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LONG-TERM PROGNOSIS OF PATIENTS WITH CHRONIC HEART FAILURE AND REDUCED LEFT VENTRICULAR EJECTION FRACTION RECEIVING CARDIAC CONTRACTILITY MODULATION THERAPY: THE IMPACT OF COMORBIDITY BURDEN ON OUTCOMES

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Aim. To investigate the association between comorbidity burden and long-term clinical outcomes of patients with reduced left ventricular ejection fraction (HFrEF) undergoing cardiac contractility modulation (CCM).

Methods. Our study included 59 patients with HFrEF, functional class II/III (NYHA), sinus rhythm, who underwent implantation of CCM system between September 2015 and December 2018 and were further followed by a multidisciplinary team. A mean follow-up period was 1916±102 days. All-cause mortality and heart transplantation were considered as primary composite endpoint. The secondary composite endpoint included all-cause mortality, heart transplantation, implantable cardioverter defibrillator shocks due to ventricular tachyarrhythmia and hospitalizations due to decompensated HF. Predicted survival rate were calculated using MAGGIC Risk Calculator and Seattle Heart Failure Model (SHFM). Initially, the Charlson comorbidity index (CCI) was calculated for all patients.

Results. Three- and five-year survival rates were 79,7% and 66,1%, respectively, which were significantly higher than predicted by MAGGIC (p=0.02) and SHFM (p=0.01). The median time to the primary endpoint was 1494 days and the annual mortality was 7%. Patients with HF NYHA class III, chronic kidney disease and CCI ≥7 points had worse prognosis (p_1=0.002, p_2=0.003, p_3=0.04 (log-rank test). There was a significant decrease in number of hospitalized patients due to HF decompensated during CCM (p<0.001) compared with the six-month period before the system implantation. Patients with CCI value ≥ 7 points reached secondary composite endpoint faster (p=0.002 and p=0.004 for three-year and five-year follow-up periods, respectively (log-rank test)).

Conclusion. Long-term survival rates of patients with HFrEF II/III (NYHA) receiving CCM and managed on multidisciplinary team were significantly higher than predicted. The heavy comorbidity burden negatively impacts on the clinical course and outcomes of HF patients following CCM implantation. Applying the Charlson index can be useful in a comprehensive assessment of the prognosis and determining the target population for the expensive implantable devices, including CCM, in risk stratification and decision-making algorithms.

Key words: chronic heart failure; cardiac contractility modulation; prognosis; comorbidity; Charlson comorbidity index

Conflict of Interests: nothing to declare.

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The growing problem of heart failure (HF) is associated with significant morbidity and a poor prognosis. In clinical practice, the necessity of HF`s high-tech treatment methods are determined by predictive risk assessment. The practice of using validated calculators of projected survival in algorithms of HF treatment is supported by current guidelines and helps to optimize treatment, especially the use of device therapy [1, 2]. At the same time, increasing numbers of elderly people, patients with multiple comorbidities, constant improvement of management approaches and development of new therapeutic options complicate prediction of outcomes in patients with heart failure.

In recent studies, close attention is paid to identifying more accurate criteria for electrophysiological devices implantation, stratifying the prognostic risks, and choosing an optimized treatment strategy [3-9]. The significant role of comorbidity in predicting patient`s outcomes was studied. Great number of studies showed negative prognostic

impact of severe comorbidity on long-term prognosis in patients with low ejection fraction HF (HFrEF), implanted with an ICD and resynchronization therapy devices (CRT-D) [3-9].

Table 1. (see continuation)
Baseline characteristics of patients, clinical course and outcomes (n=59)

Parameter	Value
Age (years), M±SD	52.3±10.4
Min/max, years	25/72
Male, n (%)	49 (83)
Smoking, n (%)	33 (56)
AH, n (%)	45 (76)
Anamnesis of paroxysmal AF, n (%)	8 (13.5)
CAD, postinfarction cardiosclerosis, n (%)	42 (71)
Myocardial revascularization, n (%)	32 (54)
Stable chronic angina pectoris II, n (%)	25 (42)
Non-coronary disease, n (%)	19(32)
ICD, n (%)	14 (22)
HF II (NYHA), n (%)	44 (74.5)
HF III (NYHA), n (%)	15 (25)
Anamnesis of HF (years), Me (Q25;Q75)	3 (2;7)
Hospitalization due to decompensated HF*, n	41
Number of patients, who had hospitalization**, n (%)	29 (49)
Non-cardiac comorbidities	
Diabetes mellitus type 2, n (%)	18 (30.5)
COPD, n (%)	20 (34)
CKD, n (%)	15 (25)
Cerebrovascular disease, n (%)	13 (22)
Peptic ulcer disease, n (%)	12 (20)
The Charlson comorbidity index, M±SD	5.2±2.4
The Charlson comorbidity index ≥ 5 points, n (%)	37 (63)
The Charlson comorbidity index ≥ 7 points, n (%)	20 (34)
Objective patient`s status at baseline	
Systolic BP (mm Hg), Me (Q25;Q75)	110 (105;120)
HR, bpm, M±SD	68.3±6.4
Body mass index (kg/m^2), M±SD	28.5±4.9
LV EF, Me (Q25;Q75), %	26 (21;30).
LV EF, min/max, %	15/39
End diastolic volume of LV, Me (Q25;Q75)	240 (206;290)
End systolic volume of LV, Me (Q25;Q75)	185 (134;234)
Sinus rhythm, n (%)	59 (100)
QRS (ms), Me (Q25;Q75)	108 (100;118)
Peak VO_2, ml/kg/min, M±SD	14.1±4.5
NT-proBNP (pg/ml) Me (Q25; Q75)	1050 (586;1746)
Potassium, M±SD	4.6±0.3
Sodium, Me (Q25;Q75)	140 (138;142)
Heamoglobin, g/l, Me (Q25;Q75)	146 (131;156)
Total cholesterol, mmol/l, M±SD	4.3±0.9
Urine acid, mmol/l, M±SD	479±139
Lymphocytes (%), Me (Q25;Q75)	28 (22;32)
GFR CKD-EPI (ml/min/1.73m^2), M±SD	80.4±19.6

However, the prognostic potential of comorbidity in patients with HFrEF receiving a relatively new method of therapy, cardiac contractility modulation (CCM) is unknown. In a few studies design, investigating the long-term outcomes of patients with CCM, the observed survival rate compared with predicted survival levels, calculated using the Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score and Seattle Heart Failure Model (SHFM). The MAGGIC calculator includes some comorbid conditions, but at the same time, the data on comorbidity diseases is not presented in the SHFM, which calculates the most long-term prognosis. It is important that independent impact of CCM on outcomes in patients with HF cannot be assessed, because most of the studies were conducted prior to the era of using angiotensin receptors and neprilysin inhibitors (ARNIs) and sodium-glucose co-transporter type 2 inhibitors, drugs that have an independent effect on such important comorbidities and predictors of HF as renal dysfunction and diabetes mellitus.

Given the above, the study of predicted and observed survival of patients with HFrEF, receiving CCM is relevance. The aim of this research was to study three- and five-year prognosis of patients with HF receiving cardiac modulation, using an integrative approach, including the analysis of clinical, laboratory and instrumental data and focusing on the predictive potential of the comorbidity burden.

METHODS

This prospective study includes 59 patients who underwent implantation of CCM devices (51 Optimizer IV generation devices and 8 Optimizer Smart devices, Impulse Dynamics, Germany) between September 2015 and December 2018 in Almazov National Medical

Research Centre (Almazov NMRC). Inclusion/exclusion criteria and the CCM implantation technique are described in detail in our previous publications [15]. The study protocol was approved by the ethics committee of Almazov National Medical Research Center (No. 62 dated March 12, 2018). All patients had sinus rhythm, II and III functional class (FC) (NYHA) of HFrEF and received optimal drug therapy according to current guidelines for at least 3 months prior to device implantation. Patients were followed up by multidisciplinary team at the Centre for Heart Failure competency of Almazov NMRC. Visits to a heart failure specialized cardiologist and a cardiac electrophysiologist were every 3–6 months, during the first year of observation, and every 6-12 months, during the second year. Further visits were at least every 18 months. Also, patients could get 24/7 online consultation with the specialists.

At baseline, anamnesis, clinical, laboratory and instrumental data were analyzed. The Charlson comorbidity index (CCI) age-adjusted was calculated [16]. Outcomes were determined over three and five years follow-up periods. Three-year prognosis data were obtained in 100% of patients. Three patients, who implant CCM in December 2018 were excluded from the five-year prognosis. Predicted survival (PS) was calculated using the MAGGIC (PSMAGGIC) and SHFM (PSSHFM) scales [17, 18]. Number of hospitalizations for the 6-month period prior to implantation of CCM was assessed for each patient.

All-cause mortality and heart transplantation were considered as primary composite endpoint (PCE). The secondary composite endpoint (CE) included all-cause mortality, heart transplantation, and implantable cardioverter defibrillator shocks due to ventricular tachyarrhythmia and hospitalizations due to decompensated HF. Data on reaching the endpoint were obtained from medical records and from patient's relatives.

Statistical analysis was performed using SPSS (version 16.0) for Windows (SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2013 year. The Kolmogorov–Smirnov test determined the distribution of quantitative parameters. Data are presented as mean ± standard deviation (M±SD), median (Me) and quartile intervals (Q25 and Q75), frequencies and percentages of the total number of observations n (%), depending on the Gaussian distribution. Differences between independent samples were compared using the Mann-Whitney test. The independent categorical parameters were analyzed using the Fisher's exact test. The observed survival was analyzed using the Kaplan-Meier method. Statistical difference between observed and pre-

Table 1. (continuation)

Baseline characteristics of patients, clinical course and outcomes (n=59)

Parameter	Value
Baseline medical treatment	
ACEi/ARB , n (%)	58 (98)
Beta-blockers, n (%)	59 (100)
Aldosterone antagonist, n (%)	56 (95)
Diuretics, n (%)	59 (100)
Statin, n (%)	48 (81)
Clinical course during five-year follow-up period	
ICD implantation, n (%)	28 (47)
First diagnosed AF, n (%)	7 (12)
AF catheter ablation, n (%)	3 (5)
Electrical cardioversion due to AF, n (%)	5 (8.5)
Replace with Optimizer IV for Optimizer Smart, n (%)	1 (1.7)
Replacing Optimizer IV leads, n (%)	11 (19)
PCI, n (%)	6 (10)
Oncology, n (%)	3 (5)
Three-year clinical outcomes (n=59)	
Survival rate, %	79.7
Cardiovascular death, %	83.3
Heart transplantation, n (%)	2 (3)
Ventricular tachyarrhythmia, requiring ICD shocks, n (%)	0
Hospitalizations due to decompensated HF, n	46
Number of patients, who had hospitalization[&], n (%)	19 (32)
All-cause hospitalizations, n	48
Five-year clinical outcomes (n=56)	
Survival rate, %	66.1
Cardiovascular death, %	73.6
Heart transplantation, n (%)	2 (3.5)
Ventricular tachyarrhythmia, requiring ICD shocks, n (%)	9 (16)
Hospitalizations due to decompensated HF, n	64
Number of patients, who had hospitalization[&&], n (%)	28 (50)
All-cause hospitalizations, n	70

Note: data are given as mean ± standard deviation, median value and 25/75 quartiles or n (%). AH - arterial hypertension; AF - atrial fibrillation; ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BP - blood pressure; CAD - coronary artery disease; CKD - chronicle kidney disease; COPD - chronic obstructive pulmonary disease; HR - heart rate; GFR - glomerular filtration rate, ICD - implantable cardioverter defibrillator; NYHA - New York Heart Association; LVEF - left ventricular ejection fraction; HF - heart failure; PCI - percutaneous coronary intervention; peak VO_2 - peak of oxygen consumption; [&&] - due to decompensated HF during five-year period.

dicted by the SHFM and the MAGGIC survival, factor`s impact on primary and secondary CE were accomplished using a log-rank test at the respective time points. Differences were considered significant at p-value <0.05.

RESULTS

The mean follow-up period was 63.9±3.4 months (1916±102 days). Clinical characteristics of patients at the baseline, clinical course and outcomes are shown in Table 1.

The mean age of the patients was 52.3±10.4 years, the majority were men with HF II FC (NYHA). The main cause of HF was coronary heart disease, 40 patients had postinfarction cardiosclerosis, in 18 cases the cause of HF was various types of non-coronary cardiomyopathies. Anamnesis of arterial hypertension was detected in most cases and counted as a competitive etiology of HF. Every third patient had chronic obstructive pulmonary disease and diabetes mellitus type 2 (DM), compensated by a diet or in combination with hypoglycemic drugs. One of four patients had chronic kidney disease (CKD). The CCI ≥5 point was observed in 63% of cases (Table 1). At baseline, 14 patients were implanted with ICDs for the primary prevention of sudden cardiac death (SCD). During the follow-up period, in addition to the CCM, ICDs were implanted in 28 more patients for the primary prevention of SCD. During the first and second years, ICD implantation was performed in 19 and 5 patients, respectively, the remaining four patients in the subsequent period.

ARNI therapy was used in 29% of patients (17 people) during entire follow-up period. Dapagliflozin was prescribed for 6 patients since 2020. Myocardial revascularization was performed to 10% of patients (6 people) during follow-up period. Eight patients had a history of paroxysmal atrial fibrillation (AF), two of them underwent AF catheter ablation 12 months prior to CCM device implantation. After 5 years of follow-up, 7 patients were first diagnosed with AF, which requires cardioversion using electrical impulse therapy / catheter ablation, and one patient was replaced with the Optimizer Smart device for Optimizer IV. Ventricular tachyarrhythmia, requiring ICD shocks were observed in 15.2% of cases (9 people) at the fifth year of follow-up.

Three years later, CCM was discontinued in three patients for various reasons, including pocket stimulation associated with insulation breaches of CCM ventricular leads. One of them underwent CCM system removal due to the technical inability of replacing device`s leads. These cases were censored at the respective time points. The proportion of therapeutic stimulation during the follow-up period was more than 70% in all respondents.One year later after device implantation a significant decrease in number

Table 2.

Dynamics of hospitalization due to HF decompensation number over 5 years during CCM

Time period	Number of hospitalized patients*, n (%)
12 months	8 (14.2)
12-24 months	5 (10)
24-36 months	6 (12.7)
36-48 months	4 (10)
48-60 months	5 (13.5)

Note: * - the number of hospitalized patients due to HF decompensation from the total number of survived patients at the end of certain follow-up period.

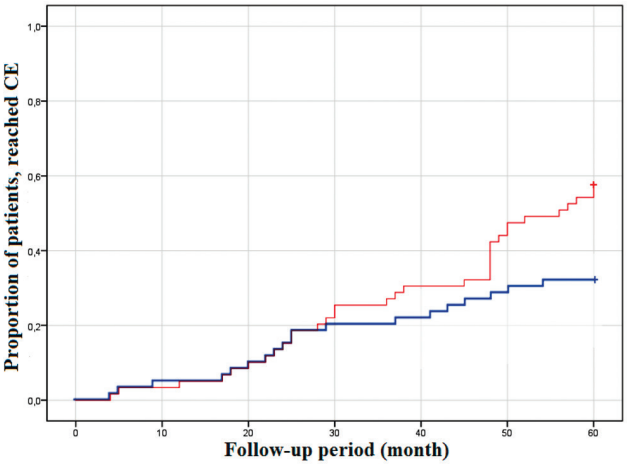

Fig. 1. Kaplan-Meier survival curves for primary (blue line) and secondary (red line) composite endpoints in cardiac contractility modulation patients.

Table 3.

Comparison of observed and predicted survival during follow-up period

Follow-up period (months)	Survival rate (%)		
	Kaplan-Meier	SHFM	MAGGIC
12	96	96	91
24	88	92	-
36	79,7	-	77,4
48	74	-	-
60	66,1	55,7	-

Note: SHFM - Seattle Heart Failure Model, MAGGIC - Meta-Analysis Global Group in Chronic Heart Failure Risk Score.

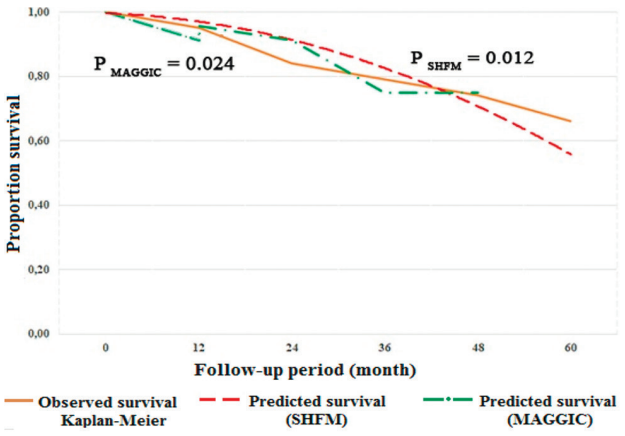

Fig. 2. Comparison of Kaplan-Meier analysis for observed survival rate and predicted survival rate by SHFM and MAGGIC in cardiac contractility modulation patients.

Table 4.

Differences in clinical, anamnestic, laboratory and instrumental parameters of patients with HF at the time of CCM implantation depending on their outcomes.

Parameter	3 year of observation			5 year of observation		
	Survived (n=47)	Patients, reached PCE (n=12)	p	Survived (n=37)	Patients, reached PCE (n=19)	p
Age (years), M±SD	54.32±10.8	58.7±9	ns	56.7±11.3	58.2±8.4	ns
HF anamnesis, years, Me (Q25;Q75)	6(4;8)	6(4;10)	ns	9(7;10)	8(6;13)	ns
CKD, n (%)	8(17)	7(58)	0.007	6(16)	9(47)	0.02
Anamnesis of AH, n (%)	34 (72)	11 (92)	ns	27 (73)	16 (84)	ns
CAD, n (%)	32 (68)	10 (83)	ns	25 (68)	15 (80)	ns
Diabetes mellitus type 2, n (%)	13 (28)	5 (42)	0.48	9 (24)	9 (47)	1.0
CCI, points, M±SD	5.1±2.5	7.1±2.5	ns	5.5±2.7	7.21±2.5	0.02
CCI ≥ 5 points, n (%)	27 (57)	10 (83)	ns	22 (59)	15 (79)	ns
CCI ≥ 7 points, n (%)	11 (23)	9 (75)	0.008	9 (24)	11 (58)	0.02
SBP, mm Hg, Me (Q25;Q75)	120 (110;120)	115 (100;124)	ns	120 (110;120)	110 (100;120)	ns
HR, bpm, Me (Q25;Q75)	66(64;72)	73(67;79)	ns	66(61;73)	75(70;82)	ns
Total cholesterol, mmol/l, M±SD	4.1±1.4	5.3±1.3	ns	4.2±1.2	4.8±0.4	ns
Potassium, M±SD	140.5±3.3	142.1±1.8	ns	138.4±4.7	139.8±5.3	ns
Sodium, Me (Q25;Q75)	4.5±0.5	4.5±0.4	ns	4.9±0.5	4.4±0.4	ns
Heamoglobin, g/l, Me (Q25;Q75)	143.8±18.4	135±17	ns	172±17.4	141.3±23	ns
Lymphocytes (%), M±SD	30.7±9.9	24.7±10	ns	33.6±21	22.4±10.6	ns
Urine acid, mmol/l, M±SD	471±122	630±228	ns	455±127	542±227	ns
BMI, kg/m^2, M±SD	29.6±5.4	28.6±3.6	ns	29.5±5.8	30.4±4.9	ns
GFR CKD-EPI (ml/min/1.73m^2), M±SD	74.5±16.5	60.8±12.5	ns	70±19	55.8±17.9	0.02
LVEF,%, M±SD	33.57±7.3	27.2±8.4	ns	36.6±9.1	26±7	0.003
LVEF < 25%, n (%)	4 (8.5)	4 (33)	0.046	3(8)	7(37)	0.02
LVEF 25-34%, n (%)	19 (40)	6 (50)	ns	11(30)	10(53)	ns
LVEF >34% , n (%)	24 (51)	2 (17)	0.049	23(62)	2(10.5)	0.0002
HF III (NYHA), n (%)	8 (17)	7 (58)	0.007	5 (13.5)	9 (47)	0.009
NT-proBNP pg/ml, Me (Q25;Q75)	492 (137;1000)	2200 (1249;11422)	ns	190 (45;610)	2020 (1215;8433)	ns
peak VO_2, ml/kg/min, M±SD	16.7±5.61	15.1±4.6	ns	23.7±5.56	14.1±4.5	0.043
ICD prior to CCM implantation, n (%)	10 (21)	4 (33)	ns	11 (30)	3 (16)	ns
ICD after 24 months CCM, n (%)	31 (66)	7 (58)	ns	27 (73)	10 (53)	ns
ACEi/ARB, n (%)	46 (98)	12 (100)	ns	37 (100)	18 (94)	ns
Beta-blockers, n (%)	47 (100)	12 (100)	ns	37 (100)	19(100)	ns
Aldosterone antagonists, n (%)	44 (93	12 (100)	ns	37 (100)	19(100)	ns
Diuretics, n (%)	47 (100)	12 (100)	ns	37 (100)	19(100)	ns.
Statin, n (%)	37 (78)	11 (92)	ns	29 (78)	19(100)	ns
ARNI* since 2018 yr , n (%)	15 (32)	2 (17)	ns	13 (33)	4 (21)	ns
Dapagliflozin since 2020 yr , n(%)	6 (10)	0(0)	ns	4 (10)		ns
Hospitalized patients [1], n (%)	22 (47)	7 (58)	ns	17 (46)	12 (63)	ns
Hospitalized patients[2], n (%)	12 (25.5)	6 (50)	ns	9 (24)	13 (68)	0.003

Note: data are given as mean ± standard deviation, median value and 25/75 quartiles or n (%), ns - non-significant differences; PCE - primary composite endpoint; CCI - Charlson`s comorbidity index; * - ARNI - angiotensin receptors and neprilysin inhibitor; [1] and [2] - number of hospitalized patients due to HF decompensation patients 6 month prior to CCM device implantation and due to HF decompensation patients during follow-up period, respectively. Other abbreviations same as table 1.

of patients, hospitalized due to decompensated HF was observed and compared with six months period prior to CCM implantation, furthermore, significance of the difference remained during whole follow-up period for each twelve-month (all p <0.001) (Table 2).

At three and five years, survival rate was 79.7% and 66.1%, respectively (Fig. 1). Primary CE (all-cause death and HT) was reached by 12 (20.3%) and 19 (33.9%) patients in the above time periods. The average event-free survival before reaching PCE was 49.8±2.21 months (1494 days).

Cardiovascular mortality was observed in 83.3% and 73.6% of cases over three and five years of follow-up, respectively, while mortality due to HF decompensation was dominated (41.6% and 47.3% for three- and five years, respectively). HT due to the progression of HF was performed in two cases during the 3-year period after the CCM. SCD were in 6.7% cases (4 people) during the entire follow-up period. There were no implantations of a mechanical circulatory support system in the study cohort. Five patients (8.4%) had severe forms of the new coronavirus infection that required hospitalization, two of them were declared with hospital deaths.

Secondary CE (including all-cause mortality, HT, ICD shocks and hospitalizations due to decompensated HF) was reached by 17 (29%) and 34 (61%) patients, respectively, during the three- and five-year follow-up periods (Fig. 1). The average event-free survival before reaching secondary CE was 46.5±2.2 months (1395 days).

Observed survival rates were compared with predicted by the SHFM and MAGGIC scales. After three and five years of follow-up, observed survival was significantly higher than PSMAGGIC and PSSHFM 79.7% and 66.1% versus 77.4% and 55.7%, respectively (p1=0.024; p2=0.012) (Table 3 and Fig. 2). The average annual mortality rate in cohort was 6.8%.

Comparative analysis between surviving and deceased patients groups, who reached primary CE, included a wide range of prognostic factors and parameters provided in the prediction survival scales. Patients with LV EF less than 25%, FC III (NYHA), CKD, CCI ≥ 7 points were more common in groups of patients who reached primary CE compared with the group of survived patients at all-time points (all p < 0.05). Higher baseline value of the CCI, as well as lower baseline values of peak oxygen consumption, glomerular filtration rate (GFR) and frequent hospitalizations due to HF decompensation during CCM therapy were associated with a poor five-year prognosis. Comparative data of groups depending on the outcome are presented in Table 4.

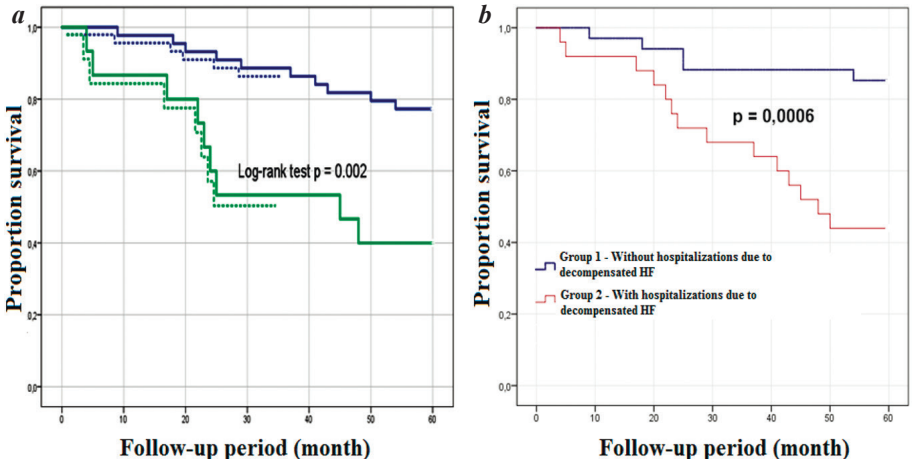

Fig. 3. Kaplan-Meier analysis of survival rates in cardiac contractility modulation patients depending on a) HF functional class (blue line - patients with HF II (NYHA), green line - patients with HF III (NYHA); b) hospitalizations due to decompensated HF during follow-up period.

A log-rank analysis was performed to determine potential factors that could influence outcomes. Age, HF etiology, fact of ICD implantation, DM type 2, and optimal drug therapy did not affect primary and secondary CE in every follow-up point. At the same time, patients with different functional classes of HF, CKD and CCI ≥ 7 points showed significant differences in the prognosis according to the log-rank test (p1 = 0.002, p2 = 0.003 and p3 = 0.036, respectively) (Fig. 3 A and Fig. 4 A, B).

Also, there was significant differences in the average lifetime between 2 groups of

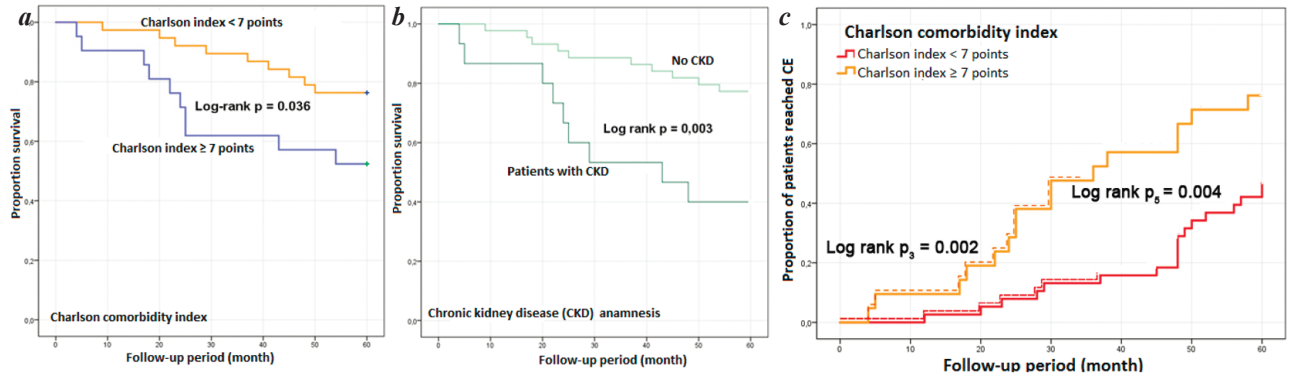

Fig. 4. Impact of comorbidity burden on clinical outcomes of HFrEF patients undergoing CCM. Kaplan-Meier survival curves depending on: a) Charlson comorbidity index; b) chronic kidney disease (CKD) anamnesis before CCM; c) 3-year (dotted lines) and 5-year survival curves for secondary combined endpoints depending on Charlson comorbidity index.

patients, depending on the fact of hospitalization due to decompensated HF during CCM (p <0.001) (Fig. 3 B).

Patients with a CCI score ≥ 7 reached secondary CE significantly faster (p3=0.002 and p5=0.004 for the three-year and five-year follow-up periods, respectively) (Fig. 4B).

DISCUSSION

This paper presents the long-term single center prospective study dedicated to analysis of survival in HFrEF patients receiving the CCM. The median event-free survival before reaching primary CE, included death or HT, was 1494 days with an annual mortality rate of 7%. It is difficult to draw a conclusion about the benefits of CCM for clinical outcomes, due to the lack of a control group in this study. Meanwhile, the three- and five-year survival rates of patients were 80% and 66%, which significantly higher than the PS, calculated by the MAGGIC and SHFM scales were. There was a significant reduction in the number of hospitalized patients due to decompensated HF treated with CCM during the entire five-year period compared to the six-month period before device implantation.

Considering the limited use of this electrophysiological treatment method throughout the world, published studies providing such long-term monitoring of patients during CCM are rare and limited to small cohorts. In a prospective study of 41 patients with HFrEF receiving CCM, the three-year survival rate was 70%. At 75 months it reached 61% that was significantly higher compared to the control group receiving drug therapy, where survival rate after 69 months was 29%. It should be noted that this study included patients with III FC (NYHA) and there were no significant differences in both mortality and hospitalizations due to HF in group of patients with LV EF < 25% [19]. Another study analyzed a cohort of 68 patients with II-III FC (NYHA) HFrEF receiving CCM and showed a significant increase in survival rate compared to the calculated by SHFM. Mean follow-up period at this study was 4.5 years [12].

This article presents unique Russian experience of long-term follow-up of patients receiving CCM by a multidisciplinary “heart team”. The severity of the clinical course of HF (FC III (NYHA) at the time of CCM implantation and frequent hospitalization due to HF decompensation) is an worsening prognostic factor, which has been previously shown in a Russian cohort of patients with HFrEF, even in the context of a multidisciplinary approach [20]. It is obvious that a personalized medical approach, early monitoring of high-risk patients at the outpatient stage, and online availability of specialists demonstrated in this study, make it possible to correct treatment in a timely manner, prevent decompensations, and determine clinical indications for a necessary high-tech treatment or hospitalization, which is partly causes lower mortality rate and better clinical results compared to calculated ones [21].

During analysis of poor prognosis predictors in studied cohort, a negative impact of the integral comorbidity index was demonstrated, along with traditional risk factors, such as HF FC, peak oxygen consumption, LV EF and CKD. It should be noted that predictive scales are usually based on randomized clinical trials results, which rarely include patients with severe comorbidity. However, comorbidity is a major problem in HF patients, which is associated with more frequent use of medical services and increased mortality rate [22]. The anamnesis of two or more chronic diseases, so-called multimorbidity, is typical for most patients with HF, regardless of LV EF and HF phenotype [23], which is confirmed by the presented data. It is important that the proportion of deaths not related to cardiovascular diseases in the present study was 17% and 26% after three and five years of follow-up.

Several authors have shown a significant increase of mortality risk in patients with HFrEF and ICD/CRT-D who have accompanying non-cardiac diseases [3–8]. Meta-analysis of 4 large randomized clinical trials, evaluated the benefits of ICD for primary prevention of SCD, showed lower efficiency of the device in group of patients with multiple comorbidities [9]. The burden of comorbidity and patient`s functional status are important components in assessing the annual prognosis and determining clinical indications for the ICD implantation in patients with HFrEF for SCD primary prevention, according to current guidelines [1]. In some articles, the impact of comorbidities on outcomes in patients with HFrEF and implanted ICD/CRT-D was assessed using the CCI [3-6]. However, there is currently no data on using this index to evaluate impact on outcomes of patients treated with cardiac modulation. At the same time, the results of the Italian RERAI (Registry of Emilia Romagna on Arrhythmia Interventions) show that patient`s age and high HF FC, in addition to a high value of CCI, are independent factors, worsening outcome of patients with HFrEF during a five-year follow-up. As in our study, in this register CCI was associated not only with survival, but also with hospitalizations frequency [6]. The presented data confirm that calculation of the Charlson index in patients with HF can be useful for risk stratification, comprehensive analysis of possible outcomes, and identification of the target population for expensive implantable devices, including CCM.

Study limitations. The small sample size and the absence of a control group contribute to the limitations of the study, including the analysis of the impact of ARNI and sodium glucose co-transporter type 2 inhibitors on composite endpoints, as well as the impact of comorbidity burden on the structure of hospitalizations in patients receiving CCM. This study did not evaluate the severity of comorbidity, as well as the quality of its therapy.

CONCLUSIONS

1. The three- and five-year survival rates of patients with HFrEF II-III FC and sinus rhythm, treated with CCM therapy was 80% and 66% and was significantly higher than the predicted survival calculated by the MAGGIC and SHFM scales.
2. Long-term cardiac contractility modulation addition to optimal medical therapy and monitoring in a multidisciplinary medical team is associated with decreased number of hospitalizations due to decompensated heart failure.
3. Our results demonstrate the negative impact of severe comorbidity on the clinical course and outcomes of HF patients with implanted CCM system, which determines the need for further research on large samples, using modern drug approaches.

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