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Cognitive Frailty and Depressive Symptoms in Heart Transplant Candidates: Rational and Study Design

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Abstract

Background: Patients with advanced heart disease have impaired cognitive abilities and higher probability of depressive symptoms. These factors contribute to negative outcomes of treatment, such as the development of comorbidities, higher hospitalization and mortality rates, poor treatment compliance and self-care, and decrease in quality of life and functionality.

Objective: To describe the prevalence and to evaluate the impact of cognitive frailty in patients in the waiting list of heart transplantation, with death while waiting transplantation and priority transplantation as clinical outcomes.

Methods: Longitudinal, prospective study evaluating cognitive frailty in 150 patients with advanced heart failure referred to transplantation in a hospital in Sao Paulo. Volunteers older than 18 years of age, hospitalized or in outpatient care, in the waiting list of transplantation will be considered eligible and will be assess within one month after being included in the waitlist. Cognitive performance will be assessed using the Montreal Cognitive Assessment and the battery of neuropsychological test Wechsler Abbreviated Scale of Intelligence (WASI). The symptoms of depression will be assessed by the Beck Depression Inventory.

Results: The study will allow to describe the prevalence of cognitive frailty and its relationship with treatment outcomes in a Brazilian population.

Conclusion: Data from this study will allow the analysis of associations between cognitive profile and severity of heart failure in patients referred to transplantation and their effects on clinical outcomes.

Keywords: Cognitive Frailty; Heart Failure; Heart Transplant.

Introduction

Frailty is understood as a state of increased vulnerability to stressors associated with loss of physiologic reserve. Frail patients, when exposed to stressors, have increased likelihood of decompensation, adverse events, functional decline and disability. In cardiac patients, frailty has also been associated with higher hospitalization rate and comorbidities and has been suggested as a strong predictor of unfavorable clinical outcomes and mortality. Compared to non-frail individuals, frail patients with heart failure

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(HF) show higher rates of mortality (16.9 vs. 4.8%) and hospitalization (20.5 vs. 13.3%).[1,2]

Patients with HF are at higher risk of cognitive frailty. The reasons are not clear, but may be associated with hemodynamic, vascular, and inflammatory issues that may occur in the process of cardiac failure.[3] Functional changes in the white and grey matter of the brain are detected in imaging tests. Decreased blood flow to the brain, reduced cardiac output, altered cerebrovascular reactivity and altered blood pressure seem to be the main mechanisms involved in the pathogenesis of cognitive impairment in HF.[4]

Cognitive impairment in HF involves several domains, including learning memory, late memory, working memory, attention, executive function and psychomotor speed. Cognitive changes affect self-care ability of patients, i.e., the active decision-making in dealing with the incident disease, promoting health maintenance and making behavioral changes towards a specific treatment. In practical terms, these changes can cause relevant difficulties in the management of cardiac patients, especially regarding the

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understanding of disease, compliance to instructions and drug therapy.[4,5]

Cognitive and mood changes in frail patients with HF have been shown to play a key role in disease progression, disability conditions and death. Many studies have recognized frailty as a multisystem measure that includes not only physical damages, but also psychosocial and cognitive problems. Therefore, identification and management of these conditions are important clinical challenges nowadays.[1,4-6]

Objective

The present study aims to evaluate the impact of cognitive impairment in patients in the waiting list of heart transplantation, with death while waiting transplantation and priority transplantation as primary clinical outcomes.

Method

Study design and population

Adult patients (older than 18 years), with diagnosis of advanced HF, of different etiologies, in the waiting list of heart transplantation of the *Hospital do Coração do Hospital das Clínicas da Faculdade de Medicina da USP* will be invited to participate in the study within 30 days after being included in the list. Patients admitted to the wards or to the intensive care units, and outpatients in the waitlist for transplantation will be considered eligible. Patients will be given information about the study, and those who accept to participate will sign an informed consent form, according to the 466/2012 resolution, and receive a copy of the document. The research protocol was approved by the local ethics committee from *Hospital das Clínicas da Faculdade de Medicina da USP* (CAAE 97526818.4.0000.0068).

Patient assessment will be preferably performed at the same visit. The three assessment instruments will be administered on the same day, except for patients with complications or institutional requirements for temporary interruption of the study. Eventual administration of the instruments on separate days will not affect the results. The battery of neuropsychological tests predicts the interruption of the tasks after a sequence of consecutive errors, which reduces the likelihood of aversion to the task or excess exposure to frustration or distress in case of poor performance. All patients will also be assessed for physical frailty according to the Fried criteria.[7]

A brief sociodemographic interview will be administered, including data on marital status, religion, self-reported race, monthly income, occupation and work activity, diagnosis awareness, psychiatric history, life habits and lifestyle. Clinical data of patients will be collected in the electronic chart and the database will be constructed using the REDCap software.

Inclusion criteria

– patients aged older than 18 years of both sexes;
– patients with diagnosis of heart failure of different etiologies, in the transplant waiting list at the Heart Institute.

Exclusion criteria

– patients with medical conditions that prevent the administration of assessment tools for cognition and/or depression (sleepiness, depressed conscious level, delirium or mental confusion, among others) or the performance of tasks involved in the assessment.
– Incomplete assessment protocol, due to clinical decompensation or refusal to continue participation.

Materials

Cognitive performance will be assessed using the Montreal Cognitive Assessment (MoCA) and the Wechsler Abbreviated Scale of Intelligence (WASI). The MoCA is a cognitive screening test that has been shown to be a practical and effective tool in the distinction of performance between adults with normal cognition and adults with decreased cognition. The battery of tests evaluates eight cognitive domains, with a maximum score of 30 points (Table 1).[8]

WASI is a quick measure of intelligence, individually administered to people aged 6-89 years. The instrument provides information about total intelligence quotient (Total IQ), executive IQ (eIQ) and verbal IQ (vIQ) using four subtests: (vocabulary, block design, similarities, and matrix reasoning) that evaluate several cognitive aspects, including verbal comprehension, visual information processing, spatial and non-verbal reasoning, and fluid and crystallized intelligence. The time of administration of the WASI varies from 30 to 60 minutes, according to patient performance. The scale can also

Table 1 – Structure of the Montreal Cognitive Assessment (MoCA)

Cognitive Domain	Task	Points
Executive functions	Trail Making Test (adapted)	1 point
	Phonemic verbal fluency	1 point
	Verbal abstraction	1 point
Visuospatial ability	Clock drawing	3 points
	Copy two-dimensional figure (cube)	1 point
Memory	Name recall	5 points
Attention and work memory	Recall of digits (forward order)	1 point
	Recall of digits (backward order)	1 point
	Sustained attention (target detection)	1 point
	Serial 7 subtraction	3 points
Language	Name 3 unfamiliar animals	3 points
	Repeat 2 syntactically complex sentences	2 points
	Phonemic verbal fluency	
Orientation	Temporal	4 points
	Spatial	2 points

In the Brazilian population, for adults with 12 years of schooling, the cutoff point is 12 years. Then, scores ≤ 26 points will be classified as frailty.

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measure TotalIQ using only two subtests (vocabulary and matrix reasoning) within 15 minutes. This battery, derived from and similar to the Wechsler family, was created to meet the need of a quick and reliable measure of intelligence in the clinical and research contexts. The test was normalized and validated to the Brazilian population in the end of 2014.[3,9,10]

Tables 1 and 2 describe the structure of the tests, the cognitive functions assessed, and the frailty criteria used in the study.

The Beck Depression Inventory (BDI) will be used to evaluate depression. The BDI is a self-report measure consisting of 21 items, aimed at measuring the presence and the severity of depressive symptoms. The instrument must be applied by a psychologist and can be used in adolescents (>13 years) and adults. The time for administration is approximately 10 minutes, but there is no maximum time to complete the test. The patient will answer items that evaluate feelings of sadness, pessimism, hopelessness, unhappiness, guilt, punishment sensitivity, self-disgust, self-blame, suicidal ideation, crisis of crying, irritability, social withdrawal, distortion of body image, work inhibition, fatigue, somatic concern, and changes in sleep, appetite, body weight and libido. Results < 13 points indicate absence of depressive symptoms; 14-19 points indicate mild depression; 20-28 points moderate depression, and 29-63 points severe depression.

Table 2 – Structure of the Wechsler Abbreviated Scale of Intelligence WASI

Task	Area	Domains analyzed
Cubes	Execution	Visuospatial organization and processing ability
		Speed of perception and organization
		Problem solving
Matrix reasoning	Execution	Fluid ability and perception organization
		Planning and prediction ability
		Visual and perceptual-motor coordination
		Attention
Vocabulary	Verbal	Lexical competencies
		Linguistic entrenchment
		Expression of thought
Similarities	Verbal	Logical thought and abstraction Formation of concepts and categories Ability to integrate and synthesize concepts Mental flexibility Immediate memory
Similarities	Verbal	Logical thought and abstraction
		Formation of concepts and categories
		Ability to integrate and synthesize concepts
		Mental flexibility
		Immediate memory

Scores of 90-110 are classified within the population mean; therefore, scores ≤ 90 will be classified as frailty.

Clinical outcomes

Primary:
- death while waiting transplantation and priority transplantation;

Secondary:
- death while waiting transplantation
- correlation of cognitive frailty with physical frailty

Statistical analysis and sample calculation

Continuous data of each variable will be compared to a normal curve using the Kolmogorov-Smirnov test and classified as parametric and non-parametric. Parametric data will be expressed as mean and standard deviation, and asymmetric data as median and interquartile range, lower quartile (25th percentile) and upper quartile (75th percentile). Data will be analyzed by parametric survival models, not necessarily considering the proportionality of risks over time.

For sample size calculation, we considered the primary endpoint of the study, and a proportion between frail and non-frail patients of 4:1. A rate of events of 30% within six months was adopted to achieve a statistical power of 80%, an alpha error of 0.05 and to detect a two-fold increase in the risk of the primary endpoint in six months. Thus, the estimated sample was 150 patients. To evaluate the relationship between cognitive frailty and death while on waitlist for heart transplantation, we will use the subdistribution hazard model by Fine and Gray, considering transplantation as the competing event.

Study limitations

This was a single-center study conducted in a quaternary referral hospital, which may cause selection or ascertainment bias. In addition, in our institution, most transplantations have been conducted in patients who have top priority in receiving heart transplants, which indicates higher severity of the study population. Finally, socioeconomic and cultural status of the Brazilian population differs from that of other countries, which may affect the external validation of the study.

Conclusion

The international literature indicates that there is a direct relationship between cognitive frailty and worse outcomes of heart transplantation. There are few data on this theme in Brazil and for this reason, we believe it is important to assess and to describe how this condition affects patient survival. The study will allow to evaluate the relationship between cognitive frailty and death while on waitlist in a quaternary hospital in Sao Paulo, Brazil.

Author Contributions

Conception and design of the research: Oliveira FM, Ikeda ET, Bacal F, Marcondes-Braga FG, Mangini S; Acquisition of data: Oliveira FM, Ikeda ET; Analysis and interpretation of the data: Oliveira FM, Seguro LFBC, Avila MS, Campos IW, Marcondes-

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Braga FG, Mangini S; Statistical analysis: Fernandes-Silva MM, Marcondes-Braga FG; Writing of the manuscript: Oliveira FM, Marcondes-Braga FG; Critical revision of the manuscript for intellectual content: Seguro LFBC, Avila MS, Campos IW, Marcondes-Braga FG, Mangini S, Santos MVB, Feltrim MIZ, Lage SHG, Bocchi EA, Issa VS, Gaiotto FA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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