CLINICAL STUDY

Impact of Preprocedural Frailty Status in Elderly Transvenous Pacemaker Recipients

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Summary

The number of TV-PM implantations in elderly people is increasing. Although frailty syndrome is common in elderly patients, the relationship between the pre-procedural frailty status and clinical outcomes has not been fully elucidated in elderly TV-PM recipients.

This study included 103 consecutive patients over 80 years old who were newly implanted with a TV-PM (age 85.7 ± 4.2, 41.7% male). We assessed the relationship between the clinical outcome and predictive factors, especially for the pre-procedural frailty status after the TV-PM implantation. The pre-procedural frailty status was retrospectively assessed from the medical records and classified on the basis of impairments in 3 domains (walking, cognition, and activities of daily living). The primary endpoint was defined as a heart failure admission.

During the follow-up period (4.1 ± 2.3 years), 20 patients (19.4%) met the primary endpoint. Frailty syndrome was identified in 40 patients (38.8%). In univariate analysis, the LVEF (HR 0.97, 95% CI 0.96-1.00 P = 0.0492), an RV pacing burden over 40% (HR 1.58, 95% CI 1.00-2.54 P = 0.0473), and presence of a frailty status (HR 1.82, 95% CI 1.13-2.87 P = 0.0134) were found to be statistically significant predictors for the study endpoint. In multivariate analysis, having frailty syndrome was the only predictive factor for a heart failure admission (HR 1.83, 95% CI 1.12-2.93 P = 0.0157).

The presence of frailty syndrome and incidence of clinical events were high and a pre-procedural frailty status assessment was key in determining the clinical outcomes in TV-PM recipients over 80 years old.

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Key words: Frail, Cardiac implantable device, Elderly patients

Cardiac pacemaker (PM) implantations are an essential treatment for severe and symptomatic bradycardia. Over the decades, the number of PM implantations has increased, and the PM implantation rate has exceeded 400,000 every year all over the world.[1)] In Japan, since cardiac PMs were first introduced, the number of cardiac PM implantations has increased steadily and approximately 60,137 PM implantations were performed in 2017 (41,895 new device implantations and 18,242 device replacements).[2)] Because of an augmented life expectancy and the development of therapeutic options, the number of elderly people who require cardiac vascular therapy has been increasing. In particular, aging is characterized by a progressive fibrosis of the conduction system resulting in bradycardia leading to an increased demand for cardiac pacing.[3)] Although a few studies have reported the survival of elderly PM recipients, most PM trials have excluded patients over 80 years old or included only a small number of elderly patients.[4)]

Frailty syndrome is generally defined as a state of increased physiological vulnerability to stressors common among elderly adults and reflects physiological rather than chronological age. In clinical practice, we often encounter these kinds of elderly patients and it has been reported that frailty syndrome is associated with in-hospital clinical events in acute coronary syndrome patients.[5,6)] However, the clinical importance of the pre-procedural frailty status in elderly patients who require a PM implantation has not been fully elucidated. Heart failure (HF) is one of the leading causes of death and hospitalizations for elderly patients[7)] and a previous study has shown that the clinical outcomes are particularly poor in elderly patients, especially those older than 80 years.[8)] Because the clinical outcome in elderly transvenous PM (TV-PM) recipients is not fully elucidated, we investigated the clinical outcomes, especially regarding heart failure admissions, and their predictive factors after implanting a TV-PM in elderly patients. In particular, we hypothesized that a frailty scale (based on walking, cognition, and activities of daily living [ADL]) would be associated with the clinical outcomes in elderly TV-PM recipients.

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Methods

Patients and study protocol: The present study was a single center retrospective clinical trial that evaluated the clinical outcomes and their predictive factors, especially regarding the relationship to frailty status after the implantation of a TV-PM in Japanese patients over 80 years old. We enrolled 103 consecutive patients (43 males, age 85.7 ± 4.2) who received a TV-PM implantation between January 2010 and February 2017 at our institution after excluding patients with an implantable cardioverter defibrillator and those undergoing cardiac resynchronization therapy (CRT). Because biventricular pacing is effective therapy for HF patients and would influence the study endpoint (HF admission), CRT recipients were excluded.

Patients 80 years of age or more, indicated for chronic cardiac pacing according to the guidelines of the Japanese Circulation Society,[2] regardless of the manufacturer, who underwent an initial TV-PM implantation and no prior history of HF admission were enrolled. The TV-PM was implanted in a standard transvenous fashion. The pacing mode was determined by the baseline disease, that is, a dual chamber pacemaker (DDD mode) was selected for atrio-ventricular conduction disease or sick sinus syndrome, and a single chamber pacemaker (VVI mode) was selected for persistent atrial fibrillation with bradycardia or specific reasons such as the patient's general condition to shorten the procedure time. Each operator was encouraged to implant the pacing lead at the ideal sensing and pacing threshold site. The patients were monitored after the procedures for 1 week for any procedure related complications.

The present study protocol was approved by the Ethics Committee of Toho University Ohashi Medical Center (reference number: H19056) and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Because of the retrospective enrolment, written informed consent from the patients was waived, however, we excluded those patients who refused participation in the study when contacted for follow-up. The relevant information about the study is openly available to the public in accordance with the ethical guidelines for medical and health research involving human subjects.

Frailty status assessment and follow-up: We retrospectively assessed the clinical information and pre-procedural frailty status of each patient from the medical records. Although various methods of assessing the frailty have been described, we utilized the simple frailty scoring system as previously reported.[6,9] Briefly, frailty was classified on the basis of impairments in 3 domains (walking, cognition, and activities of daily living) and each domain was scored from 0 to 2 points. We calculated the score for each patient by summing across the 3 frailty variables (score ranged from 0 to 6 points) and assessed the severity (0: normal, 1-2: mild frailty, and 3-6 severe frailty). The medical records were reviewed independently, and the frailty status score was reconciled by 2 physicians.

The patients were seen in the follow-up PM clinic within 1 month after the implantation. If the PM function was satisfactory, the patients were seen every 6 months in the PM clinic. A clinical evaluation and device interrogation were carried out at each follow-up visit. The right ventricular (RV) pacing ratio was recorded as the last 6-month pacing ratio. With respect to RV pacing burden, an RV pacing threshold over 40% was assessed because of a previous replicated association with increased heart failure rates at this level in the DAVID and MOST trials.[10,11] Because the occurrence rate of advanced AVB in patients with SSS is relatively high,[12] we analyzed all patients who needed pacing regardless of the underlying disease.

The pacing QRS duration was measured by surface 12 lead ECGs at the time of PM clinic visits. Physicians were encouraged to optimize the device setting and follow the current practice guidelines for pharmacologic therapy if the patients were taking any medications depending on their clinical status. Patients who were lost to follow-up after the first clinic visit were censored at the date of the last follow-up.

Definitions and study endpoints: Procedural related complications were defined as any vascular problem, pneumothorax, pericardial effusion, or cardiac tamponade, and pocket related complications (i.e., infections or hematomas that required additional intervention) within a week after the procedure. Frailty syndrome (i.e., frail status) was defined as one or more than one point calculated by the frailty scoring system as previously described. In the present study, an HF admission was the primary study endpoint (clinical events). Since the increased RV pacing ratio related to HF admission[10,11] and it is unpredictable in preoperative procedures, predicting factors of HF hospitalization in elderly TV-PM patients in preoperative patient backgrounds were assessed. An HF admission was judged by each physician (physician discretion) including clinical symptoms of more than NYHA grade of class 2, chest X-ray findings, and blood biomarkers in the absence of other alternative diagnoses.

Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) < 60 mL/m^2. The causes of death were classified as cardiac and non-cardiac. Cardiac death was classified when no clear non-cardiac cause, such as any trauma, malignancy, infection, respiratory, or renal failure was found.

Statistical analysis: The data are presented as the mean ± SD or counts (%). Categorical data were compared with the chi-squared test or Fisher's exact test when the cell values were less than 5. Continuous data were compared using a 2-tailed unpaired *t*-test. A probability value of < 0.05 was considered statistically significant. A Cox proportional hazard model analysis was used to identify the univariate predictors of the primary composite outcomes. The selection of the variables for the univariate analysis was based on the clinical importance. The variables associated with a *P*-value of < 0.05 in the univariate analysis and that were a clinically important factor were entered into the multivariate regression analysis to find the parameters associated with the predictive factors predisposing to the endpoints. Since previous reports showed AF and age have clinical impacts on HF admission,[13,14] we selected AF and age as clinically important factors in multivariate analysis. The clinical event (heart failure admis-

Table I. Baseline Patient Characteristics in the Present Study

Variable	Total (n = 103 median value* or n (%))	Frail (n = 40 (%))	Non-frail (n = 63 (%))	P-value
Age (years)	85 (82-89)	88 (84-91)	84 (82-88)	< 0.001
Male (%)	43 (41.7)	11 (27.5)	32 (50.8)	0.0195
Diabetes	16 (15.5)	8 (20)	8 (12.7)	0.99
Hypertension	72 (69.9)	30 (75)	42 (66.7)	0.36
Atrial fibrillation	38 (36.9)	15 (37.5)	23 (36.5)	0.91
Chronic kidney disease	28 (27.2)	12 (30)	16 (25.4)	0.61
Ischemic heart disease	12 (11.7)	4 (10)	8 (12.7)	0.67
Sick sinus syndrome	41 (39.8)	18 (45)	23 (36.5)	0.47
Atrio-ventricular block	54 (52.4)	17 (42.5)	37 (58.7)	0.10
LVEF (%)	62 (57-69)	62 (53-69)	63 (58-70)	0.41
Dual chamber pacing (DDD)	89 (86.4)	30 (75)	59 (93.7)	0.0071
Procedural complication (%)	3 (2.91)	2 (5)	1 (1.59)	0.31
Pacing QRS duration (ms)	140 (109-159)	142 (112-160)	131 (104-159)	0.13
RV pacing burden 40% <	65 (63.1)	27 (67.5)	38 (60.3)	0.46
NT-proBNP (pg/mL)	1,047 (446-3,406)	2,762 (804-4,533)	860 (352-1,946)	0.39

*A median value expressed as 25th-75th percentile.

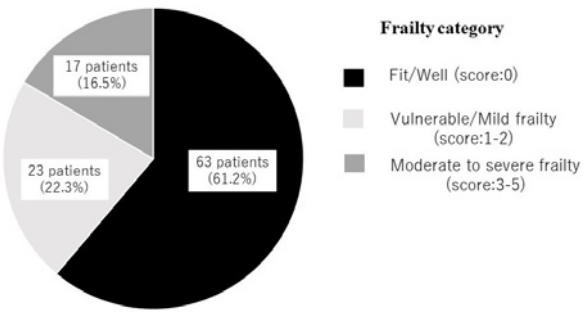

Figure 1. The frailty status distribution among the study group (n = 103).

sion) free curves were calculated by the Kaplan-Meier method, and comparisons between the frail and non-frail groups of patients were performed with the log-rank test. JMP™ 11 software (SAS Institute Inc, Cary, NC, USA) was used for all statistical analyses.

Results

The demographic clinical characteristics of the 103 TV-PM recipients are shown in Table I. The mean age of the patients at the time of the implant was 85.7 ± 4.21 years (range, 80-100 years), 43 patients (41.7%) were male, and the mean left ventricular ejection fraction (LVEF) was 65.9 ± 11.1%. The indication for a PM included atrio-ventricular block (AVB) in 54 patients (52.4%), sick sinus syndrome (SSS) in 41 (39.8%), and persistent atrial fibrillation (AF) with bradycardia in 9 (8.7%). Documented co-morbidities included diabetes in 16 patients (15.5%), hypertension in 72 (69.9%), ischemic heart disease in 12 (11.7%), chronic kidney disease in 28 (27.2%), and any type of AF in 38 (36.9%). Frailty syndrome (≥ 1 frailty score) was identified in 40 patients (38.8%) and the mean frailty score was 1.1 ± 1.7 in the entire group (range, 0 to 6). The biomarker of HF was relatively high at the time of TV-PM implantation (mean NT-proBNP 3,554 ± 688 pg/mL). As shown in Figure 1, 23 patients (22.3%) had vulnerable or mild frailty, and 17 (16.5%) had moderate to severe frailty.

According to the procedural indexing, a single chamber PM (VVI) was implanted in 14 patients (13.6%) and a dual chamber PM (DDD) in 89 (86.4%). In recipients with a VVI pacemaker, 9 patients were AF with bradycardia and 3 patients were AF with complete AV block. Two VVI recipients were intolerant to undergoing a prolonged procedure and so DDD pacemaker implantation was not performed. The right ventricular (RV) lead was placed on the RV septum in 58 patients (56.2%) and in the RV apex in the remaining patients. The devices were successfully implanted in all patients. However, 3 patients suffered from major complications (2.9%) including 1 each of cardiac tamponade, pericardial effusion, and pocket infection. All of the patients recovered after appropriate treatment and were discharged without any other complications.

Comparison of the frail and non-frail groups revealed the proportion of males was significantly lower (27.5% versus 50.8%, P = 0.0195), age at the time of the device implantation significantly older (87.6 ± 4.46 versus 84.6 ± 3.62 years old, P < 0.001), and proportion of dual chamber pacemaker implantations significantly lower (75% versus 93.7%, P = 0.0071) in the frail patient group. The underlying disease, procedural complication rate, and baseline NT-proBNP value did not statistically differ between the 2 groups (Table I).

During the follow-up period (4.1 ± 2.3 years), 20 patients (19.4%) met the primary endpoint (heart failure admission) and 29 (28.2%) died from any cause. The cause of death was cardiac death in 8 patients (6 patients with HF; 20.7%, and 2 with others) and non-cardiac death in 21 (5 patients with pneumonia; 17.2%, 5 with malignancy; 17.2%, 4 with respiratory failure; 13.8%, 2 with renal failure; 6.9%, and 5 with others). The worsening factors for HF admission included infection in 8 patients, worsening valve disease in 2 patients, ischemic heart disease in 1 patient, AF tachycardia in 1 patient, and pulmonary embolism in 1 patient. The specific etiology was un-

Table II. Univariate and Multivariate Analyses of the Predictive Factors for the Study Endpoint

Variable	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age (years)*	1.04 (0.98-1.11)	0.14	1.02 (0.96-1.08)	0.46
Male	0.95 (0.61-1.49)	0.82		
Diabetes	1.21 (0.6-2.19)	0.56		
HT	0.76 (0.48-1.23)	0.25		
AF	1.29 (0.79-2.08)	0.29	1.38 (0.82-2.25)	0.20
CKD	1.15 (0.62-2.03)	0.62		
IHD	1.14 (0.58-2.59)	0.71		
LVEF (%)**	0.97 (0.96-1.00)	0.0492	0.97 (0.96-1.00)	0.052
RV lead position (RVS)	0.68 (0.25-2.81)	0.54		
RV pacing burden 40% <	1.58 (1.00-2.54)	0.0473	1.47 (0.93-2.37)	0.10
Paced QRS duration (ms)**	1.00 (0.99-1.01)	0.48		
Frail status	1.82 (1.13-2.87)	0.0134	1.83 (1.12-2.93)	0.0157
NT-proBNP (pg/mL)**	1.00 (0.99-1.00)	0.14		

*Per one year increase in age, and **per unit increase. AF indicates atrial fibrillation; HT, hypertension; CKD, chronic kidney disease; IHD, ischemic heart disease; LVEF, left ventricular-ejection fraction; and RVS, right ventricle septum.

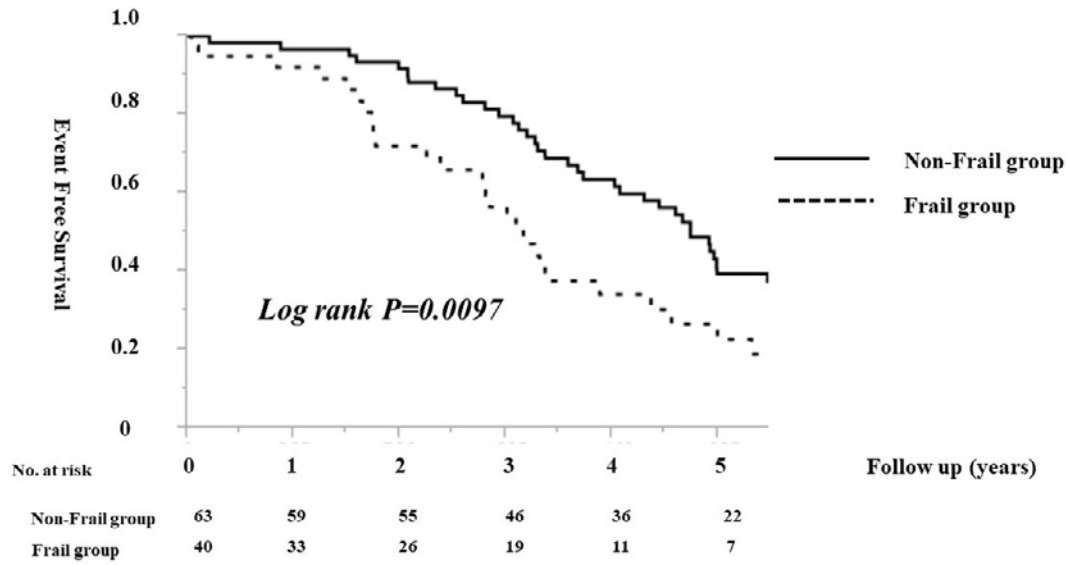

Figure 2. Kaplan-Meier analysis for HF admission in the frail group versus non-frail group. Kaplan-Meier survival curve showing the study endpoint (heart failure) for the frail versus non-frail groups. Black solid line indicates non-frail group, and black dotted line, frail group.

known in the remaining patients. With regard to the RV pacing ratio, even in SSS patients, 28 patients (68.3%) developed RV pacing burden over 40% during the follow-up period.

In the univariate analysis, the left ventricular ejection fraction (LVEF) (HR 0.97, 95% CI 0.96-1.00 P = 0.0492), an RV pacing burden over 40% (HR 1.58, 95% CI 1.00-2.54 P = 0.0473), and the presence of a frailty status (HR 1.82, 95% CI 1.13-2.87 P = 0.0134) were found to be statistically significant predictors of HF admissions among elderly TV-PM recipients. Multivariate analysis identified that only mild or severely frail patients, that is those with a frail status, were an independent predictor of the study endpoint among elderly TV-PM recipients (HR 1.83, 95% CI 1.12-2.93 P = 0.0157) (Table II). As shown in Figure 2, the Kaplan-Meier curve analysis for HF admissions exhibited a statistically significant difference between the frail and non-frail groups during the follow-up period (log rank P = 0.0097).

Discussion

To the best of our knowledge, this is the first study investigating the association between the frailty status and hospitalizations for heart failure in patients over 80 years old after the implantation of a TV-PM. The findings of the present study can be summarized as follows: 1) During the 4.1 ± 2.3 year follow-up period, the incidence of an HF admission was high (19.4%; 20 heart failure admissions) in patients over 80 years old after implantation of a TV-PM. 2) Frail syndrome was identified in 38.8% of TV-PM recipients over 80 years old. 3) The preprocedural

frailty status was key to determining heart failure admissions in TV-PM recipients over 80 years old.

The proportion of elderly patients requiring a TV-PM implantation has increased over the last decade due to increases in life expectancy. A previous survey reported that up to 80% of pacemakers are implanted in the elderly, and the average age of a pacemaker recipient was 75 ± 10 years in that study.[15] Further, Schmidt, *et al.* reported that almost one third of all patients requiring permanent pacing are aged ≥ 80 years old.[16] However, most previous reports focused on the procedure related complications or in-hospital mortality, while clinical evidence of the long-term outcome of the PM therapy in elderly patients is still limited.[17,18] A few studies have reported on the prognosis in elderly TV-PM recipients and the survival rate ranged from 16.9-24% over about a 2-year follow-up.[4,19] Consistent with those reports, our study demonstrated that the mortality rate was 28.2% over a 4-year follow-up. Of those, 27.6% were cardiac deaths and the major cause of cardiac death was HF in elderly TV-PM recipients. Another report also has shown that heart failure (HF) is one of the leading causes of death and hospitalizations for elderly patients[7] and we defined heart failure admission as the primary study endpoint in the present study.

Recently, Tayal, *et al.* reported a large epidemiological study that demonstrated the risk of HF in patients with RV pacing devices and the factors associated with an HF risk.[21] According to their report, 10.6% of the PM recipients developed HF including fatal HF during a 2-year follow-up period. They also found that male gender, prior MI, and chronic kidney disease were factors associated with an increased risk of HF in TV-PM recipients.[20] In contrast to this report, CKD (HR 1.15, 95% CI 0.62-2.03 $P = 0.62$) and IHD (HR 1.14, 95% CI 0.58-2.59 $P = 0.71$) were not predictors of HF admissions among elderly TV-PM recipients. These results might be influenced by the baseline characteristics, especially in age (median age: 77 years old[20] versus mean age: 85.7 ± 4.21 years old (present study)).

Regarding the pacing related factors, prior studies have shown that the paced QRS duration and RV pacing burden play a key role in HF admissions in TV-PM recipients. In the MOST trial, a first HF hospitalization was nearly 3-fold more likely among those with >40% RV pacing as compared to those with a pacing burden ≤ 40% during a median follow-up of 33.1 months in SSS patients with a normal LVEF and little to no HF symptoms who underwent TV-PM implantations.[11] In the present study, although we include SSS patients, 68.3% of SSS patients developed RV pacing burden over 40%. For the paced QRS duration, Lee, *et al.* reported that a post-pacemaker implant pacing QRS duration of ≥ 163 ms was the most important predictor of an HF admission.[21]

In contrast to prior studies, we did not find any significant differences suggesting that those factors were predictive factors for a heart failure admission, with the exception of RV pacing burden. This was because the present study focused on elderly patients (> 80 years) and included a smaller number of patients, and it might have led to no statistically significant differences. On the other hand, our study showed that the LVEF (HR 0.97, 95% CI 0.96-1.00 $P = 0.0492$), an RV pacing burden over 40% (HR 1.58, 95% CI 1.00-2.54 $P = 0.0473$), and the presence of a frail status (HR 1.82, 95% CI 1.13-2.87 $P = 0.0134$) were found to be statistically significant for predicting the study endpoint in univariate analysis. Further, a frail status was the only independent predictor of an HF admission among elderly TV-PM recipients (HR 1.83, 95% CI 1.12-2.93 $P = 0.0157$).

Importantly, we found that the presence of frailty syndrome was the only predictive factor for heart failure admissions in elderly TV-PM recipients. Frailty syndrome is generally defined as a state of increased physiological vulnerability to stressors common among elderly adults and reflects the physiological rather than chronological age of the patient. Frailty syndrome, whose role has been validated in many reports,[22,23] and the assessment of frailty are instrumental in refining the estimates of the risk and for guiding patients toward personalized treatment plans that will maximize their likelihood of a positive outcome. In the present study, a frail status was identified in 38.8% of the TV-PM recipients over 80 years old. Consistent with our study, a previous study documented that frailty syndrome was diagnosed in 25.1% of patients with cardiac arrhythmias, whereas a further 40% were at a high risk for frailty syndrome.[24] Because elderly TV-PM recipients have heterogenous characteristics compared to young TV-PM recipients, a frail status might play an important role in predicting the clinical outcome. Overall, our study results suggested that the presence of a frail status was high in octogenarian TV-PM recipients, and if the elderly TV-PM recipients were in a frail status, these kinds of patients had a potential risk of suffering from a poor clinical outcome, especially for heart failure admissions, as compared to non-frail status elderly patients. Therefore, we should consider another approach in these kinds of patients in our daily clinical practice.

Recently, remote monitoring systems have been introduced to improve clinical efficacy by reducing the need for conventional in-office follow-up visits. The COMPAS trial, [25] which was a randomized, multicenter, non-inferiority trial, examined the safety of long-term remote monitoring of pacemakers and showed that the long-term remote monitoring system decreased the number of ambulatory visits and enabled the early detection of important clinical and device-related adverse events. Although we did not investigate the efficacy of a remote monitoring system for octogenarian TV-PM recipients, remote monitoring systems may have a potential as a safe substitute for conventional follow-ups. Also, because it is difficult for elderly or frail patients to visit the out-patient clinic repeatedly, home monitoring systems are a useful way to assess the condition of elderly and frail TV-PM recipients. Further study, such as assessing the efficacy of remote-monitoring systems, is warranted for reducing the mortality or risk of an HF hospitalization without compromising the safety of elderly and frail TV-PM recipients.

Study limitations: This study has several limitations. First, we based our frailty assessment on the available elements (walking, congestion, and ADLs) that differed from the prior classification schemes using physical measurements. However, this scoring system was easy to use and

we believe there was a firm theoretical grounding of our method based on the Rockwood conceptualization of frailty.[9] Second, we likely underestimated the prevalence of frailty, given our reliance on the chart documentation of the elements included in our frailty score, as well as the potential for survival bias (if the patients with the greatest degree of frailty died early in-hospital without a documented frailty status). Third, our analysis was performed as a retrospective review in a small number of patients. Thus, we did not perform sample size calculation at the beginning of the study and the limited number of patients may not have allowed a precise determination of the predictive factors of the study endpoint. Fourth, because the follow-up period varied widely (mean ± SD; 4.1 ± 2.3 years), the incidences of the primary endpoints might have differed according to the follow-up period. Moreover, some patients underwent single chamber pacemaker (VVI) implantation due to the presence of frailty and this might have led to atrio-ventricular dysynchrony resulting in an increase in the number of hospitalizations. Finally, although we attempted to identify the best cut-off value of the pre-procedural frailty score for the study endpoint (for example; using Receiver Operating Characteristic curves), we could not identify an ideal cut-off value because the frailty score varied widely due to the small number of patients.

Conclusion

The presence of a frail status and the incidence of clinical events was high in octogenarian TV-PM recipients. Also, the preprocedural frailty status was significantly associated with poor clinical outcomes. The assessment of frailty status is important for risk stratification, and in order to improve the clinical outcome, another approach should be considered to manage these kinds of patients.

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Disclosure

Conflicts of interest: The authors declare that there are no conflicts of interest to report.

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