The impact of frailty in older patients with non-ischaemic cardiomyopathy after implantation of cardiac resynchronization therapy defibrillator

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Aims
Frailty status impacts the prognosis in older patients with heart disease. However, frailty status impact is unknown in patients with non-ischaemic cardiomyopathy after cardiac resynchronization therapy (CRT).

Methods and results
Functional measures of baseline frailty and clinical data were collected for all patients with non-ischaemic cardiomyopathy before CRT defibrillator (CRT-D) implantation. The level of frailty was assessed using the Fried and Walston definition. Cox proportional hazard regression models were used to examine the association between baseline frailty and decompenated heart failure (HF) at the 12 months follow-up. The cohort study consisted of 102 patients with a mean age of 73 ± 4 years, 53% of which were male patients. Twenty-nine patients (28%) were classified as frail before CRT-D implantation. Twenty-seven patients experienced decompensated HF after CRT-D implantation at the 12-month follow-up. In the non-frail group, 12 of 73 patients (16.4%) experienced episodes of decompensated HF. In contrast, 15 of 29 (55.6%) frail patients experienced higher proportions of decompensated HF (P = 0.001). Patients who were frail (hazard ratio 4.55, 95% confidence interval 1.726–12.013) were at increased risk for the decompensated HF (P for trend = 0.002) compared with those who were not frail.

Conclusion
Frailty is a strong predictor of adverse post-implantation outcome in patients with non-ischaemic cardiomyopathy undergoing CRT-D.

Keywords
Frail elderly • Cardiac resynchronization therapy-defibrillator • Non-ischaemic cardiomyopathy • Heart failure

Introduction
Clinical trials have shown that cardiac resynchronization therapy (CRT) improves symptoms, readmission, and reduces mortality among selected patients with advanced chronic heart failure (HF) and left ventricular systolic dysfunction.1 Following broad implementation of CRT, it was recognized that one-third to one-half of patients who received the therapy for HF did not improve.2 Likewise, the majority of clinical trial data upon which this recommendation is based on, comes aged <70 years—considerably younger than the ‘real-world’ population of patients with chronic HF.3 Therefore, the identification of patients likely to benefit from CRT is particularly important, because CRT defibrillator (CRT-D) implantation is expensive, invasive, and associated with important procedural risks.3

Frailty, defined as a syndrome of impaired physiologic reserve and decreased resistance to stressors,4 is captured by the core domains of wasting and malnutrition, weakness, slowness, and inactivity4 and is closely linked to the development of subsequent disability.5 No study to date has examined the relationship between baseline frailty and outcomes after CRT-D implantation in patients with non-ischaemic cardiomyopathy. Therefore, we evaluated the association between baseline frailty and clinical outcomes at 12 months follow-up after CRT-D implantation in patients with non-ischaemic cardiomyopathy.

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What’s new?

- We evaluated the association between baseline frailty and clinical outcomes at 12 months follow-up after cardiac resynchronization therapy-defibrillator implantation in patients with non-ischaemic cardiomyopathy.
- Patients who were frail are at increased risk for the decompensated heart failure compared with those who were not frail.
- Frailty may represent an important high-risk marker to help identify patients who may need closer follow-up or more aggressive rehabilitation post-implantation.
- Interventions aimed at reducing frailty in these patients could help decrease or control the already overwhelmingly high healthcare utilization and costs associated with heart failure.
- Frailty is a strong predictor of adverse post-implantation outcomes in patients with non-ischaemic cardiomyopathy undergoing cardiac resynchronization therapy-defibrillator.

Methods

Study design

A prospective cohort design was used, evaluating patients with HF undergoing CRT-D implantation. The inclusion criteria for CRT-D implantation in the study population were patients with NYHA class III and class IV HF, left ventricular ejection fraction < 30%, and QRS ≥ 120 milliseconds (left bundle branch block). The diagnosis of HF was made if symptoms were associated with objective evidence of left ventricular dysfunction on echo-cardiography. The diagnosis of ischaemic cardiomyopathy was made if systolic dysfunction was associated with a history of myocardial infarction or if there was angiographically documented coronary heart disease (> 50% stenosis in ≥ 1 coronary arteries). Late gadolinium enhancement cardiovascular magnetic resonance was also used to distinguish between ischaemic and non-ischaemic cardiomyopathy, according to Assomull et al. Patients with left ventricular dysfunction in combination with the finding of transmural or subendocardial late gadolinium uptake were classified as having ischaemic cardiomyopathy, whereas patients with left ventricular dysfunction and no gadolinium uptake, patchy uptake, or mid-wall hyperenhancement were classified as having non-ischaemic cardiomyopathy.

Frailty was assessed using the Fried and Walston definition. The five qualitative methods were unintended weight loss (≥ 10 lb in the preceding year), exhaustion, physical activity, time required to walk a length of 15 feet, and a grip strength using a Jamar handgrip dynamometer. Exhaustion was measured by the subscale of the Center of Epidemiological Studies-Depression subscale in which subjects were asked two questions: How often in the past week did they feel the following (1) I felt that everything I did was an effort, and (2) I could not get going. Subjects who answered ‘a moderate amount of time’ (3 to 4 days) or ‘most of the time’ to either of the statements were categorized as meeting the exhaustion criteria for frailty. Frailty was defined as present if the subjects had three or more core elements. Trained nurse practitioners or clinical associates conducted the interview with patients and family members concerning the Barthel index, an internationally validated measure of dependency in elderly patients.

The treating physicians and their patients were blinded to the frailty and Barthel index results so as not to influence their decision to proceed with the CRT-D implantation. A signed informed consent was obtained from each participant before enrollment in the study, in accordance with the principles stated in the Declaration of Helsinki. The protocol was reviewed and approved by the local ethics committee.

Participants

Inclusion criteria were (1) 70 years of age and older and (2) scheduled to undergo CRT-D. Exclusion criteria were (1) clinical instability, defined as decompensated HF not yet stabilized, or any acute process causing significant symptoms or abnormal vital signs; (2) patients with intermediate frailty (defined as the presence of one or two characteristics, of the five different components of the frailty syndrome); and (3) severe neuropsychiatric condition causing inability to cooperate with the study procedures.

Outcome of the study

The primary endpoints were decompensated HF admitted in the Department of Cardiology during the follow-up. Decompensated HF was defined as need for extra intravenous diuretics and elevated brain natriuretic peptide levels. A 12 month follow-up was conducted by trained research personnel. Follow-up phone calls were made when follow-up visits were not possible.

Statistical analysis

Continuous variables were reported as means and standard deviations. Frailty and non-frailty groups were compared using age, length of stay, body mass index, peak oxygen uptake, minute ventilation/carbon dioxide production slope, hemoglobin, and Charlson index and Bartel index with Mann Whitney test. The Charlson Index contains 19 categories of comorbidity and predicts the 10 year mortality for a patient who may have a range of co-morbid conditions. Each condition is assigned with a score of 1, 2, 3, or 6 depending on the risk of dying associated with this condition. Categorical variables were reported as frequencies and percentages. Proportions were compared using chi² test or Fisher’s exact test where appropriate. The effect of frailty was estimated in terms of hazard ratios and 95% confidence intervals.

Included in the Cox regression analysis are variables with a P value < 0.20 in the bivariate analysis. We constructed two partial Cox regression models to predict time to major adverse cardiovascular event (decompensated HF). The first model only includes frailty as an independent variable, the second model includes frailty, controlling for dyslipidemia, hypertension, diabetes, and minute ventilation/carbon dioxide production slope. In order to analyse the time to major adverse cardiovascular event, we censored data for the final follow-up, 365 days later. Kaplan–Meier time-to-event curves were compared with log-rank test. Data management and analysis were performed with the use of SPSS v. 17.0. All P values lower than 0.05 were considered statistically significant.

Results

The cohort study consisted of 102 patients (Figure 1) with a mean age of 73 ± 3 years; and 53% were male patients. All patients had an ejection fraction of < 30% and were in NYHA Class III-IV. Twenty-nine patients (28%) were classified as frail before CRT-D implantation. The baseline characteristics before CRT-D implantation are presented in Table 1. There were no differences in procedure-related complications between both groups. There were no significant differences between groups regarding age, gender, body mass index, obesity, hemoglobin levels, Charlson index, smoking, and length of stay in-hospital. Non-frail patients presented higher rates of arterial hypertension and diabetes mellitus. However, frail patients had
higher rates of dyslipidemia. There were no significant differences in the groups regarding comorbidity of chronic obstructive pulmonary disease and chronic renal failure. In both groups, the medical treatment at the 12 month follow-up and baseline treatment before CRT-D implantation was similar.

All enrolled patients underwent a cardiopulmonary exercise testing before CRT-D implantation. The mean peak oxygen uptake was of 13.98 $\pm$ 1.96 mLO$_2$ $\times$ kg$^{-1}$ $\times$ min$^{-1}$ and the minute ventilation/carbon dioxide production slope of 35.15 $\pm$ 3.41. There were no significant differences between groups regarding gas exchange measurements with the exception of minute ventilation/carbon dioxide production slope (Table 1). In both groups, the Barthel index of activities of daily living assessment was similar.

Twenty-seven patients experienced the decompensated HF after CRT-D implantation at the 12 month of follow-up. In the non-frail group 12 of 73 patients (16.4%) experienced episodes of decompensated HF. In contrast, a higher proportion of patients in frail group suffered from decompensated HF ($P$, 0.001). At 1 year follow-up, none of the patients enrolled in the study died.

We constructed two partial Cox regression models. The first model showed that frailty was an independent predictor of decompensated HF. The second model controlling for dyslipidemia, hypertension, diabetes, and minute ventilation/carbon dioxide production slope, showed that frailty was associated with a 4.5-fold increase in the decompensated HF after CRT-D implantation (Table 2). Hundred per cent of the cohort study was available for a follow-up study 365 days later. The Kaplan–Meier curve revealed that the cumulative rate from events in non-frail was lower than in frail ($P < 0.001$, Figure 2).

**Discussion**

The principal finding of this study is that baseline frailty is an incremental predictor of decompensated HF after CRT-D implantation in patients with non-ischaemic cardiomyopathy. There are no previous studies specifically focusing on the use of baseline frailty as a predictor of morbidity at the 12 month follow-up in patients with non-ischaemic cardiomyopathy undergoing CRT-D.

Heart failure is a clinical syndrome associated with progressive derangement of neurohormonal and metabolic pathways in addition to end-organ injury resulting from circulatory failure. Skeletal muscle oxidative capacity, capillary density, and fibre cross-sectional area are diminished in patients with advanced HF. Derangement of skeletal muscle structure and metabolic function contribute to diminished exercise tolerance and the frailty phenotype with increased morbidity and mortality. Frailty has been identified as an important prognostic marker in various patient cohorts including the elderly, subclinical cardiovascular disease, coronary artery disease, patients undergoing cardiac surgery, and in older adults who undergo transcatheter aortic valve replacement for symptomatic aortic stenosis. Furthermore, recent studies have demonstrated that pre-operative frailty is associated with worse outcomes after implantation of a left ventricular assist device as destination therapy. Although frailty assessments have been applied to patients with a variety of medical conditions, it was never used in patients with non-ischaemic cardiomyopathy undergoing CRT-D.

In this study, 28% of the patients are frail. Previously published studies on the prevalence of frailty among patients with HF have used varying definitions, which impacts our ability to compare. In general, however, the data indicate that frailty is prevalent among patients with HF.

Few studies have investigated the prognostic role of frailty in patients with HF. In a long-term study by Cacciatore et al., patients with chronic HF who were frail had substantially lower probability of surviving $>10$ years. Lupón et al. demonstrated that patients with chronic HF who were frail had a higher risk of mortality at 1 year, HF hospitalizations, and impaired quality of life. Chaudhry et al. showed that slow gait speed was the most powerful predictor of hospitalizations, conferring a 30% increase; weak grip strength was also predictive, conferring a 16% increase. In our study, the patients with
Frailty in older patients with non-ischaemic cardiomyopathy who have been implanted with a CRT-D: their baseline frailty status was independently associated with an increased risk for rehospitalization by decompensated HF at the 12 month of follow-up.

Recently have been demonstrated that the body mass index, exercise capacity, Barthel index, and number of comorbidities are positively associated with frailty. In our study, we did not find a significant association between frailty and the body mass index, Barthel index or number of comorbidities, probably due to the relatively small number of patients enrolled. However, the patients classified as frail before CRT-D implantation has poorer ventilatory efficiency with the exercise.

There are major clinical implications associated with these data. First, frailty may represent a useful prognostic tool to aid in patient assessment with non-ischaemic cardiomyopathy prior to implantation of CRT-D. Although it is just one factor to consider, it may also represent an important high-risk marker to help identify patients

Table 1  Baseline characteristics of the population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-frail (n = 73)</th>
<th>Frail (n = 29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73 ± 3</td>
<td>74 ± 4</td>
<td>0.86</td>
</tr>
<tr>
<td>Male sex</td>
<td>40 (55)</td>
<td>14 (48)</td>
<td>0.55</td>
</tr>
<tr>
<td>Length of in-hospital stay (days)</td>
<td>14 ± 7.0</td>
<td>14 ± 5.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>11.7 ± 1.05</td>
<td>11.7 ± 0.94</td>
<td>0.80</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 3.7</td>
<td>27 ± 3.1</td>
<td>0.44</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>39 (53.4)</td>
<td>29 (28.4)</td>
<td>0.037</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46 (63.9)</td>
<td>27 (37)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>30 (41.1)</td>
<td>19 (65.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Smoking status</td>
<td>7 (9.6)</td>
<td>1 (3.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Obesity</td>
<td>10 (13.7)</td>
<td>8 (28.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (15.1)</td>
<td>4 (13.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>21 (28.8)</td>
<td>7 (24.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>Peak oxygen uptake (mLO₂ × kg⁻¹ × min⁻¹)</td>
<td>14 ± 2.1</td>
<td>14 ± 1.6</td>
<td>0.99</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>35 ± 3.5</td>
<td>37 ± 2.7</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF</td>
<td>24 ± 4</td>
<td>25 ± 3</td>
<td>0.39</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.8 ± 0.71</td>
<td>1.8 ± 0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>III</td>
<td>37 (50.6)</td>
<td>15 (51.7)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>36 (49.4)</td>
<td>14 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Barthel Index</td>
<td>87 ± 22.1</td>
<td>88 ± 16.1</td>
<td>0.39</td>
</tr>
<tr>
<td>Charlson Index</td>
<td>4.6 ± 0.71</td>
<td>4.7 ± 0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>Treatment previous CRT-D implantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>73 (100)</td>
<td>29 (100)</td>
<td>1</td>
</tr>
<tr>
<td>ACEI</td>
<td>73 (100)</td>
<td>29 (100)</td>
<td>1</td>
</tr>
<tr>
<td>β-blockers</td>
<td>62 (85)</td>
<td>26 (90)</td>
<td>0.86</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>70 (96)</td>
<td>29 (100)</td>
<td>0.95</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>20 (27)</td>
<td>7 (24)</td>
<td>0.90</td>
</tr>
<tr>
<td>Digoxin</td>
<td>73 (100)</td>
<td>27 (93)</td>
<td>0.89</td>
</tr>
<tr>
<td>Nitrates + hydralazine</td>
<td>7 (9)</td>
<td>2 (7)</td>
<td>0.83</td>
</tr>
<tr>
<td>Statins</td>
<td>73 (100)</td>
<td>29 (100)</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).
ACEI, angiotensin-converting enzyme inhibitors; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; VE/VCO₂, minute ventilation/carbon dioxide production.

Table 2  Risk-adjusted impact of frailty on primary composite endpoint of mortality and decompensated HF

<table>
<thead>
<tr>
<th>Model</th>
<th>Wald test</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Frailty (category of reference: non-frailty)</td>
<td>13.808</td>
<td>4.24</td>
<td>1.979–9.088</td>
</tr>
<tr>
<td>Model 2</td>
<td>Frailty (category of reference: non-frailty)</td>
<td>9.376</td>
<td>4.55</td>
<td>1.726–12.013</td>
</tr>
<tr>
<td></td>
<td>Dyslipidemia</td>
<td>5.594</td>
<td>3.12</td>
<td>1.215–8.018</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>4.391</td>
<td>3.03</td>
<td>1.020–9.927</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>0.466</td>
<td>1.405</td>
<td>0.529–3.729</td>
</tr>
<tr>
<td></td>
<td>VE/VCO₂ slope</td>
<td>0.544</td>
<td>1.054</td>
<td>0.916–1.213</td>
</tr>
</tbody>
</table>

HF, heart failure; HR, hazard ratio; CI, confidence interval; VE/VCO₂, minute ventilation/carbon dioxide production.
who may need closer follow-up or more aggressive rehabilitation post-implantation. Second, although controversy exists as to whether frailty is modifiable, particularly in the setting of a life-threatening advanced illness such as HF, studies such as the Frailty Intervention Trial are under way that may provide insight into potential methods to treat frail individuals. Finally, interventions aimed at reducing frailty in these patients could help decrease or control the already overwhelmingly high healthcare utilization and costs associated with HF.19–21

Limitations
Our study has some limitations. The number of patients in this study was modest and the 95% confidence intervals surrounding the effect estimates were wide. In our study, we have not analysed if CRT-D implantation after 1 year changed the frailty index. Information concerning the late functional status of patients, beyond discharge, would fully inform us more about the potential for eventual recovery of frailty in these patients.

Conclusions
In conclusion, we found frailty is a strong predictor of adverse post-implantation outcomes in patients with non-ischaemic cardiomyopathy. In conclusion, we found frailty is a strong predictor of adverse post-implantation outcomes in patients with non-ischaemic cardiomyopathy. In conclusion, we found frailty is a strong predictor of adverse post-implantation outcomes in patients with non-ischaemic cardiomyopathy. In conclusion, we found frailty is a strong predictor of adverse post-implantation outcomes in patients with non-ischaemic cardiomyopathy.

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Conflict of interest: none declared.

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16. Chaudhry SI, Wang Y, Gill TM, Krumholz HM. Potential methods to treat frail individuals. Finally, interventions aimed at reducing frailty in these patients could help decrease or control the already overwhelmingly high healthcare utilization and costs associated with HF.19–21

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