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THE ROLE OF FRAILTY IN SELECTING PATIENTS FOR HEART TRANSPLANTATION

N.N. Koloskova[1], A.O. Shevchenko[1–3]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Sechenov University, Moscow, Russian Federation

[3] Pirogov Russian National Research Medical University, Moscow, Russian Federation

The role of frailty in cardiovascular disease is becoming increasingly recognized. Up to 79% of patients with heart failure are frail. Frailty is associated with reduced quality of life and poor prognosis. This review summarizes the available literature on frailty and its key role in waitlisting patients for heart transplantation.

Keywords: heart failure, heart transplantation, frailty.

Over the past decade, patients with end-stage heart failure (HF) requiring heart transplantation (HTx) have significantly increased in number all over the world [1, 2]. In the Russian Federation, the prevalence of New York Heart Association (NYHA) classes I–IV HF is 7% of the general population (about 7.9 million people); 2.1% (2.4 million people) have end-stage HF (NYHA classes III–IV) [3]. Analysis of heart transplants performed at Shumakov National Medical Research Center of Transplantology and Artificial Organs from 1986 to 2018 have shown that the number of heart transplants performed annually is clearly rising. For example, 194 heart transplant surgeries were performed in 2018 alone [4]. Although HTx remains the only effective method of radical treatment for end-stage HF, and the criteria for inclusion in the waiting list (WL) have significantly expanded during the last decade, the possibility of performing it in high-risk patients remains a subject of active discussion among specialists in cardiothoracic transplantology [5]. So, along with the indications for inclusion in heart transplant WL, there are absolute and relative contraindications to this type of surgical treatment (Table 1).

As can be seen from the table, a number of comorbidities previously considered as absolute contraindications for HTx are now considered as relative ones, which aggravates the contingent of patients coming to transplant centers for end-stage HF. In this regard, the revision of WL inclusion criteria, taking into account a comprehensive assessment of the severity of comorbidity and its impact on the body as a whole, becomes an urgent task. The use of frailty assessment criteria as one of the factors that determine whether a patient should be included on the heart transplant WL is widely discussed [8]. English-language literature uses the term "frailty" as such a criterion, which has no clear analogue in Russian literature and is often used in the context of malaise, fatigue, cachexia and general asthenia and their influence on the early and long-term postoperative prognosis in heart recipients.

The objective of our review was to summarize the currently available data on frailty in potential heart recipients and its impact on survival after HTx.

Frailty is characterized by decreased endurance, depressed physiological functions and reduced body reserves, which in turn is accompanied by increased susceptibility to various pathogenic factors and stressors, leading to decompensation of the underlying disease and/or concomitant pathology, increased frequency of hospitalizations and worsened patient survival prognosis [6, 7].

In the guidelines of the International Society of Heart and Lung Transplantation revised and published in 2016, frailty syndrome and its importance as a prognostic marker of the outcomes of upcoming surgical treatment was included for the first time in the criteria for selection of patients for HTx [1].

In February 2018, a consensus conference was held in Phoenix (Arizona), the main purpose of which was to standardize nomenclature in the assessment of frailty, to determine the main methods of diagnosis of this syndrome, and to assess the significance of the syndrome in persons in need of solid organ transplantation [8]. Thus, the relevance of this problem is beyond doubt and requires further research in this area.

PATHOPHYSIOLOGY OF FRAILTY

Currently, there is no consensus on the pathophysiological mechanisms of frailty, which is due to its multifactorial nature. One of the factors of this syndrome is chronic inflammatory response characterized by long-term steady increase in the level of cytokines, IL-6,

Corresponding author: Nadezhda Koloskova. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (926) 651-40-64. E-mail: nkrasotka@mail.ru

tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ) and C-reactive protein (CRP). Endocrine dysfunction is important, with decreased levels of insulin-like growth factor-1 (IGF-1) and 25-hydroxy vitamin D [9].

The combination of chronic inflammatory response with endocrine dysfunction, as well as a number of other factors can cause changes in the human body that are characteristic of chronological aging processes. Such changes include apoptosis, mitochondrial dysfunction, DNA damage, stem cell depletion, immune aging and pronounced inflammatory response in reaction to the effects of stressors [10, 11]. In natural aging, the disruption of body homeostasis against the background of stressors does not entail severe consequences and is easily restored by the body's own physiological reserves. On the contrary, disruption of homeostasis in frailty syndrome is of an unregulated nature, which is manifested by severe functional abnormalities in the body in response to minor stressors and its inability to quickly restore its normal physiological state.

A peculiarity of frailty is that it can have a negative impact on several organs and systems of the patient's body at once, including the central nervous system, immune, endocrine and musculoskeletal systems. The central nervous system is affected due to dystrophic changes in the brain, clinically manifested as cognitive disorders [12, 13].

Sunita R Jha et al. assessed the presence of physical frailty in 156 patients (109 men, 47 women), aged 53 ± 13 years, diagnosed with HF and left ventricular ejection fraction of 27% ± 14%. All the patients underwent physical frailty assessment using the Fried Frailty Phenotype (FFP). Cognition was assessed with the Montreal Cognitive Assessment (MoCA), and depression with the Depression in Medical Illness questionnaire. Thus, to predict long-term outcomes, the authors assessed the value of 4 composite frailty measures: physical frailty (PF ≥ 3 of 5 = frailty), "cognitive frailty" (CogF ≥ 3 of 6 = frail), "depressive frailty" (DepF ≥ 3 of 6 = frail), and "cognitive-depressive frailty" (ComF ≥ 3 of 7 = frail) in predicting outcomes.

During follow-up, 28 patients died before any surgical treatment for heart failure (ventricular assist device implantation and/or HTx). The one-year survival rate among patients with normal or mildly reduced test scores was 81% ± 5% vs 58% ± 10% ($p < 0.02$) in the frail cohorts.

Table 1

Indications and contraindications for inclusion in heart transplant waiting list

Absolute indications	1. Hemodynamic disorders against the background of heart failure: – Refractory cardiogenic shock – Documented dependence on intravenous inotropic support to maintain adequate organ perfusion 2. Peak VO_2 less than 14 mL/kg/minute with achievement of anaerobic metabolism or less than 12 mL/kg/minute with the use of β-blockers 3. Severe symptoms of ischemia that consistently limit routine activity and are not amenable to myocardial revascularization 4. Recurrent symptomatic ventricular arrhythmias refractory to all therapeutic and surgical modalities
Absolute contraindications	1. Systemic disease with life expectancy <2 years: – Active neoplasm (if preexisting, evaluation with an oncologist is necessary to stratify the risk of recurrence and establish a time to wait after remission) · – Systemic disease with multi-organ involvement (systemic lupus erythematosus, amyloidosis, sarcoidosis) – Severe chronic obstructive pulmonary disease (FEV1 <1 L · – Renal or hepatic severe dysfunction, if associated renal or liver transplant is not feasible 2. Irreversible pulmonary hypertension – Pulmonary artery systolic pressure >50 mmHg · – Transpulmonary gradient >12 mmHg – Pulmonary vascular resistance >3 Wood units despite treatment and nitric oxide challenge
Relative contraindications	1. Age >70 years (carefully selected patients may be considered) 2. Diabetes with end-organ damage (except non-proliferative retinopathy) or persistent poor glycemic control (HbA1c >7.5%) despite treatment 3. Active infection, except VAD infection. Patients with HIV, hepatitis, Chagas disease and tuberculosis can be considered under strict eligibility criteria 4. Severe peripheral arterial or cerebrovascular disease, if revascularization before HTx is not possible 5. Other serious comorbidities with poor prognosis, such as neuromuscular diseases 6. Obesity: BMI >35 kg/m^2 7. Cachexia: BMI <18 kg/m^2 8. Current tobacco, alcohol or drug abuse 9. Insufficient social support 10. Elevated panel-reactive antibody test defined as >10%

The authors showed that frail patients had a worse prognosis of survival in both the preoperative and postoperative periods [14].

Wilson et al. conducted a retrospective cohort analysis of 144 patients in need of lung transplantation and evaluated the effect of frailty on the post-transplant survival of recipients. The authors showed that pre-transplant frailty was an independent predictor of decreased survival after lung transplantation [15].

In postoperative management, heart recipients need lifelong administration of immunosuppressive drugs to prevent acute rejection and graft dysfunction. In this regard, preservation of cognitive functions in patients requiring HTx is important to ensure adequate long-term administration of life-sustaining medications [16].

Sarcopenia is another manifestation of frailty. It is caused by constantly elevated levels of inflammatory cytokines, decreased levels of anabolic hormones, micronutrient deficiencies, lack of physical activity, and disruption in the normal functioning of the central nervous and endocrine systems. Thus, disruption of homeostasis mechanisms that maintain the normal balance between muscle cell preservation and catabolism leads to loss of muscle mass and skeletal muscular dystrophy. Reduced physical activity and lack of appetite triggers a vicious cycle of further reduction in muscle mass and reduces the quantity of amino acids the body needs during stress [17]. The main associations between frailty and comorbidity are shown in Figure.

As can be seen from Figure 1, a long history of cardiovascular disease leading to subclinical failure of other organs and systems of the body, such as heart failure, also influence the development of frailty syndrome [18].

ASSESSING THE SEVERITY OF FRAILTY

The frailty assessment scale was first proposed by Linda P. Fried, and its effectiveness was confirmed in the Cardiovascular Health Study. According to the FFP scale, the presence of three or more criteria can indicate the development of the clinical phenotype of frailty syndrome (Table 2) [19, 20].

Table 2

Predictors of frailty

Criteria	Comments
Weight loss	Weight loss of >4.5 kg within the past year
Muscle loss	>20% decrease in muscle strength measured by dynamometry adjusted for age, sex, and body mass index
Fatigue	Decreased exercise tolerance
Slowness	Slow walking speed given gender and height
Low levels of physical activity	Lowest kilocalorie expenditure in the past week as measured by Minnesota Leisure Activity Scale

Muscle strength and gait speed are quantitative criteria for the FFP scale and provide a more objective assessment of physical frailty than the other three measures [21]. The presence of three or more criteria assessed with this scale indicates the presence of frailty in a patient. The FFP scale scores have been derived and used to assess disease prognosis and mortality among HF inpatients of the general patient population [22–24].

In patients with chronic heart failure, fluid retention in the body can lead to weight fluctuations and make it difficult to assess true weight loss. In this situation, decreased serum albumin levels are a more accurate marker of weight loss due to patient malnutrition.

The Frailty Index provides a more accurate quantitative assessment of the severity of the syndrome to the FFP scale. The Frailty Index is calculated using a questionnaire based on 30 to 70 different indicators, including the presence of various comorbidities, changes in laboratory values, and functional deficits [25].

Another method of assessing the presence of frailty is the Short Physical Performance Battery (SPPB), which measures a patient's physical characteristics. This test includes assessing gait speed, the number of times a chair is lifted, and holding tandem balance for a certain amount

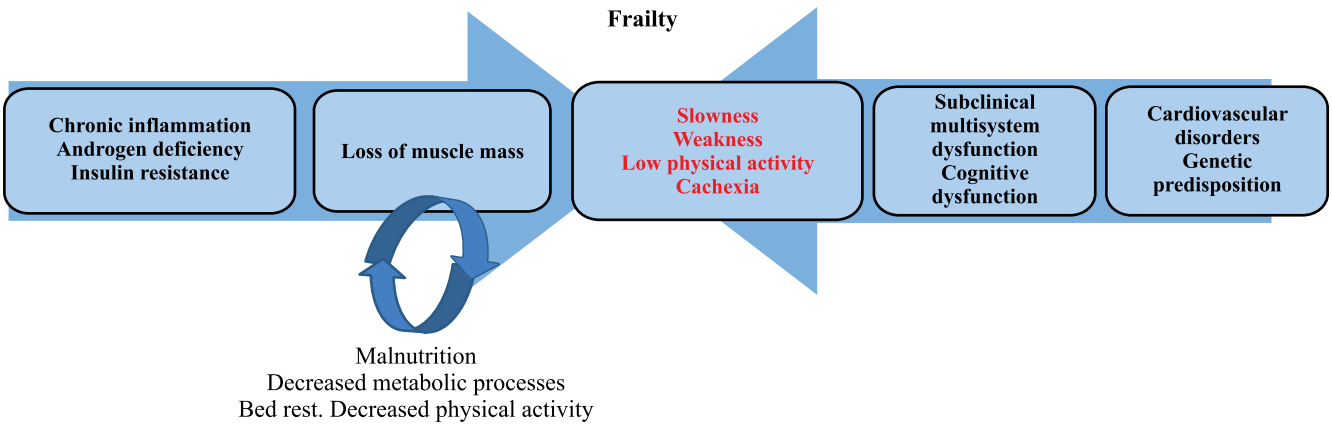

Fig. Association between frailty and comorbidity

of time. Each indicator is scored from 1 to 4; a total score of less than 5 indicates that the person is frail [26–29].

FRAILTY IN PATIENTS WITH HEART FAILURE

In patients with HF, frailty is a predictor of adverse events regardless of commonly known cardiovascular risk factors [30, 31].

In their work Volpato S. et al. showed that among patients hospitalized for decompensated HF and assessed by the SPPB scale, low score at admission was associated with longer hospital stay, and low SPPB score at discharge was associated with unfavorable prognosis of repeated hospitalizations and mortality [32]. Similar data were obtained in a FRAIL-HF study, where it was shown that frail patients hospitalized for decompensated HF had significantly worse 1-year survival prognosis than the control group [33].

In a study by Jha SR et al, frailty was diagnosed in 120 patients who needed and/or were on the heart transplant WL. The diagnosis was made on the basis of data obtained from the FFP scale, markers of heart failure severity, and the severity of cognitive impairment assessed by MoCA. The authors showed that frailty was diagnosed in one-third of the waitlisted patients, and this syndrome was associated with increased annual mortality, which was 50% in patients with this syndrome compared with 20% in the comparison group [34–36].

A group of authors led by Peter S. Macdonald conducted a retrospective analysis of 140 patients who underwent orthotopic HTx. Of the 140 recipients, 43 were frail (F) six months or more before transplantation; the remaining 97 were non-frail (NF). Post-transplant survival rates for the NF cohort at 1 and 12 months were 97% and 95% (95% CI), respectively. In contrast, post-transplant survival rates for the F cohort at the same time points were 86% and 74% ($p < 0.0008$ vs NF cohort), respectively. The authors concluded that frailty in heart recipients was independently associated with post-transplant mortality with a hazard ratio of 3.8 (95% CI: 1.4–10.5). Intensive care unit and hospital length of stay were significantly longer in the F cohort than in the NF cohort ($p < 0.05$) [37].

Today, the question about the criteria for frailty reversibility after radical surgical treatment for HF by implantation of long-term mechanical circulatory support systems or HTx remains open. How do we distinguish between reversible and irreversible frailty? What is the role of "pre-rehabilitation" to reduce the risk of adverse prognosis after cardiac surgery for patients with reversible frailty? Is implantation of long-term mechanical circulatory support systems as a "bridge to heart transplantation" in this category of patients for the purpose of rehabilitation and preparation for subsequent transplantation reasonable? [38].

Currently, there is no simple test that can accurately assess the reversibility of frailty against the background of radical correction of HF. Relatively young patients with a clinical picture of severe HF in the absence of concomitant pathology have a favorable prognosis of reversibility of functional reserves of the body against the background of surgical treatment. The age category of recipients with severe comorbid pathology contributing to frailty has the least favorable prognosis due to lack of complete recovery of the body against implantation of long-term mechanical circulatory support systems or HTx [39].

Maurer et al. evaluated the regression of weakness syndrome in 29 elderly patients (mean age 71 years) who had a left ventricular assist device (LVAD) implanted in them. The authors showed that despite the improvement in clinical condition 6 months after LVAD implantation, 53% of the patients still had clinical manifestations of frailty. So, they concluded that frailty cannot be completely reversible in this age group [40].

Data available in the literature are currently insufficient to answer the question of whether it is reasonable to include frail patients on the heart transplant WL. Frailty is associated with significantly higher postoperative mortality, but this conclusion is based on a single observation and requires further research [34].

CONCLUSION

According to the literature, frailty is an independent predictor of poor survival in end-stage HF requiring implantation of long-term mechanical circulatory support systems or heart transplantation [41, 42]. However, due to the absence of a unified algorithm for diagnosing this condition, it is not possible to make unequivocal conclusions about the severity and reversibility of this syndrome in patients with HF, which requires further research [1, 43].

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