Prevalence, Characteristics, and Impact of Frailty in Patients with Functional Tricuspid Regurgitation

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Summary

Little is known as regards frailty in patients with functional tricuspid regurgitation (FTR). Thus, in this study, we aimed to investigate the prevalence, characteristics, and impact of frailty on patients with severe FTR.

This prospective study included 110 consecutive patients with severe FTR who were assessed via transthoracic echocardiography at an outpatient clinic. Patients were dichotomized using short physical performance battery (SPPB). To better understand the whole picture of frailty in patients with FTR, other frailty scales were also assessed (frailty checklist, clinical frailty scale, gait speed, and Columbia frailty scale). The primary endpoint was the combination of all-cause mortality and heart failure hospitalization.

According to each definition of frailty, 28%-46% were identified to be frail. Those with SPPB score of < 9 were older, had greater New York Heart Association (NYHA) functional classification, and had lower albumin level and estimated glomerular filtration rate compared with those with SPPB score of ≥ 9. They also have smaller tricuspid valve coaptation depth and worse right ventricular fractional area change (RV-FAC) than those with SPPB score of ≥ 9 despite having similar TR severity. The primary endpoint at 1 year was noted in 31% of patients. The SPPB score has excellent discriminatory performance for predicting the primary endpoint (area under the curve 0.82, 95% confidence interval [CI] 0.76-0.91) in receiver operating characteristic analysis and was independently associated with the primary endpoint after adjustment in multivariate analysis (adjusted hazard ratio 0.81, 95% CI, 0.73-0.90; \(P < 0.001\)).

Frailty has been widely prevalent in the elderly patient population with FTR; in fact, it has been determined to be strong parameter for poor outcomes.

Key words: All-cause mortality

Frailty has become one of the major themes in cardiovascular diseases, particularly in patients with heart failure. It has been associated with an increased risk of mortality and re-hospitalization, which can be attributed to the aging population and the increasingly complex nature of this disease.\(^1\) Functional tricuspid regurgitation (FTR) may occur as an anatomical consequence of tricuspid annular dilatation or leaflet tethering in elderly individuals who have chronic atrial fibrillation or right ventricular (RV) remodeling caused by pressure/volume overload due to left heart diseases.\(^3\) Although significant FTR may be asymptomatic for an extended period, it may result in progressive RV dysfunction, heart failure, and increased mortality risk.\(^4,9\) According to a large database in the United States, tricuspid surgery is often linked with high morbidity and mortality because of the variable degrees of RV dysfunction, pulmonary vascular disease, and multiple comorbidities.\(^10-14\) As transcatheter aortic and mitral valve therapies have evolved to become the standard treatments for patients with valvular diseases, multiple novel transcatheter tricuspid valve devices are also being developed.\(^15-19\) A recent propensity score-matched analysis using a large retrospective registry suggested that transcatheter tricuspid valve interventions may be associated with greater survival and reduced heart failure re-hospitalization compared with medical therapy alone.\(^19\) However, information as regards the impact of frailty in FTR remains to be scarce, and careful frailty assessment will be required particularly in patients with advanced frailty before any intervention.\(^20\) Hence, in this study, we aimed to investigate the incidence and prognostic impact of frailty among patients with severe FTR.
Methods

This prospective study has examined 110 consecutive patients presenting with severe FTR at Sakakibara Heart Institute and Sakakibara Heart Clinic between February 2017 and February 2019. All patients were at least followed up for 1 year. The exclusion criteria were as follows: age < 60 years, significant coronary and (aortic or mitral) valvular disease, primary tricuspid regurgitation, tricuspid regurgitation due to a pacemaker lead, a history of open-heart surgery or transcatheter therapies within 6 months, an indication for left-sided valve surgery, and no consent to participate. Notably, no patients in this present study were considered for surgical (or transcatheter interventional) indication by primary care physician during the present study period according to the US guidelines published in 2014.21) This study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by our institutional review board (16-069). Additionally, all patients included in this study provided informed consent for their participation in this study. Follow-up information was obtained from patients’ medical records or through telephone interviews.

The short physical performance battery (SPPB) consists of a 4-m walking velocity, time to rise from a seated position five times (sit-and-stand), and standing balance. Details have been previously reported.22) Scores were summed to obtain the SPPB score (range 0-12), with higher scores reflecting better physical function. Based on a previous study, an SPPB score < 9 was defined as frail, and the participants were stratified into two groups based on their SPPB score with the cut-off between 8 and 9 (0-8, 9-12) for a better understanding of the impact of frailty on the outcomes in patients with FTR.23) Gait speed and hand grip strength were tested, as previously mentioned.23)

In general, a gait speed of < 0.8 m/second is considered as frail. Frailty checklist consists of 25 items divided into 7 categories: physical strength, nutrition, eating, socialization, memory, mood, and lifestyle. Each category is rated on a pass/fail basis, and the sum of all indices ranges from 0 to 25, with higher scores reflecting a more frail status.24) In general, a frailty checklist score of > 6 is considered as frail, and higher score in each section suggests more advanced status in each parameter (e.g., higher score in cognitive impairment suggests patients have worse cognitive function, while a higher score in depressed mood suggests patients are in a more depressive state). The clinical frailty scale (range 1-9) was completed based on the patient’s functional status as previously described, with higher scores reflecting more frail status.25) In general, clinical frailty scale > 4 is considered as frail.25) Columbia frailty scale consists of four items with each scored 0-3 for composite score of 0-12: gait speed, grip strength, serum albumin, and disability in activity of daily living.25) In general, the score > 6 is considered as frail.

Primary endpoint was the combination of all-cause mortality and heart failure hospitalization. The secondary endpoint was all-cause mortality. As per the ACC/AHA guidelines, echocardiographic findings were analyzed by full-time academic echocardiographers. RV function was assessed using RV fractional area change (RV-FAC), tricuspid annular plane systolic excursion, and RV tissue Doppler S’ according to the ASE guidelines.

Continuous variables are expressed as the mean ± standard deviation or the median with interquartile range, whereas categorical variables are presented as number and percentage. The normality of distribution for continuous variables was tested using the Shapiro-Wilk test. To determine the influence of background parameters on the primary endpoint, variables (as shown in Table I) with P-values < 0.15 in the univariate analysis were entered into the multivariate Cox proportional hazards analysis, and the hazard ratio was adjusted using the variables. As the clinical frailty scale and the SPPB score are both frailty markers, having them in the same model was considered inappropriate. Thus, the clinical frailty scale was tested in the multivariate Cox proportional hazards model without the SPPB score in the sensitivity analysis. Receiver operating characteristic analysis was also performed using the primary and secondary endpoints at 1 year. All analyses were performed using the SPSS version 26.0 (IBM, Armonk, NY, USA).

Results

The patients’ demographics and clinical characteristics at baseline are summarized in Table I. More than half of the participants were women, with a median age of 80 years. Moreover, 24% had undergone previous cardiac surgery, and 93% had atrial fibrillation. Of the 110 patients, 28%-46% were considered frail according to each frailty definition (Figure 1). Laboratory data indicated mild anemia and moderate renal dysfunction in the group as a whole. Wide vena contracta and regurgitant area were consistent with severe FTR. In particular, patients with SPPB score of < 9 were older, had greater NYHA functional class with higher N-terminal-pro-brain-type natriuretic peptide (NT-pro-BNP) level, and had lower albumin level and estimated glomerular filtration rate compared with those with SPPB score of ≥ 9. The characteristics of frailty in patients with FTR are confirmed using the multifrailty assessment. According to the frailty index, patients with SPPB score of < 9 are more immobile and more inactive and had more cognitive impairment and more depressed mood. They have smaller tricuspid valve coaptation depth and worse RV-FAC, which suggests advanced RV dysfunction. Conversely, they had similar TR severity to those with SPPB score ≥ 9.

The primary endpoint (all-cause mortality and heart failure hospitalization) and secondary endpoint (all-cause mortality) at 1 year were observed in 31% and 13% of the patients, respectively (Figure 2). Kaplan-Meier curves for all-cause mortality, cardiovascular mortality, and heart failure hospitalization are summarized in Supplemental Figure.

After the univariate Cox proportional hazards analysis, age, New York Heart Association classification ≥ III, SPPB score, dyslipidemia, chronic lung disease, hemoglobin, estimated glomerular filtration rate, albumin level, bilirubin, NT-pro-BNP, left ventricular ejection fraction, RV-FAC, tricuspid annular plane systolic, and RV tissue
Doppler S’ were entered into the multivariate Cox proportional hazards analysis, wherein it revealed that the SPPB score was independently associated with the primary endpoint after adjustment using the variables (adjusted hazard ratio 0.81, confidence interval, 0.71–0.88; \( P < 0.001 \)) (Table II). Notably, in the sensitivity analysis, the clinical frailty scale was not independently associated with the primary endpoint (adjusted hazard ratio 1.47, confidence interval, 0.58–3.71; \( P = 0.409 \)) after adjustment in the multivariate analysis.

In the receiver operating characteristic analysis, the area under the curve of the SPPB for the primary and secondary endpoint was 0.82 (95% confidence interval, 0.72–0.91; \( P < 0.001 \)) with the best cut-off point between 8 and 9 and 0.81 (95% confidence interval, 0.69–0.93; \( P < 0.001 \)) with the best cut-off point between 6 and 7, respectively (Figure 3).
Discussion

The strength of our study lies in its prospective nature with a detailed assessment using multiple frailty tools to clarify the phenotype of frailty in this population. To the best of our knowledge, this study is the first to examine frailty in patients with severe FTR.

In this study, the patients’ background characteristics, including advanced age, a high prevalence of atrial fibrillation, renal dysfunction, and very wide vena contracta, were consistent with truly severe FTR. Although cardiac surgery in this study population with or without heart failure symptom was not indicated as per the guidelines, the rates of all-cause mortality and heart failure hospitalization at 1 year were high, which is consistent with the findings of other observational studies focused on FTR.\(^{48,26}\) If the study includes only inpatients (sicker patients), the incidence of frailty and events rates would be higher. According to our analysis, patients with an SPPB score of < 9 were older, had more severe heart failure, and might have worse right ventricular dysfunction as assessed by RV-FAC despite similar TR severity. Moreover, in terms of frailty assessment, they are weaker, more inactive, have greater scores in cognitive impairment, and have depressed mood, whereas weight loss is not different, probably because of fluid retention caused by heart failure with severe FTR. Therefore, in patients with FTR, change in body weight or body mass index may not be a good marker for frailty assessment according to the results. Notably, for patients with extreme frailty, careful decision-making will be required before starting on any less invasive transcatheter intervention.\(^{20}\)

The SPPB score had an excellent discriminatory performance for predicting poor outcomes in our study, and as demonstrated in previous studies, it was the independent predictor of poor outcomes.\(^{1,12,22,31,27}\) In contrast to the clinical frailty scale, which is not an independent predictor of outcomes in this study, the SPPB focuses more on physical frail status and encompasses the multi-item frailty tools that is similar to the original Fried scale.\(^{1,28}\) Frailty is multifactorial and should be assessed using multiple objective (rather than subjective) parameters. Furthermore, taking history about patient’ lifestyle and activity of daily living (for assessing clinical frailty scale) may not be enough in this population probably because patients with FTR are sometimes asymptomatic due to right-side...
Figure 1. Prevalence of frailty in each frailty definition. In patients with severe functional tricuspid regurgitation, 28–46% were considered frail according to each frailty definition (short physical performance battery [SPPB], frailty checklist, clinical frailty scale, gait speed, and Columbia frailty scale).

Figure 2. Bar graph stratified by short physical performance battery score. Primary endpoint (all-cause mortality and heart failure hospitalization) at 1 year was 37% in patients with short physical performance battery (SPPB) score 0–8 and 9% in patients with SPPB score 9–12, respectively ($P < 0.001$). Secondary endpoint (all-cause mortality) at 1 year was 27% in patients with SPPB score 0–8 and 6% in patients with SPPB score 9–12, respectively ($P < 0.001$).

In patients with SPPB score of < 9, RV-FAC was significantly lower than those with SPPB score of ≥ 9. The pathological association can be explained by the intimate connection between the tricuspid valve and the right ventricle. RV dysfunction occurs in the late stage of FTR, which can result in gastrointestinal congestion leading to malabsorption, malnutrition and immunological deficiencies, and subsequent chronic systemic inflammation - all of which seems to contribute to frailty. Furthermore, patients with FTR may have significant exercise intolerance due to low cardiac output syndrome, which, in turn, leads to a diminution of lean muscle mass; and they usually have cardiac and extra-cardiac comorbidities, which are significantly involved in frailty. Hence, the degree of frailty may be more advanced as RV function deteriorates in patients with FTR. In addition, RV dysfunction and concomitant frailty may result in vulnerability to stressors that also contribute to poor outcomes in patients with FTR. Thus, frailty assessment may be one of the key components for patients with FTR to determine a better timing of interventions. Interestingly, TAPSE and Doppler S’, also one of the markers of RV dysfunction, were not determined to be an independent predictor of outcomes. This can be attributed to the small population size or the insensitivity of those metrics. Nonetheless, RV dysfunction, as assessed using RV-FAC, was determined to be significantly correlated with frailty in the analysis.

This study has some important limitations. First, this study was conducted with a relatively small number of patients; nonetheless, our findings suggest an important index of frailty in this population. Second, FTR grading was defined according to the current guidelines, and an effective regurgitant orifice area was not obtained in our study because the new definition, which includes torrential and massive tricuspid regurgitation, was not employed when the study was started. However, despite the semiquantitative assessment, echocardiographic data, such as the average vena contracta of 10 mm and high mortality rate, suggest that the population includes extremely severe heart disease. Although it can affect liver function (albumin production) or appetite, both can attribute to frailty as well. Patients with severe aortic stenosis commonly have shortness of breath due to left-side heart disease, which, in turn, strongly limits their daily activity. This contributes to muscle weakness or cognitive impairment. Therefore, taking history in patients with severe aortic stenosis may be easier than in patients with FTR, for example, clinical frailty scale assessment may be less accurate in patients with FTR than those with severe aortic stenosis. Conversely, frailty checklist using 25 closed questions divided into 7 categories may be more accurate and objective than clinical frailty scale.
Frailty in FTR was widely prevalent as same as other population, and it was characterized by weakness, inactivity, cognitive impairment, and depressed mood, but not weight loss. Frailty in this population may be associated with poor RV dysfunction; thus, care should be taken for poor outcomes because of their possible synergetic effect.

Conclusions

Frailty in FTR was widely prevalent as same as other population, and it was characterized by weakness, inactivity, cognitive impairment, and depressed mood, but not weight loss. Frailty in this population may be associated with poor RV dysfunction; thus, care should be taken for poor outcomes because of their possible synergetic effect.

Disclosure

Conflicts of interest: None.

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Supplemental Files
Supplemental Figure
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