Quality of life in patients with heart failure and improved ejection fraction: one-year changes and prognosis

Elisabet Zamora1,2,3, Beatriz González1, Josep Lupón1,2,3, Andrea Borrellas1, Mar Domingo1, Evelyn Santiago-Vacas1, Germán Cediel1, Pau Codina1,2, Carmen Rivas1, Ana Pulido1, Eva Crespo1, Patricia Velayos1, Violeta Diaz1 and Antoni Bayes-Genis1,2,3*

1Heart Failure Clinic and Cardiology Service, University Hospital Germans Trias i Pujol, Barcelona, Spain; 2Department of Medicine, Universitat Autonoma de Barcelona, Barcelona, Spain; and 3CIBERCV, Instituto de Salud Carlos III, Madrid, Spain

Abstract

Aims The criteria for patients with heart failure (HF) and improved ejection fraction (HFimpEF) are a baseline left ventricular ejection fraction (LVEF) ≤40%, a ≥10-point increase from baseline LVEF, and a second LVEF measurement >40%. We aimed to (i) assess patients with HFrEF at baseline and compare quality of life (QoL) changes between those that fulfilled and those that did not fulfill the HFimpEF criteria 1 year later and (ii) assess the prognostic role of QoL in patients with HFimpEF.

Methods We reviewed data from a prospective registry of real-world outpatients with HF that were assessed for LVEF and QoL at a first visit to the HF clinic and 1 year later. QoL was evaluated with the Minnesota Living with Heart Failure Questionnaire (MLWHFQ). The primary prognostic endpoint was the composite of all-cause death or HF hospitalization.

Results Baseline and 1-year LVEF and MLWHFQ scores were available for 1040 patients with an initial LVEF ≤40% (mean age, 65.2 ± 11.7 years; 75.9% men). The main etiology was ischemic heart disease (52.9%), and patients were mostly in New York Heart Association Classes II (71.1%) and III (21.6%). At baseline, the mean LVEF was 28.5% ± 7.3, and the mean MLWHFQ score was 30.2 ± 19.5. After 1 year, the mean LVEF increased to 38.0% ± 12.2, and the MLWHFQ scores improved to 17.4 ± 16.0. In 361 patients that fulfilled the HFimpEF criteria (34.7%), significant improvements were observed in both LVEF (from 28.7% ± 6.6 to 50.9% ± 7.6, P < 0.001) and QoL (from 32.9 ± 20.6 to 16.9 ± 16.0, P < 0.001). Patients that did not fulfill the HFimpEF criteria also showed significant improvements in LVEF (from 28.4% ± 7.6 to 31.1% ± 7.9, P < 0.001) and QoL (from 28.7 ± 18.8 to 17.6 ± 15.9, P < 0.001). However, the QoL improvement was significantly higher in the HFimpEF group (−16.0 ± 23.8 vs. −11.1 ± 20.3, P = 0.001), despite the worse mean baseline MLWHFQ score, compared with the non-HFimpEF group (P = 0.001). The 1-year QoL was similar between groups (P = 0.50). The 1-year MLWHFQ score was independently associated with outcomes; the hazard ratio for the composite endpoint was 1.02 (95% CI: 1.01–1.03, P = 0.006). In contrast, the QoL improvement (with a cut-off ≥5 points) was not independently associated with the composite outcome.

Conclusions Patients with HFrEF showed improved QoL after 1 year, regardless of whether they met the HFimpEF criteria. The similar 1-year QoL perception between groups suggested that factors other than LVEF influenced QoL perception. The 1-year QoL was superior to the QoL change from baseline for predicting prognosis in patients with HFimpEF.

Keywords Heart failure; Quality of life; Left ventricular ejection fraction; Heart failure with improved ejection fraction; Outcomes

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*Correspondence to: Antoni Bayes-Genis, Heart Institute, Hospital Universitari Germans Trias i Pujol, Carretera del Canyet, s/n, 08916 Badalona, Barcelona, Spain. Tel: +34 934978915; Fax: +34 934978935. Email: abayesgenis@gmail.com

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Introduction

Heart failure (HF) is a chronic condition with signs and symptoms that affect the patient’s quality of life (QoL).1 From the very start of implementing QoL questionnaires in HF, QoL was reported to be related to many factors, including age, sex, New York Heart Association (NYHA) functional class, hospitalizations, fragility, and different new HF treatments, among others.5–10 However, studies have provided inconsistent and controversial results about the association between QoL and left ventricular ejection fraction (LVEF).2,3,6,11–13 The 2021 universal definition of HF specifically describes the criteria for patients with HF that have shown improved LVEF (HFimpEF) as follows: HF with a baseline LVEF ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF >40%.14 Improvement or recovery in LVEF has been associated with better clinical outcomes, including HF-related hospitalizations and survival.15–23 However, the influence of LVEF improvement (or LVEF recovery) on QoL, although reported in a small number of studies,6,22–24 has not been completely established. Indeed, it has been widely reported that QoL could predict outcomes in HF.25–30 Moreover, it remains to be defined whether the QoL or QoL changes actually influence the outcomes in patients with HFimpEF.

The present study included patients with HF and reduced LVEF (HFrEF) at a first visit to an outpatient HF clinic. The Minnesota Living with Heart Failure Questionnaire (MLWHFQ) was administered to assess QoL at the first visit and at the 1-year follow-up. We aimed to determine (i) whether patients that fulfilled the HFimpEF criteria after 1 year experienced greater QoL improvement than patients that did not fulfill the HFimpEF criteria after 1 year and (ii) whether QoL had prognostic value for outcomes in patients with HFimpEF.

Methods

Study population

We reviewed a prospective registry of real-world outpatients with HF to identify consecutive, ambulatory patients admitted to a structured multidisciplinary HF clinic at a university hospital between August 2001 and August 2021. All patients were evaluated to determine LVEF and QoL with the MLWHFQ at their first visit to the HF clinic and at a 1-year follow-up. The study inclusion criteria were a diagnosis of HFrEF at baseline, a prospectively scheduled second LVEF measurement, and two QoL assessments with the MLWHFQ, one at baseline and one at 1 year. Patients were referred to the HF clinic mostly by the cardiology or internal medicine department, and to a lesser extent, by the emergency department or other hospital departments. The criteria for referral to the HF clinic were HF diagnosed according to the European Society of Cardiology guidelines, regardless of aetiology, and at least one HF hospitalization and/or reduced LVEF.31,32 All patients were examined regularly during follow-up visits at the HF clinic, according to their clinical needs. All patients were treated according to a unified protocol. Follow-up visits included a minimum of one visit with a nurse every 3 months and one visit with a physician (cardiologist, internist, or family physician) every 6 months. Patients also attended optional visits with specialists in geriatrics, psychiatry, and rehabilitation,31,32 and in recent years, visits with a nephrologist and endocrinologist were included.

Outcomes

The primary study endpoint was the change in QoL related to an improvement in LVEF. Secondary clinical outcome endpoints included the composite endpoint of all-cause death or HF-related hospitalization, all-cause death alone, and the number of subsequent HF-related hospitalizations. Fatal events were identified from patient health records (including records from hospital wards, the emergency room, and general practitioners) or by contacting relatives. Data were verified with the Catalan and Spanish Health Systems databases and the Spanish National Death Registry. Adjudication of events was performed by an ad hoc committee (JL, MdeA, BG, and MD), and discrepancies were resolved by two independent researchers (PM and GC). Hospitalizations were identified from the clinical records of patients with HF, from hospital ward records, and from the electronic Catalan history records.

All patients provided written informed consent, during the baseline visit, for the use of their clinical data for research purposes. The study was performed in compliance with the laws protecting personal data, in accordance with the international guidelines on clinical investigations from the World Medical Association’s Declaration of Helsinki. The local ethics committee approved the study.

HF type definition

LVEF was assessed at the first visit and at the 1-year follow-up, according to the recommendations of the American Echocardiography Society guidelines. LVEF was measured from apical two-chamber and four-chamber views with Simpson’s method. Patients were first classified by their ventricular function, according to the 2021 universal definition of HF.14 Only patients with LVEF ≤40% at the first visit were included in the present study. After 1 year, echocardiography was performed, and patients were reclassified into two groups: (i) HFimpEF: HF with a baseline LVEF ≤40%, ≥10-point increase...
from baseline LVEF, and a second measurement of LVEF >40%; (ii) non-HFimpEF: patients who did not fulfill such criteria (permanent HFrEF, HfmrEF without 10-point increase in LVEF).

**QoL assessment**

QoL was measured with an HF-specific QoL questionnaire, the MLWHFQ. The Spanish version of this questionnaire has been widely used and was prospectively validated. The MLWHFQ consisted of 21 questions that evaluated the impact of HF on physical, psychological, and social aspects of the patient’s life. Answers ranged from 0 (no limitation) to 5 (maximal limitation); thus, the global scores ranged from 0 to 105, and higher scores reflected a worse QoL. A 5-point change was considered the minimally important difference; thus, in addition to the magnitude of change between the two assessments (baseline and 1 year), we categorized patients according to whether they showed a 5-point improvement in the score (i.e., a 5-point reduction in the MLWHFQ score was considered an improved QoL).

When necessary, an HF-specialized nurse assisted patients in completing the questionnaire. The level of assistance depended on the patient’s reading and writing capabilities. When a patient had difficulty completing the questionnaire, the nurse read the MLWHFQ aloud and completed each question, based on the patient’s oral answer. In all cases, the nurses attempted to ensure that they did not alter the response of the patient in any way, but simply intervened for guidance or assistance; they never acted in an interested way that could compromise the patient’s independence.

**Statistical analysis**

Categorical variables are expressed as percentages. Continuous variables are expressed as the mean [standard deviation (SD)] or median [interquartile range: Q1–Q3 (IQR)], according to whether the data were normally or non-normally distributed. Normally distributed data were assessed with normal Q-to-Q plots. Differences between HF types were assessed with the chi-squared test, Student’s t-test, or Mann–Whitney U test, as appropriate. Univariable and multivariable binomial logistic regression was performed to assess which variables were associated with QoL improvement, and results are expressed as the odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (95% CI).

The prognostic role of QoL in HFimpEF was assessed with Cox regression analyses. Univariable and multivariable analyses were performed. Multivariable models included covariates with P values < 0.10 in the univariable analyses. Recurrent HF-related hospitalizations were analysed with binomial negative regression (univariable and multivariable), and results are expressed as the incidence rate ratio (IRR). For the latter analyses, an out-of-hospital death due to HF was considered an additional event. Statistical analyses were performed with SPSS 24 (SPSS Inc., Chicago, Illinois) and Stata. A two-sided P < 0.05 was considered significant.

**Results**

We retrieved data from August 2001 to August 2021 and identified 1040 patients with both baseline and 1-year LVEF and MLWHFQ scores and an initial LVEF ≤40%. Table 1 shows the baseline demographic and clinical characteristics of patients and the treatments administered during follow-up. The mean age was 65.2 ± 11.7 years, 75.9% of the patients were men, the main aetiology was ischaemic heart disease (52.9%), and most patients were in New York heart Association Classes II (71.1%) and III (21.6%). Most patients received currently recommended HF treatments. Table S1 shows the treatments administered at baseline, at 1 year, and during follow-up.

**Changes in LVEF and MLWHFQ**

The mean baseline LVEF was 28.5% ± 7.3, and the mean baseline MLWHFQ score was 30.2 ± 19.5. At 1 year, the mean LVEF increased to 38.0% ± 12.2, and the mean MLWHFQ score improved to 17.4 ± 16.0 (LVEF, Figure 1; MLWHFQ, Figure 2).

The HFimpEF criteria were fulfilled by 361 patients (34.7%). These patients showed significant, marked improvements in both LVEF (from 28.7% ± 6.6 to 50.9% ± 7.6, P < 0.001) and QoL (from 32.9 ± 20.6 to 16.9 ± 16.0 points, P < 0.001). Patients that did not fulfil the HFimpEF criteria also showed improvements in LVEF (from 28.4% ± 7.6 to 31.1% ± 7.9, P < 0.001) and QoL (from 28.7 ± 18.8 to 17.6 ± 15.9, P < 0.001). The improvement in QoL was significantly higher in the HFimpEF group (−16.0 ± 23.8 vs. −11.1 ± 20.3 points, P = 0.001), because the baseline MLWHFQ score was worse in the HFimpEF group (P = 0.001) than in the non-HFimpEF. However, at 1 year, the QoL scores were similar between groups (P = 0.50).

When patients were categorized into those with and without at least a 5-point improvement in the MLWHFQ score (improved QoL and non-improved QoL, respectively), QoL improvement was observed significantly more frequently in the HFimpEF group (67.9%) than in the non-HFimpEF group (61.4%, P = 0.04). Indeed, in univariable logistic regression, HFimpEF was significantly associated with an improved QoL (OR: 1.33, 95% CI: 1.01–1.74, P = 0.04). However, when other variables classically associated with QoL, such as age, sex, NYHA functional class, and the number of HF-related hospitalizations in the previous year were added to a multivariable model, HFimpEF did not remain independently associated with an improved QoL (Table 2).
Relationship between QoL and outcomes

Among the 361 patients with HFimpEF, during a mean follow-up of 6.7 ± 4.6 years, 152 patients died [50.7% from non-cardiovascular causes (Table S2)], 86 patients experienced 166 HF-related hospitalizations (Table S3), and 175 patients experienced the composite endpoint of all-cause death or HF-related hospitalization.

Analyses of the relationships between an improved QoL and HFimpEF outcomes showed that a QoL improvement was significantly associated with the composite endpoint of all-cause death or HF-related hospitalization in the univariable analysis (HR: 0.73, 95% CI: 0.54–0.999; P = 0.049), but this association did not remain significant in a multivariable analysis, when age, sex, NYHA functional class, ischaemic aetiology, and the number of HF admissions in the previous year were included in the model (Table S4).

In contrast, the 1-year MLWHFQ score showed a significant association with the composite endpoint, both in the univariable analysis and in a very comprehensive multivariable Cox regression analysis (Table 3). Figure 3 shows a forest plot representation of different potential QoL assessments and their associations with all-cause death and the composite endpoint of all-cause death or HF hospitalization.

A QoL improvement was not associated with either all-cause death (HR: 0.80, 95% CI: 0.57–1.11) or recurrent HF-related hospitalizations (IRR: 0.90, IQR: 0.43–1.86; P = 0.77). In contrast, the 1-year MLWHFQ score was significantly associated with all-cause death in both the univariable and multivariable analyses (Table 4). However, its association with recurrent HF-related hospitalizations was only significant in the univariable analysis (Table S5).

Discussion

The two main findings in this study were: (i) Patients with HFimpEF showed greater improvement in QoL than those with non-HFimpEF, although the groups showed similar one-year MLWHFQ scores; and (ii) QoL was significantly associated with outcomes in HFimpEF, which was not previously

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Table 1 Baseline clinical characteristics of patients with HFrEF that either showed improved EF (HFimpEF) or no EF improvement (no HFimpEF)

| Characteristic                                | HFimpEF N = 361 | Non-HFimpEF N = 679 | P value |
|-----------------------------------------------|-----------------|----------------------|---------|
| Age, years                                    | 63.4 ± 12.1     | 66.2 ± 11.3          | <0.001  |
| Male sex, n (%)                               | 255 (70.6)      | 535 (78.8)           | 0.003   |
| Ischaemic HD                                  | 114 (31.6)      | 437 (64.4)           | <0.001  |
| Dilated CM                                    | 96 (26.6)       | 101 (14.9)           |         |
| Hypertensive CM                               | 26 (7.2)        | 33 (4.9)             |         |
| Alcoholic CM                                  | 50 (13.9)       | 21 (3.1)             |         |
| Drug-induced CM                              | 16 (4.4)        | 17 (2.5)             |         |
| Valvular disease                              | 31 (8.6)        | 35 (5.2)             |         |
| Other                                         | 28 (7.8)        | 35 (5.2)             |         |
| LVEF, %a                                      | 28.2 ± 6.6      | 28.4 ± 7.6           | 0.55    |
| NYHA class, n (%)                             | 2 (1–12)        | 12 (2–60)            | <0.001  |
| ACEI or ARB                                   | 331 (91.7)      | 580 (85.4)           | 0.37    |
| Beta-blockers                                 | 342 (94.7)      | 640 (94.4)           | 0.75    |
| ARNI                                          | 271 (75.1)      | 501 (73.8)           | 0.65    |
| Loop diuretics                                | 334 (92.5)      | 639 (94.1)           | 0.32    |
| ARNI                                          | 64 (17.7)       | 118 (17.4)           | 0.89    |
| Digoxin                                       | 145 (40.2)      | 312 (45.9)           | 0.07    |
| Ivabradine                                    | 122 (33.8)      | 157 (23.1)           | <0.001  |
| CRT                                           | 40 (11.1)       | 138 (20.3)           | <0.001  |
| ICD                                           | 39 (10.8)       | 184 (27.1)           | <0.001  |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CM, cardiomyopathy; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardiac defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

a At any moment during follow-up.
described, to the best of our knowledge. As a prognostic factor, the 1-year QoL score was stronger to the change in QoL from baseline. QoL is enormously important to patients with HF; among the chronic diseases, HF has one of the largest effects on QOL.14,34 Indeed, in some patients with advanced diseases, relief from symptoms35 and QoL36 were reported to be even more important than life expectancy.

The prevalence of HFimpEF depends strongly on the cohort characteristics and the definition and cut-offs used. We found that 34.7% of our patients with non-HFimpEF evolved to HFimpEF. In the meta-analysis performed by He et al.,37 the pooled prevalence of HFimpEF was only 22.64%, although it ranged from 10 to 52%.

The first major result of this study was that both HFimpEF and non-HFimpEF groups showed significant improvements in the perception of QoL. In previous studies, we25 and others5,38 showed that QoL improved during specialized HF management. In the present study, the improved QoL from baseline HFrEF in the entire cohort during the first year was likely to be due to therapy optimization and the structured educational and monitoring programme carried out by HF-specialized nurses, who performed all the follow-ups every 3 months. Moreover, improvements in depressive symptoms39 may have influenced the improvement in QoL. However, the association between QoL and LVEF has been controversial, because many authors did not find any relationship.3,11–13 Nevertheless, QoL affects all patients with HF; thus, we expected to find that the perceived QoL improved more among patients with HFimpEF than in those with non-HFimpEF. In a small sample of 35 patients with HFrEF that showed improved LVEFs to 50% or more, Wohlfahrt et al.24 showed that recovery of systolic function was associated with HF-associated QoL improvements, and for each 10% increase in LVEF, the Kansas City Cardiomyopathy Questionnaire score improved by a mean (SD) of 4.8 ± 1.6 points (P = 0.003). In addition, DeVore et al.22 very recently reported QoL improvements related to a ≥10% increase in LVEF in 635 patients out of 2092 with initial HFrEF. Among patients with HFimpEF, the Kansas City Cardiomyopathy Questionnaire overall summary score changed by a mean of 7.6 points (range: 6.0–9.2), compared with 3.5 points (range: 2.3–4.8) in those with non-HFimpEF (P < 0.001). Moreover, the statistical difference between groups persisted after adjusting for clinical variables, such as age, baseline LVEF, blood pressure, serum creatinine, and the baseline score. In addition, the difference between groups remained significant, when the model was adjusted for other variables, such as sex, history of HF, history of coronary artery disease, and history of diabetes mellitus. However, the latter adjustment decreased the effect estimate to 2.98. In the present study, we also observed greater improvement in QoL in the HFimpEF group, compared with the non-HFimpEF group.
but the difference was due to a lower baseline QoL in the HFimpEF group. At 1 year, the MLWHFQ scores were quite similar between the HFimpEF and non-HFimpEF groups, which indicated a similar perception of QoL at the end of the study period.

The issue of how to interpret the differences in QoL improvement is debatable. On one hand, it could be simply a matter of chance that the patients with HFimpEF had a worse QoL. However, our results showed that, compared with the non-HFimpEF group, the HFimpEF group had a shorter HF duration, a larger proportion was classified as NYHA I–II, and the HF aetiology was distributed differently; all these factors could have influenced our results. On the other hand, if the HFimpEF group improved to the same extent as the non-HFimpEF group, at 1 year, the perception of QoL would have been worse. Instead, at the end of the study, the groups reported similar levels of QoL.

QoL is a subjective assessment affected by multiple factors, such as age, sex, previous hospitalizations, diabetes, treatments, etc. Indeed, the physical dimension is also very important in the QoL assessment; it is not surprising that QoL was reported to be worse in patients with more co-morbidities or higher NYHA functional classes. Previous studies revealed that an improvement in the NYHA class translated into a favourable impact on QoL. In the present study, we found that the perceived QoL improvement in patients with HFimpEF was mainly related to the number of HF-related hospitalizations experienced in the previous year and with the NYHA functional class.

Our second study aim represented a novelty, to our knowledge, and it is probably the most important finding of our results. Previous studies have shown that patients with HFimpEF or ‘recovered’ LVEF had a better prognosis, but that was not the objective of the present study. Moreover, QoL was previously associated with outcomes in patients with HF. However, no study had investigated how QoL might influence the prognosis of patients with HFimpEF. Based on our results, we concluded that

### Table 2 Characteristics associated with QoL improvement

| Characteristic                  | Univariable | Multivariable |
|--------------------------------|-------------|---------------|
|                                | OR 95% CI P value | OR 95% CI P value |
| Age                            | 1.00 0.99–1.01 0.60 | 1.01 1.00–1.02 0.22 |
| Female sex                     | 1.07 0.79–1.44 0.18 | 0.74 0.77–1.43 0.74 |
| NYHA improvement               | 1.66 1.18–2.33 0.76 | 1.68 1.19–2.37 0.003 |
| HF hospitalizations in previous year | 0.74 0.56–0.97 0.03 | 0.51 0.37–0.70 <0.001 |
| HF durationb                   | 0.90 0.85–0.94 <0.001 | 0.75 0.57–0.98 0.04 |
| HFimpEF                        | 1.33 1.01–1.74 0.04 | 1.24 0.85–1.52 0.39 |

HF, heart failure; HFimpEF, heart failure with improved ejection fraction; mo, months; NYHA, New York Heart Association; QoL, quality of life.

### Table 3 Characteristics associated with the composite primary endpoint of all-cause death or HF-related hospitalization in patients with HFimpEF

| Characteristic                  | Univariable | Multivariable |
|--------------------------------|-------------|---------------|
|                                | HR 95% CI P value | HR 95% CI P value |
| Age                            | 1.06 1.04–1.07 <0.001 | 1.05 1.03–1.07 <0.001 |
| Female sex                     | 1.10 0.79–1.51 0.58 | 0.77 0.54–1.10 0.15 |
| One-year NYHA class            | 2.22 1.62–3.12 <0.001 | 1.47 0.97–2.22 0.07 |
| HF hospitalizations in previous year | 4.04 2.75–5.97 <0.001 | 4.61 3.10–6.86 <0.001 |
| Ischaemic aetiology            | 1.71 1.26–2.32 <0.001 | 1.53 1.10–2.12 0.01 |
| Diabetes                       | 1.60 1.19–2.16 0.002 | 1.43 1.04–1.98 0.03 |
| COPD                           | 1.45 0.98–2.15 0.06 | 1.13 0.74–1.74 0.57 |
| ACEI or ARB FU                 | 0.34 0.19–0.59 <0.001 | 0.44 0.25–0.80 0.007 |
| Beta-blockers FU               | 0.33 0.19–0.56 <0.001 | 0.39 0.21–0.73 0.003 |
| ARNI FU                        | 0.55 0.33–0.94 0.03 | 0.70 0.39–1.26 0.24 |
| Ivabradine FU                  | 0.69 0.48–0.97 0.03 | 0.88 0.61–1.28 0.51 |
| One-year MLWHFQ score          | 1.02 1.01–1.02 0.001 | 1.02 1.01–1.03 0.006 |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; FU, follow-up; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association.

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Figure 3  Forest plots show associations between different QoL assessments and either all-cause death or the composite end-point of all-cause death or HF hospitalization. (A) QoL assessed as the delta change between baseline and 1-year MLWHFQ scores (per 1%). (B) QoL improvement assessed as the continuous change between baseline and 1-year MLWHFQ scores (per 1 point). (C) QoL assessed as a significant categorical improvement in MLWHFQ scores (the minimal significant improvement was 5 points). (D) QoL assessed as the continuous 1-year MLWHFQ score (per 1 point). Blue = all-cause death; red = the primary composite endpoint of all-cause death or HF-related hospitalization. Note that the scale on the x-axis is not the same for all plots.

Table 4  Characteristics associated with all-cause death in patients with HFimpEF

| Characteristic                          | Univariable       | Multivariable     |
|----------------------------------------|-------------------|-------------------|
|                                        | HR    | 95% CI     | P value | HR    | 95% CI     | P value |
| Age                                    | 1.07  | 1.05–1.08  | <0.001  | 1.05  | 1.03–1.07  | <0.001  |
| Female sex                             | 1.09  | 0.77–1.55  | 0.61    | 0.75  | 0.51–1.10  | 0.14    |
| One-year NYHA class                    | 2.08  | 1.46–2.95  | <0.001  | 1.34  | 0.86–2.07  | 0.19    |
| HF hospitalizations in previous year   | 2.03  | 1.36–3.03  | 0.001   | 1.59  | 1.05–2.40  | 0.03    |
| HF duration<sup>a</sup>                | 1.06  | 0.99–1.13  | 0.09    | 1.08  | 1.00–1.17  | 0.04    |
| Ischaemic aetiology                    | 1.96  | 1.42–2.72  | <0.001  | 1.80  | 1.24–2.61  | 0.002   |
| Diabetes                               | 1.54  | 1.12–2.13  | 0.008   | 1.27  | 0.90–1.78  | 0.18    |
| ACEI or ARB FU                         | 0.32  | 0.17–0.58  | <0.001  | 0.37  | 0.20–0.70  | 0.002   |
| Beta-blockers FU                       | 0.25  | 0.14–0.45  | <0.001  | 0.22  | 0.11–0.40  | <0.001  |
| ARNI FU                                | 0.40  | 0.20–0.78  | 0.007   | 0.48  | 0.22–0.40  | 0.07    |
| Ivabradine                             | 0.64  | 0.43–0.94  | 0.02    | 0.90  | 0.59–1.36  | 0.61    |
| One-year MLWHFQ score                  | 1.01  | 1.00–1.02  | 0.01    | 1.01  | 1.00–1.03  | 0.03    |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; FU, follow-up; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; mo, months; NYHA, New York Heart Association.

<sup>a</sup>Months, Log(2) transformed.
the QoL at the 1-year follow-up was significantly associated with outcomes in patients with HFimpEF. By definition, these patients had significantly improved their LVEFs. Moreover, remarkably, QoL was prognostically important, independent of other strong prognostic factors, like age, previous hospital admissions, ischaemic aetiology, diabetes, NYHA functional class, and treatments. Indeed, the perception of QoL at 1 year was independently associated with outcomes, whereas the change in QoL from baseline was not. A similar result was observed in a secondary analysis of the TOPCAT and HF-ACTION studies.29 Those studies conducted serial QoL assessments in patients with non-HFimpEF and HFrEF, respectively. They measured the current, prior, and change in the Kansas City Cardiomyopathy Questionnaire score and found that the most recent assessment provided the most important information about the risks of subsequent clinical events. Thus, from the prognostic point of view, the future outcome was related to how the QoL was perceived by patients at one specific moment, independent of how they felt previously. In this sense, the perception of QoL might be considered a prognostic biomarker in this subgroup of patients. Extensive studies have shown that improvements in LVEF had prognostic implications on ‘hard’ endpoints, like death or HF-related hospitalizations. However, increasingly, QoL has been considered an important endpoint for both patient well-being and its association with outcomes. In this study, we showed that QoL was related to outcomes beyond the improvement in LVEF; thus, the measurement of QoL perception is of clinical interest and important, particularly in patients with improved cardiac function.

Limitations

This study had some limitations. First, LVEF was measured with quantitative transthoracic echocardiography. However, LV function and volumes might have been assessed more precisely with 3D echocardiography or cardiac MRI. Second, similar to previous studies, we only included patients that had both baseline and 1-year echocardiography data available for analysis. Third, the QoL is a subjective measure that is difficult to measure on a group level.40 However, we implemented a valid approach for highlighting the importance of the prognostic value of MLWHFQ scores. Another potential limitation was the lack of data on sodium/glucose co-transporter 2 inhibitor treatments. However, those data were of limited use in the study, and thus, they were not included in the analyses; consequently, we could not ascertain whether the use of these inhibitors could have influenced the results. Finally, this study was conducted in a single centre; our population was a general population with HF, treated at a specific, multidisciplinary HF unit in a tertiary hospital; and most patients were referred from the cardiology department. Therefore, our study population comprised mainly relatively young men with HF of ischaemic aetiology and reduced LVEF. Consequently, the results we obtained might not necessarily be extrapolated to a community-based HF population. Moreover, it remains to be determined whether the data for this study might be generalizable to a larger population of mainly older women with less systolic dysfunction.

In conclusion, our results showed that QoL improved in patients treated for HF, regardless of whether they achieved HFimpEF in 1 year. The QoL perception at 1 year was similar in both groups—HFimpEF and non-HFimpEF—which suggested that factors other than LVEF had influenced the QoL perception. Remarkably, QoL at 1 year was found to be an independent prognostic factor, contrary to the QoL change from baseline.

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Conflict of interest

None declared.

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None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Treatments.
Table S2. Causes of death in HFimpEF patients.
Table S3. Number of HF-related hospitalizations in HFimpEF patients.
Table S4. Cox regression for the composite primary end-point of all-cause death or HF-related hospitalization in HFimpEF patients using QoL-improved as the variable of interest.
Table S5. Binomial negative regression for recurrent HF hospitalizations.
References

1. Moradi M, Daneshi F, Belzadimehr R, Kafemanesh H, Bouya S, Raesli M. Quality of life of chronic heart failure patients: A systematic review and meta-analysis. Heart Fail Rev 2020; 25: 993–1006.

2. Quitian M, Wiesinger GF, Crevenna R, Nuh MJ, Posch M, Hulsman M, Müller D, Pacher R, Fialka-Moser V. Cross-cultural adaptation of the Minnesota living with heart failure questionnaire for German-speaking patients. J Rehabil Med 2001; 33: 182–186.

3. Parajón T, Lupón J, González B, Urrutia A, Altimír S, Coll R, Prats M, Valle V. Use of the Minnesota living with heart failure quality of life questionnaire in Spain. Rev Esp Cardiol 2004; 57: 155–160.

4. Gastelurrutia P, Lupón J, Altimír S, de Antonio M, González B, Cabanes R, Cano L, Urrutia A, Domingo M, Zamora E, Díez C, Coll R, Bayes-Genís A. Effect of fragility on quality of life in patients with heart failure. Am J Cardiol 2013; 112: 1785–1789.

5. Hole T, Grundtvig M, Gulstad L, Flønæs B, Westheim A. Improved quality of life in Norwegian heart failure patients after follow-up in outpatient heart failure clinics: Results from the Norwegian heart failure registry. Eur J Heart Fail 2010; 12: 1247–1252.

6. Joyce E, Chung C, Badloe S, Oudotay K, Desai A, Givertz MM, Nohria A, Lakdawala NK, Stewart GC, Young M, Weintraub J, Stevenson LW, Lewis EF. Variable contribution of heart failure to quality of life in ambulatory heart failure with reduced, better, or preserved ejection fraction. JACC Heart Fail 2016; 4: 184–193.

7. Lewis EF, Caggeiti BL, McMurray JFV, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Zile MR, Desai AS, Solomon SD, Swedberg K. Health-related quality of life outcomes in PARADIGM-HF. Circ Heart Fail 2017; 10: e003430.

8. Ekman I, Chassany O, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L, Swedberg K. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: Results from the SHIFT study. Eur Heart J 2011; 32: 2395–2404.

9. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with ferric carboxymaltose in patients with chronic heart failure and iron deficiency. Eur Heart J 2015; 36: 657–668.

10. McMurray JFV, Solomon SD, Inzucchi SE, Kober L, Kosiборod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Böhm M, Boysen G, Chiang CE, Chopra VK, de Boer RA, Desai AS, Díez M, Drozdz J, Dukat A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O’Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KP, Jhund PS, Bengtsson O, Sjöström M, Langkilde AM, DAPA-HF Trial Committee and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381: 1995–2008.

11. Riegel B, Moser DK, Glaser D, Carlson B, Deaton C, Armola P, Sethares K, Shively M, Evangelista I, Albert N. The Minnesota living with heart failure questionnaire: Sensitivity to differences and responsiveness to intervention intensity in a clinical population. Nurs Res 2002; 51: 209–218.

12. Austin BA, Wang Y, Smith GL, Vaccarino V, Krumholz HM, McNamara RL. Systolic function as a predictor of mortality and quality of life in long-term survivors with heart failure. Clin Cardiol 2008; 31: 119–124.

13. Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zueck C, Herzog W, Haass M. Health related quality of life in patients with congestive heart failure: Comparison with other chronic diseases and relation to functional variables. Heart 2002; 87: 235–241.

14. Bozkurtt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Michael Felker G, Filipatios G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsuy T, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferovic P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail 2021; 23: 352–380.

15. Lupón J, Díez-López C, de Antonio M, Domingo M, Zamora E, Moliner P, González B, Santesteban J, Troya M, Bayés-Genís A. Recovered heart failure with reduced ejection fraction and outcomes: A prospective study. Eur J Heart Fail 2017; 19: 1615–1623.

16. Cioffi G, Stefaneli C, Tarantini L, Opsicich C. Chronic left ventricular failure in the community: Prevalence, prognosis, and predictors of the complete clinical recovery with return of cardiac size and function to normal in patients undergoing optimal therapy. J Card Fail 2004; 10: 250–257.

17. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol 2011; 57: 1468–1476.

18. Kalogeropoulos AP, Fonarow GC, Georgioupolou V, Burkman G, Siwamogsath S, Patel A, Li S, Papadimitriou I, Butler J. Characteristics and outcomes of adult outliers with heart failure and improved or recovered ejection fraction. JAMA Cardiol 2016; 1: 510–518.

19. De Groote P, Fertin M, Duva Pentiah A, Gömmine C, Lamblin B, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after β-blocker therapy. Circ Heart Fail 2014; 7: 434–439.

20. Savarese G, Vedan O, D’Amario D, Ujlj A, Dahlström U, Rosano G, Lam CSP, Lund IH. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. JACC Heart Fail 2019; 7: 306–317.

21. Strange G, Playford D, Scalia GM, Colerajmajer DS, Prior D, Codie J, Chan YK, Bulsara MK, Stewart S, NEDA Investigators. Change in ejection fraction and long-term mortality in adults referred for echocardiography. Eur J Heart Fail 2021; 23: 555–563.

22. DeVore AD, Hellkamp AS, Thomas L, Albert NM, Butler J, Patterson JH, Spertus JA, Williams FB, Shen X, Hernandez AF, Fonarow GC. The association of improvement in left ventricular ejection fraction with outcomes in patients with heart failure with reduced ejection fraction: Data from CHAMP-HF. Eur J Heart Fail 2022; 24: 762–770.

23. Wang K, Youngson E, Bakal JA, Thomas J, McAlister FA, Oudit GY. Cardiac reverse remodelling and health status in patients with chronic heart failure. ESC Heart Fail 2021; 8: 3106–3118.

24. Wohltaft P, Nativ-Nicolau J, Zhang M, Selzman CH, Greene T, Conte J, Biber JE, Hess R, Mondsie FL, Weyer-Pinzon O, Drakos SG, Gilbert EM, Kemelewou L, LaSalle B, Steinberg BA, Shah R, Fang JC, Sperl JA, Stehlik J. Quality of life in patients with heart failure with recovered ejection fraction. JAMA Cardiol 2021; 6: 957–962.

25. Lupón J, Gastelurrutia P, de Antonio M, González B, Cano L, Cabanes R, Urrutia A, Díez C, Coll R, Altirimir S, Bayes-Genís A. Quality of life monitoring in ambulatory heart failure patients: Temporal

E. Zamora et al.
Quality of life in patients with heart failure and improved ejection fraction: one-year changes and prognosis

changes and prognostic value. *Eur J Heart Fail* 2013; 15: 103–109.

26. Gastelurrutia P, Lupón J, Moliner P, Yang X, Cediel G, de Antonio M, Domingo M, Altimir S, González B, Rodríguez M, Rivas C, Díaz V, Fung E, Zamora E, Santesmases J, Núñez J, Woo J, Bayes-Genis A. Comorbidities, fragility, and quality of life in heart failure patients with midrange ejection fraction. *Mayo Clin Proc Innov Qual Outcomes* 2018; 2: 176–185.

27. Konstam V, Salem D, Pouleur H, Kostis J, Gorkin L, Shumaker S, Mottard I, Woods P, Konstam MA, Yusuf S. Baseline quality of life as a predictor of mortality and hospitalisation in 5,025 patients with congestive heart failure. Studies of the SOLVD investigators. *Am J Cardiol* 1996; 78: 890–895.

28. Sepehrvand N, Savu A, Spertus JA, Dyck JRB, Anderson T, Howlett J, Paterson I, Oudit GY, Kaul P, McAlister FA, Ezekowitz JA, Alberti HI. Change of health-related quality of life over time and its association with patient outcomes in patients with heart failure. *J Am Coll Cardiol* 2020; 9: e017278.

29. Pokharel Y, Khariton Y, Tang Y, Nassif ME, Chan PS, Arnold SV, Jones PG, Spertus JA. Association of Serial Kansas City cardiomyopathy questionnaire assessments with death and hospitalization in patients with heart failure with preserved and reduced ejection fraction: A secondary analysis of 2 randomized clinical trials. *JAMA Cardiol* 2017; 2: 1315–1321.

30. Alta F, Briançon S, Guillemin F, Jullièère Y, Mertès PM, Villemot JP, Zannad F. EPICAL investigators. Self-rating of quality of life provides additional prognostic information in heart failure. Insights into the EPICAL study. *Eur J Heart Fail* 2002; 4: 337–343.

31. Zamora E, Lupón J, Vila J, Urrutia A, de Antonio M, Sanz H, Grau M, Ara J, Bayés-Genis A. Estimated glomerular filtration rate and prognosis in heart failure: Value of the modification of diet in renal disease Study-4, chronic kidney disease epidemiology collaboration, and Cockcroft-Gault formulas. *J Am Coll Cardiol* 2012; 59: 1709–1715.

32. Lupón J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, López-Ayerbe J, Domingo M, Núñez J, Zamora E, Moliner P, Díaz-Ruata P, Santesmases J, Bayés-Genis A. Dynamic trajectories of left ventricular ejection fraction in heart failure. *J Am Coll Cardiol* 2018; 72: 591–601.

33. Garin O, Soriano N, Ribera A, Ferrer M, Pont A, Alonso J, Permyaner G, Grupo IC-QoL. Validation of the Spanish version of the Minnesota living with heart failure questionnaire. *Rev Esp Cardiol* 2008; 61: 251–259.

34. McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heart failure: Public and private health burden. *Eur Heart J* 1998; 19: 9–12.

35. Stanek E, Oates M, McChan F, Denofrio D, Loh E. Preferences for treatment outcomes in patients with heart failure: Symptoms versus survival. *J Card Fail* 2000; 3: 225–232.

36. Lewis EF, Johnson PA, Johnson W, Collins C, Griffin L, Stevenson LW. Preferences for quality of life or survival expressed by patients with heart failure. *J Heart Lung Transplant* 2001; 20: 1016–1024.

37. He Y, Ling Y, Guo W, Li Q, Yu S, Huang H, Zhang R, Gong Z, Liu J, Mo L, Yi S, Lai D, Yao Y, Liu J, Chen J, Liu Y, Chen S. Prevalence and prognosis of HFImpEF developed from patients with heart failure with reduced ejection fraction: Systematic review and meta-analysis. *Front Cardiovasc Med* 2021; 8: 757596.

38. Konstam V, Gregory D, Chen J, Weintraub A, Patel A, Levine D, Venesy D, Perry K, Delano C, Konstam MA. Health-related quality of life in a multicenter randomized controlled comparison of telephonic disease management and automated home monitoring in patients recently hospitalized with heart failure: SPAN-CHF II trial. *J Card Fail* 2011; 17: 151–157.

39. Diez-Quevedo C, Lupón J, González B, Urrutia A, Cano L, Cabanes R, Altimir S, Coll R, Pascual T, de Antonio M, Bayes-Genis A. Depession, antidepressants, and long-term mortality in heart failure. *Int J Cardiol* 2013; 167: 1217–1225.

40. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patient referred for cardiac transplant evaluation. *Circulation* 1997; 95: 2660–2667.