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Солдатова Анна Михайловна, e-mail: amsoldatova@mail.ru.

Frailty and long-term survival in patients undergoing cardiac resynchronization therapy

Anna M. Soldatova[1], Tatiana N. Enina[1], Diana S. Malishevskaia[2]

[1] Tyumen Cardiology Research Center, Tomsk National Research Medical Center, Russian Academy of Sciences (Tyumen Cardiology Research Center, Tomsk NRMC), 111, Melnikaite str., Tyumen, 625026, Russian Federation

[2] International Heart Center,
6, Tverskaya str., Saint-Petersburg, 191015, Russian Federation

Abstract

Aim: To access frailty and its impact on 10-year survival in patients with implanted devices for cardiac resynchronization therapy (CRT).

Methods: 77 patients with congestive heart failure (74% men, 26% women; mean age of 58.7 ± 10.7 years) with NYHA class II–IV were enrolled. Frailty Index was calculated using 31 parameters (the ability to perform daily activities, clinical status, laboratory markers, comorbidities). Based on the frailty index patients were identified as not frail (< 0.375; *n* = 41; 53%), and frail (≥ 0.375; *n* = 36; 47%).

Results: The mean follow-up period was 49.0 ± 34.2 months. Survival at 10-year follow-up was 87.5% for non-frail patients, compared to 47.2% for frail patients (log-rank test $p < 0.001$). In univariate analysis, frailty associated with 10-year mortality (OR 7.824; 95% CI 2.495 – 24.533; p < 0.001). After adjustment for age, gender, rhythm,

NYHA class, left ventricular ejection fraction, left bundle branch block, and QRS width, frailty remained a significant prognostic factor associated with 10-year mortality (OR 9.528; 95% CI 2.720 – 33.368; p < 0.001). Also, according to logistic regression, the presence of frailty reduced the chance of superresponse (decrease of left-ventricular end -systolic volume ≥ 30%) to CRT (OR 0.278; 95% CI 0.100–0.770; *p* = 0.014).

Conclusion: Frailty is widespread in patients with heart failure and implanted devices for CRT. In these patients frailty is associated with a more than seven-fold increased risk of death during 10-year follow-up and with a lower chance of superresponse to CRT.

Keywords: cardiac resynchronization therapy, congestive heart failure, frailty, long-term mortality.

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Adherence to ethical standards: the study was conducted in accordance with the ethical standards of the Local Institutional Review Board and with the 1964 Helsinki declaration and its later amendments. The study protocol was approved by the institutional review board. All patients gave their written informed consent before the study.

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Синдром frailty и отдаленная выживаемость пациентов на фоне сердечной ресинхронизирующей терапии

А.М. Солдатова[1], Т.Н. Енина[1], Д.С. Малишевская[2]

[1] Тюменский кардиологический научный центр, филиал Федерального государственного бюджетного научного учреждения «Томский национальный

исследовательский медицинский центр Российской академии наук» (Тюменский кардиологический научный центр – филиал Томского НИМЦ),
625026, Российская Федерация, Тюмень, ул. Мельникайте, 111

[2] Общество с ограниченной ответственностью «Международный центр сердца» (ООО «МЦС»),
191015, Российская Федерация, Санкт-Петербург, ул. Тверская, 6.

Аннотация

Цель: Оценить 10-летнюю выживаемость в зависимости от наличия синдрома frailty у пациентов с хронической сердечной недостаточностью (ХСН) и имплантированными устройствами для сердечной ресинхронизирующей терапии (СРТ).

Материал и методы. В исследование были включены 77 пациентов (74% мужчин, 26% женщин, средний возраст обследуемых 58,7 ± 10,7 года) с ХСН II–IV функционального класса (ФК) по классификации NYHA. Frailty индекс был рассчитан на основании 31 показателя (анамнез, данные клинического и лабораторного обследований, результаты анкетирования на предмет выявления ограничений в привычной физической активности). В зависимости от величины индекса пациенты были разделены на 2 группы: < 0,375 (n = 41) – отсутствие синдрома frailty; ≥ 0,375 (n = 36) – пациенты с наличием синдрома frailty.

Результаты. Средний срок наблюдения составил 49,0 ± 34,2 мес. 10-летняя выживаемость пациентов первой группы составила 87,5%, пациентов второй группы – 47,2% (log rank test p < 0,001). По результатам универиантного анализа наличие синдрома frailty значимо ассоциировалось с риском смерти в течение 10 лет (ОШ 7,824; 95 доверительный интервал (ДИ) 2,495–24,533; p < 0,001). При включении в мультивариантный анализ пола, возраста, исходного ритма, ФК ХСН по NYHA, размера фракции выброса левого желудочка, блокады левой ножки

пучка Гиса, величины QRS наличие синдрома frailty оставалось значимым предиктором смертности в течение 10 лет (ОШ 9,528; 95% ДИ 2,720–33,368; $p < 0,001$). Также по результатам логистической регрессии наличие синдрома frailty значимо снижало шанс развития суперответа (снижение конечно-систолического объема левого желудочка ≥ 30%) на СРТ (ОШ 0,278; 95% ДИ 0,100–0,770; $p = 0,014$).

Заключение. Синдром frailty широко распространен среди пациентов с ХСН, имеющих показания для проведения СРТ. Наличие синдрома frailty ассоциируется с более чем 7-кратным возрастанием риска смерти от всех причин в течение 10-летнего наблюдения на фоне СРТ, а также с меньшим шансом развития суперответа на СРТ.

Ключевые слова: синдром frailty, сердечная ресинхронизирующая терапия, хроническая сердечная недостаточность, отдаленная выживаемость.

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Финансирование: никто из авторов не имеет финансовой заинтересованности в представленных материалах или методах.

Соответствие принципам этики: исследование было выполнено в соответствии со стандартами надлежащей клинической практики локального этического комитета и принципами Хельсинкской Декларации (1964). До включения в исследование у всех участников было получено письменное информированное согласие.

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Introduction

Cardiac resynchronization therapy (CRT) has a wide range of therapeutic benefits in appropriately selected patients with congestive heart failure (CHF), while the appropriate selection remains one of the main issues of CRT use. In clinical trials, CRT improves symptoms, quality of life and reduces mortality in patients with NYHA functional class II–IV CHF, left ventricular ejection fraction (LVEF) < 35%, QRS duration ≥ 150 ms and left bundle branch block (LBBB) [1, 2]. Apart from the current CRT indication criteria, patients' functional status and co-morbidities significantly affect cardiac prognosis and CRT efficacy [3, 4]. The effect of CRT can be influenced by multiple factors and, thus, estimating risk on an individual basis is very difficult, although it is critically important considering the coast and potential complications of the procedure.

Currently there is no standard definition of frailty. Potentially it can be defined as a reduced physiologic reserve to cope with minor stressors leading to impaired functional status. The presence of frailty is associated with worse survival in patients with heart failure [5]. In patients with indications for CRT it can be associated with its lower efficacy and reduced positive effects.

The aim of the study was to access the prevalence of frailty and its impact on long-term prognosis in patients with CHF and implanted devices for CRT.

Material and Methods

Patient selection

All consecutive patients undergoing CRT implantation in Tyumen cardiology Research Center from June 2012 through May 2018 who completed the pre-implantation questionnaire addressing limitations of activities of daily living were included. At baseline, in 1, 3 and every 6 months we performed clinical examination, electrocardiography, echocardiography, laboratory tests. Standard echocardiography was

performed using a commercially available system Philips IE 33. All patients received therapy in accordance with the current guidelines [2]. The device implantation was effective in all patients and occurred without complications.

Frailty definition

Frailty index (FI) was assessed using the Rockwood deficit index which has been previously validated in patients with cardiovascular diseases [6]. It is based on 31 items derived from patient's clinical status, comorbidities, information about the ability to perform daily activities, and laboratory markers. The first fourteen items (ability to perform activities of daily living) were collected from the routine pre-visit patient questionnaire obtained prior to CRT implantation. The remaining 17 parameters required to calculate the FI were abstracted from the medical record. Patients were excluded if more than 2 parameters for FI assessment were missing. To calculate the FI, the sum of points was divided by the number of parameters. If 2 or less items were missing the denominator adjusted accordingly. Based on the median of FI value patients were identified as not frail (< 0.375; $n = 41$; 53%), and frail (≥ 0.375; $n = 36$; 47%).

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages and differences between groups were evaluated using the Chi-square test. In case of normal distribution continuous variables were reported as mean ± standard deviation and differences between groups were assessed using Student's *t*-test, non-normal variables were reported as median and interquartile range and differences between groups were assessed by Mann Whitney *U* test. The association between frailty and mortality was examined using the Kaplan Meier method with censoring at death or last follow-up. Overall group differences in survival were evaluated using log-rank tests. Cox proportional hazards modeling was used to evaluate the associations of frailty and

mortality with adjusting for potential confounders. Since hypertension, diabetes, renal function, anemia, and history of myocardial infarction, were included in the FI, these variables were not considered separately in the adjusted model. Logistic regression was used to evaluate the association of frailty and superresponse to CRT. $p < 0.05$ was considered to be significant.

Results

A total of 77 patients (74% men, 26% women; mean age of 58.7 ± 10.7 years) were included. All CRT implantations were performed de novo. Ischemic cardiomyopathy was the underlying etiology of CHF in 66.2 % of patients. LBBB was present in 59.7 % of patients. Clinical characteristics of the study participants are shown in Table 1.

Table 1. Clinical characteristics of the study participants

Таблица 1. Клиническая характеристика пациентов, включенных в исследование

Parameter Параметр	Not frail Без синдрома frailty, *n* = 41	Frail С наличием синдрома frailty, *n* = 36	*p*
Male, *n* (%) Мужской пол, *n* (%)	27 (65.9)	30 (83.3)	0.081
Age, years Возраст, лет	56.8 ± 10.9	60.9 ± 10.2	0.092
Body mass index, kg/m^2 Индекс массы тела, кг/м^2	30.0 [25.5; 34.3]	28,6 [24.7; 37.2]	0.967
QRS ≥ 150 ms, *n* (%) QRS ≥ 150 мс, *n* (%)	26 (63.4)	21 (58.3)	0.648
CAD, *n* (%) ИБС, *n* (%)	22 (53.7)	29 (80.6)	0.013

Myocardial infarction, *n* (%) Инфаркт миокарда в анамнезе, *n* (%)	8 (19.5)	22 (61.1)	< 0.001
Diabetes, *n* (%) Сахарный диабет, *n* (%)	6 (14.6)	9 (25.0)	0.252
LBBB, *n* (%) БЛНПГ, *n* (%)	24 (58.5)	22 (61.1)	0.818
NYHA III/IV, *n* (%) ФК по NYHA, *n* (%)	16 (39.0)	16 (44.4)	0.630
Atrial fibrillation, *n* (%) Фибрилляция предсердий, *n* (%)	12 (29.3)	15 (41.7)	0.255
Left ventricular end-systolic volume, ml Конечно-систолический объем левого желудочка, мл	140.0 [117.0; 184.9]	169.9 [153.1; 220.9]	0.003
Left ventricular end-diastolic volume, ml Конечно-диастолический объем левого желудочка, мл	209.0 [180.0; 264.0]	239.0 [216.0; 307.0]	0.005
LVEF, % ФВЛЖ, %	33.0 [29.0; 35.5]	31.0 [27.5; 32.0]	0.011

Note: CAD – coronary artery disease, NYHA – New York Heart Association, LBBB – left bundle branch block, LVEF – left ventricular ejection fraction.
Примечание: ИБС – ишемическая болезнь сердца, ФК по NYHA – функциональный класс по классификации Нью-Йоркской ассоциации сердца, БЛНПГ – блокада левой ножки пучка Гиса, ФВЛЖ – фракция выброса левого желудочка.

Frailty and outcomes

The mean follow-up period was 49.0 ± 34.2 months (maximum 165 months).

Kaplan – Meier estimated 10-year survival worsened with the presence of frailty (log rank test $p < 0.0001$, Figure 1). Survival at 10-year follow-up was 87.5% for non-frail patients, compared to 47.2% for frail (log-rank test $p < 0.001$).

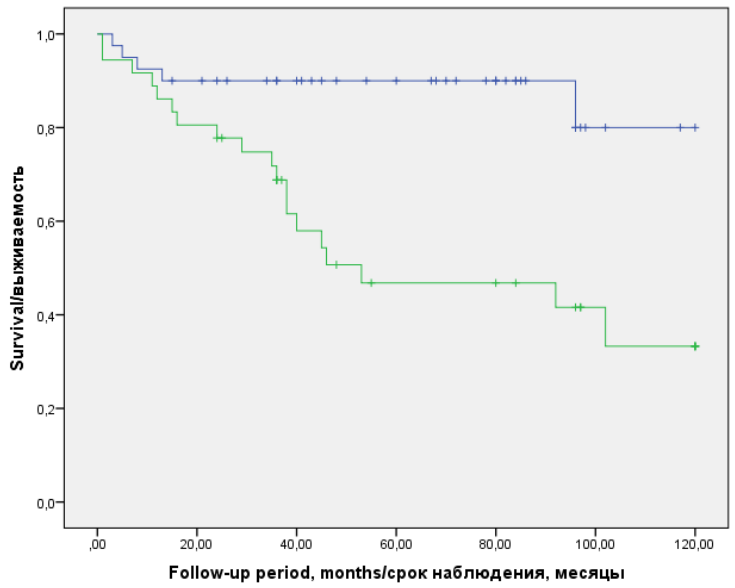

Fig. 1. Kaplan – Meier curves in groups according to the presence of frailty: blue line – non-frail (87.5%), green line – frail (47.2%); log rank test $p < 0.0001$.

Рис. 1. Выживаемость пациентов в зависимости от наличия синдрома frailty: синий – frailty index < 0,375 (87,5%); зеленый – frailty index ≥ 0,375 (47,2%); log-rank test $p < 0,001$.

According to univariate analysis, frailty was associated with 10-year mortality (OR 7.824; 95% CI 2.495–24.533; $p < 0.001$) (Table 2). Multivariate analysis adjusted for age, sex, NYHA class, rhythm, LVEF, QRS width, and presence of LBBB, frailty (HR 9.528; 95% CI 2.720–33.368; $p < 0.001$) and QRS width (OR 0.976; 95% CI 0.958–0.995; $p = 0.013$) were significantly associated with 10-year mortality.

Table 2. Univariate cox-regression analysis for 10-year mortality

Таблица 2. Унивариантая регрессия Кокса для прогнозирования риска смерти в течение 10 лет

Parameter Параметр	OR (95% CI) ОШ (95% ДИ)	Log-rank *p* value

Male gender Мужской пол	0.187 (0.039–0.890)	0.035
Age Возраст	1.007 (0.962–1.055)	0.754
NYHA ФК по NYHA	1.504 (0.734–3.082)	0.265
Sinus rhythm Синусовый ритм	2.714 (0.991–7.436)	0.052
Frailty index ≥ 0.375 Индекс frailty ≥ 0,375	7.824 (2.495–24.533)	< 0.001
QRS complex Комплекс QRS	0.981 (0.966 – 0.996)	0.015
LBBB БЛНПГ	0.529 (0.198–1.415)	0.205
LVEF ФВЛЖ	0.946 (0.859–1.043)	0.266

Note: NYHA – New York Heart Association, LBBB – left bundle branch block, LVEF – left ventricular ejection fraction, OR – odds ratio, CI – confidence interval
Примечание: ФК по NYHA – функциональный класс по классификации Нью-Йоркской ассоциации сердца, БЛНПГ – блокада левой ножки пучка Гиса, ФВЛЖ – фракция выброса левого желудочка, ОШ – отношение шансов, ДИ – доверительный интервал.

Superresponse to CRT was defined as the decrease of left-ventricular end-systolic volume ≥ 30% from baseline values. In the first group (n = 41) 43.9% of patients were identified as superresponders versus 25% of patients in the second group (n = 36) (p = 0.012). In the logistic regression the presence of frailty was associated with less chance of superresponse to CRT (OR 0.278; 95% CI 0.100 – 0.770; p = 0.014).

Discussion

The major finding of our study is that frailty occurs in more than 45% of patients undergoing CRT implantation, and is associated with increased mortality. In particular, frailty is associated with a more than a seven-fold risk of death during 10-year follow-up

(OR 7.824; 95% CI 2.495–24.533; $p < 0.001$). These data add to the growing evidence that frailty should be an essential component of the decision process when undertaking procedures intended to improve mortality in patients with heart failure. Additionally, the presence of frailty significantly decreased the chance of superresponse to CRT (OR 0.278; 95% CI 0.100–0.770; $p = 0.014$).

CRT indications were based on the results of large clinical trials, which demonstrated the best effect of CRT in patients with wide QRS and LBBB morphology of the QRS, however, most of trials excluded patients with significant co-morbidities [7, 8]. «Presence of any disease, other than the main cardiac disease, associated with a reduced chance of survival, appearance of cancer, uremia (BUN > 70 mg/dl or creatinine > 3.0 mg/dl), liver failure, etc…», was a part of MADIT-CRT protocol exclusion criteria [8]. In real clinical practice, the level of co-morbidities in patients with CHF is very high, and it can play an incremental role in the prognosis even in patients with "classical" indications to CRT. Diabetes and renal dysfunction are widely distributed important comorbidities known as independent factors associated with high risk of mortality in CHF patients [3, 4]. In real clinical practice more than 80% of CHF patients who receive CRT have at least three comorbid conditions [9, 10]. Few previous studies have addressed frailty among CRT patients, and results are mixed due to small numbers and variable scales, which impacts ability to compare [11, 12]. In the study of Dominguez-Rodriguez frailty was recognized in 28%, however, frailty index did not include co-morbidity and authors mentioned that non-frail patients presented higher rates of arterial hypertension and diabetes mellitus, and there were no significant differences in the groups regarding chronic obstructive pulmonary disease and chronic renal failure. Additionally this study included patients only with non-ischemic etiology of CHF [13]. In other studies distribution of Frailty defined by Tilburg Frailty Indicator questionnaire or Canadian Study of Health and Aging Clinical Frailty Scale in patients eligible for CRT was found in a range of 60–81% [14, 15]. While some identified an increased risk of CHF decompensation or increased risk of hospitalization, data on

mortality was inconclusive. M. Kubala et al. defined frailty in 61% of CRT patients by ONCODAGE questionnaire (G8), which was primary validated for oncology patients. In 9 month follow-up frailty was associated with a higher cumulative probability of hospitalization and of all-cause death [16]. In the study of A. Mlynarska et al. frailty defined by Tilburg Frailty Indicator was recognized in 75.64% patients. The mortality did not differ among patients who were diagnosed with frailty syndrome compared to robust patients; however, in the multivariable regression model frailty was associated with an increased risk for decompensation [15].

We did not evaluate the effect of CRT on CHF symptoms in frail vs non-frail patients, while patients may expect CRT to reduce CHF symptoms or decrease frequency of hospitalization without the expectation of improved survival. However, CRT-related complication rates are increasing as patients with more co-morbidities undergo CRT, and it is important to correlate symptom reduction with the risk of the procedure itself, as risks may be associated with increased mortality. It remains unclear if frailty is modifiable or not, especially in patients with severe life-threatening CHF. Our results argue for further study to determine if prospective assessment of frailty is a better predictor of poor outcomes of this.

We do not ask to refuse CRT in frail patients, but we note that the decision should be made on a case-by-case basis and goals should be clearly defined to meet patient expectations, especially in those of high risk of reduced life expectancy due to infirmity, or other concomitant diseases. Current guidelines recommend the need for collaborative decision making when implanting a cardioverter-defibrillator for primary prevention, and such recommendations should be extended to CRT. Many patients with late-stage CHF have not completed an advanced directive and most conversations with their physicians do not address their wishes for life-prolonging technologies. Incorporating frailty into the pre-procedural discussion for CRT can allow providers to have more successful and informed conversations.

Conclusions

Frailty is common in patients with CHF undergoing CRT. Despite the proven positive effect of CRT in reducing symptoms and reducing mortality, the presence of frailty is associated with more than a seven-fold increase in the risk of death during a 10-year follow-up. Frailty assessment should be included into shared decision-making pre implantation of CRT devices, and patients should be informed of the goals and expectations.

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Information on author contributions

Soldatova A.M. – concept and design development, data analysis and interpretation, preparation of the manuscript for publication, verification of critical intellectual content, and final approval of the manuscript for publication.

Enina T.N. – data collection and analysis, verification of critical intellectual content, and final approval of the manuscript for publication.

Malishevskaia D.S. – data analysis and interpretation, statistical analysis, preparation of the manuscript for publication.

All authors have agreed to be responsible for all aspects of the work.

Информация о вкладе авторов

Солдатова А.М. – разработка концепции и дизайна, анализ и интерпретация данных, написание статьи, проверка критически важного интеллектуального содержания и окончательное утверждении рукописи.

Енина Т.Н. – обследование пациентов и сбор материала, проверка критически важного интеллектуального содержания и окончательное утверждение рукописи.

Малишевская Д.С. – анализ и интерпретации данных, статистический анализ, написание статьи.

Все авторы дали согласие нести ответственность за все аспекты работы.

Information about the authors

Anna M. Soldatova, Dr. Sci. (Med.), Research Scientist, Laboratory of Instrumental Diagnostics of the Scientific Division of Instrumental Research Methods, Tyumen Cardiology Research Center, Tyumen Cardiology Research Center, Tomsk NRMC, Tyumen. https://orcid.org/0000-0001-5389-0973.

E-mail: amsoldatova@mail.ru.

Tatiana N. Enina, Dr. Sci. (Med.), Leading Research Scientist, Arterial Hypertension and Coronary Insufficiency Department of the Scientific Division of Clinical Cardiology, Tyumen Cardiology Research Center, Tomsk NRMC, Tyumen. https://orcid.org/0000-0002-7443-2952.

E-mail: enina@infarkta.net.

Diana S. Malishevskaia, Cardiologist, International Heart Center, Saint-Petersburg. ORCID 0000-0003-1226-7442.

E-mail: di_bogdanova@mail.ru.

Anna M. Soldatova, e-mail: amsoldatova@mail.ru.

Сведения об авторах

Солдатова Анна Михайловна, д-р мед. наук, научный сотрудник, лаборатория инструментальной диагностики научного отдела инструментальных методов исследования, Тюменский кардиологический научный центр, филиал Томского НИМЦ. https://orcid.org/0000-0001-5389-0973.

E-mail: amsoldatova@mail.ru.

Енина Татьяна Николаевна, д-р мед. наук, ведущий научный сотрудник, отделение артериальной гипертонии и коронарной недостаточности, научный отдел клинической кардиологии, Тюменский кардиологический научный центр, филиал Томского НИМЦ, Тюмень. https://orcid.org/0000-0002-7443-2952.

E-mail: enina@infarkta.net.

Малишевская Диана Сергеевна, врач кардиолог, ООО «МЦС», Санкт-Петербург. https://orcid.org/0000-0003-1226-7442.

E-mail: di_bogdanova@mail.ru.

Солдатова Анна Михайловна, e-mail: amsoldatova@mail.ru.

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