpatient level. The seamless model of specialized medical care for patients with CHF solved this problem very effectively in the Russian Federation.

Conclusion

1. Follow-up at the specialized CHF treatment center reduces the risks of all-cause, cardiovascular, ADHF mortality, and combined cardiovascular and ADHF mortality.
2. The critical «vulnerable» period for the risk of ADHF mortality and all other adverse outcomes is the first 3 and 6 months after discharge from the hospital, respectively.
3. SHOKS score was a sensitive risk factor for adverse outcomes that worsened the prognosis in patients after ADHF for a long-term follow-up period, and the baseline levels of LVEF and CHF FC did not affect the long-term prognosis in patients after ADHF.
4. The female sex, higher 6MWD, and SBP levels were protective factors for patients after ADHF.

Limitations of the study

The study groups were formed based on a patient's decision to be followed up as an outpatient at the CHF treatment center or at the local outpatient clinic, which depended on clinical severity and low mobility of the patient. The study findings should be interpreted with caution and taking these factors into consideration.

No conflict of interest is reported.

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