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The frailty syndrome and mortality among very old patients with symptomatic severe aortic stenosis under different treatments☆

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ABSTRACT

Background: The role of frailty as a prognostic factor in non-selected patients with symptomatic severe aortic stenosis (SAS) is still uncertain. This study aims to examine the association between the frailty syndrome and mortality among very old patients with symptomatic SAS, and to assess whether the association varies with the type of SAS treatment.

Methods and results: Prospective study of 606 patients aged ≥75 years with symptomatic SAS, recruited from February 2010 to January 2015, who were followed up through June 2015. At baseline, frailty was defined as having at least three of the following five criteria: muscle weakness, slow gait speed, low physical activity, exhaustion, and unintentional weight loss. Statistical analyses were performed with multivariate Cox regression. At baseline, 49.3% patients were frail. During a mean follow-up of 98 weeks, 35.3% of patients died. The hazard ratio (95% confidence interval) of mortality among frail versus non-frail patients was 1.83 (1.33–2.51). The corresponding results were 1.58 (1.09–2.28) among patients under medical treatment, 3.06 (1.25–7.50) in those with transcatheter aortic valve replacement, and 1.97 (0.83–4.67) in those with surgical aortic valve replacement, p for interaction = 0.21. When the frailty criteria were considered separately, mortality was also higher among patients with slow gait speed [1.52 (1.05–2.19)] or low physical activity [1.35 (1.00–1.85)].

Conclusions: Frailty is associated with increased mortality among patients with symptomatic SAS, and this association does not vary with the type of SAS treatment. Future studies evaluating the benefits of different treatments in SAS patients should account for baseline frailty.

1. Introduction

Frailty is a geriatric syndrome characterized by increased vulnerability to even minor stressors, which results from a decline in multiple physiologic systems [1–4]. Given that the frailty syndrome predicts adverse clinical outcomes (hospitalization, institutionalization or death), frailty assessment has been recommended to guide treatment decisions in patients with SAS [5–7]. Specifically, several studies in patients undergoing cardiac surgery and transcatheter aortic valve replacement (TAVR) have shown that frailty is a risk factor for mortality, functional decline, and institutionalization [8–9]. The risk of perioperative mortality and institutionalization at discharge [8,10–12], as well as one-year mortality [13], is also increased in frail cardiac surgery patients. Moreover, frail SAS patients treated with TAVR are at higher risk of perioperative and

Abbreviations: ADL, Activities of Daily Living; CGA, Comprehensive Geriatric Assessment; CHS, Cardiovascular Health Study; IADL, Instrumental Activities of Daily Living; NYHA, New York Heart Association; MMSE, Mini-Mental State Examination; NTproBNP, N-terminal pro BNP peptide; PASE, Physical Activity Scale for the Elderly; SAS, Severe Aortic Stenosis; SAVR, Surgical Aortic Valve Replacement; STS, Society of Thoracic Surgeons; TAVR, Transcatheter Aortic Valve Replacement.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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one-year mortality [14–15], functional decline at 6 months [16], and one-year major cardiovascular and cerebral adverse events [17]. However, these studies have included selected groups of patients and have used different measures of frailty, which have sometimes combined frailty and disability. Therefore, no previous studies have specifically analyzed the role of frailty as a prognostic factor in non-selected elderly patients with SAS undergoing different types of treatments.

Although the diagnosis of frailty is usually based on the coexistence of a number of criteria [1] or the accumulations of deficits [3], it has been suggested that gait speed could be a simple measure of frailty [18–19]. This is based on the fact that slowness is a good predictor of morbidity and mortality in community-dwelling older adults [20–23], in patients with coronary heart disease [24] and in those undergoing cardiac surgery [11]; nevertheless, Green et al. did not find an association of gait speed with one-year mortality in patients with SAS under TAVR treatment [15]. Low grip strength has also been linked to worsen survival in older adults living in the community [25], but the association between strength and mortality has not yet been studied in patients with SAS. Thus, the role of gait speed, grip strength, and the other components of the frailty phenotype in the prognosis of SAS patients under different treatment modalities is still uncertain.

This study examined the association between the frailty syndrome and mortality in very old patients with symptomatic SAS; it also assessed whether the association varied with the type of SAS treatment and identified the individual frailty criteria which were associated with mortality risk.

2. Methods

2.1. Study design and participants

This study included consecutive ambulatory patients diagnosed with SAS who were recruited between February 1, 2010 and January 30, 2015 from the department of echocardiography in one hospital. We also checked with the cardiac surgery and interventional cardiology departments to ensure that all patients meeting inclusion criteria were recruited. To be included, patients had to fulfill three criteria: a) Age 75 years or older; b) Echocardiography-based criteria for SAS, such as valvular area ≤ 1 cm^2 or an indexed valvular area ≤ 0.6 cm^2/m^2. If the valvular area could not be measured, inclusion was based on the echocardiographer's written diagnosis when the medium transvalvular gradient was ≥40 mmHg or the transvalvular jet velocity was ≥4 m/s; and c) symptoms potentially attributable to SAS, such as effort dyspnea, angina, syncope, or a previous diagnosis of heart failure. Exclusion criteria were a life expectancy <6 months based on the researcher's opinion, severe cognitive impairment, being bed-bound or unable to attend follow-up visits, and previous TAVR or surgical aortic valve replacement (SAVR). Selection criteria were assessed in an SAS outpatient clinic and discussed in heart team meetings.

Study participants were prospectively followed up through June 30, 2015, to assess their vital status. Follow-up was performed at the periodic clinical outpatient visits and also by reviewing the medical charts or by telephone contact with relatives.

Informed written consent was given by study participants, and the study protocol was approved by the local institutional review board. The study was registered in clinical trials.gov (NCT02745314).

2.2. Study variables

We recorded sociodemographic and biomedical variables as well as the results of a comprehensive geriatric assessment (CGA). Sociodemographic data included age, sex and educational level. Among the biomedical variables, we registered: a) Time from SAS diagnosis to treatment; b) Comorbidity, including the Charlson index as a summary indicator [26]; c) Society of Thoracic Surgeons (STS) and logistic EuroSCORE surgical risk scores; d) Echocardiographic data: left ventricle ejection fraction, aortic valve area, medium aortic transvalvular gradient; e) Symptom-based data: New York Heart Association (NYHA) functional class, Canadian Cardiovascular Society functional class for angina, syncope; f) Anthropometric variables: height, weight, body mass index and body surface; g) Laboratory determinations: N-terminal pro BNP peptide (NTproBNP) and the glomerular filtration rate, as estimated with the Modified Diet in Renal Disease formula; renal failure was defined as glomerular filtration rate < 60 mL/min, or serum creatinine >1.2 mg/dL in a steady state, and h) SAS treatment: medical, TAVR or SAVR. When SAVR was not performed, we registered up to two reasons from the following list: a) patient refusal despite the recommendation of SAVR treatment; b) severe comorbidity which, in the surgeon's opinion, led to unacceptably high surgical risk or limited effectiveness of surgery; c) extremely advanced age (94 years or older); d) severe frailty in the surgeon's opinion, and based on either a very slow gait (gait speed <0.15 m/s or unable to perform a walk test), severe weakness (grip strength <5 kg or unable to perform a strength test), or exhaustion; however, as explained below, these criteria were not used to define frailty in this analysis; e) high score on the STS or EuroSCORE, f) technical reasons; g) severe disability or rapid functional decline; h) symptoms not limiting activities of daily living; and i) death before SAVR.

We also registered the following variables from a CGA: a) Cognitive function as per the Spanish adaptation of the Mini-Mental State Examination (MMSE) [27]; b) Depression, with the 15-item Yesavage Geriatric Depression Scale [28]; c) Limitations in activities of daily living (ADL) based on the Katz index [29], and in instrumental activities of daily living (IADL) with the Lawton-Brody index [30]; d) Mobility limitation based on the following scale: 1, no walking limitation; 2, use of a walking cane or stick; 3, use of a Zimmer frame or needing help from one person; and 4, wheelchair-bound or needing help from two people for ambulation; e) Health-related quality of life, assessed with the EuroQol-5D questionnaire [31] and the Minnesota Living with Heart Failure Questionnaire [32]; and f) Frailty, assessed with the phenotypic criteria proposed by Fried et al. in the Cardiovascular Health Study (CHS) (Table 1) [1]: 1) Low grip strength; 2) Slowness; 3) Low physical activity, as assessed with the Physical Activity Scale for the Elderly (PASE) questionnaire [33]; 4) Exhaustion, based on the Centre for Epidemiologic Studies Depression Scale [34]; and 5) Unintentional weight loss. Individuals were classified as frail when they had three or more of the above criteria, as prefrail when having one or two, and as robust when no one was present. For this analysis, robust and prefrail patients were grouped as non-frail.

The study end-point was all-cause mortality during the follow-up, which ended on July 31, 2015.

2.3. Statistical analysis

From the 609 patients participating in the study, one was excluded because of missing data on frailty and two because they were lost to follow-up. Therefore, the analyses were performed with 606 patients.

Differences in sociodemographic, biomedical and CGA variables across groups of frailty were tested with a chi-square test for categorical variables, and Student's t-test for continuous variables. The differences between the three groups of treatment were tested with the ANOVA test.

The association between baseline variables and subsequent mortality was summarized with hazard ratios (HR) and their 95% confidence interval (CI) obtained from Cox regression. The frailty syndrome and the variables associated with mortality ($P < 0.10$) on univariate analysis were selected for a multivariate analysis, where a backward stepwise procedure was used to identify variables independently associated with mortality. To assess if the association between frailty and mortality varied with the SAS treatment, we stratified analyses by treatment and used interaction terms defined as the product of frailty by categories of SAS treatment. Next, a p-value for interaction was calculated based on a likelihood ratio test which compared models with and without interaction