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ORIGINAL ARTICLE

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

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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 HF and reduced LVEF (HFrEF) at baseline and compare quality of life (QoL) changes between those that fulfilled and those that did not fulfil 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 MLWFQ scores were available for 1040 patients with an initial LVEF ≤40% (mean age, 65.2 ± 11.7 years; 75.9% men). The main aetiology was ischaemic 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 fulfil 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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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.[2–10] 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 fulfil 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 fulfil such criteria (permanent HFrEF, HFmrEF without 10-point increase in LVEF).

QoL assessment

QoL was measured with an HF-specific QoL questionnaire, the MLWHFQ.[1] The Spanish version of this questionnaire has been widely used[3] and was prospectively validated.[33] 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 (https://qol.thoracic.org/sections/instruments/ko/pages/mlwhfq.html); 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.[3] 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 MLWFQ 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*).

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
Aetiology, *n* (%)			<0.001
Ischaemic HD	114 (31.6)	437 (64.4)	
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
HF duration, months	2 (1–12)	12 (2–60)	<0.001
NYHA class, *n* (%)			0.001
I	29 (8.0)	41 (6.0)	
II	273 (75.6)	467 (68.8)	
III	58 (16.1)	166 (24.4)	
IV	1 (0.3)	5 (0.7)	
Diabetes, *n* (%)	144 (39.9)	276 (40.6)	0.81
Hypertension, *n* (%)	226 (62.6)	405 (59.6)	0.35
COPD, *n* (%)	51 (14.1)	123 (18.1)	0.81
Atrial fibrillation/flutter	63 (17.5)	112 (16.5)	0.10
Treatments FU[a], *n* (%)			
ACEI or ARB	331 (91.7)	580 (85.4)	0.37
Beta-blockers	342 (94.7)	640 (94.4)	0.75
ARM	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.

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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Figure 1 Violin plots of baseline and one-year LVEF measurements. Each violin plot illustrates the kernel probability density (i.e. the width of the shaded area represents the proportion of the data located there). Inside the violin plots, boxplots indicate the median and interquartile range; the whiskers indicate 1.5 times the interquartile range. Green violin plots represent the baseline LVEFs. Orange violin plots represent the 1-year LVEFs.

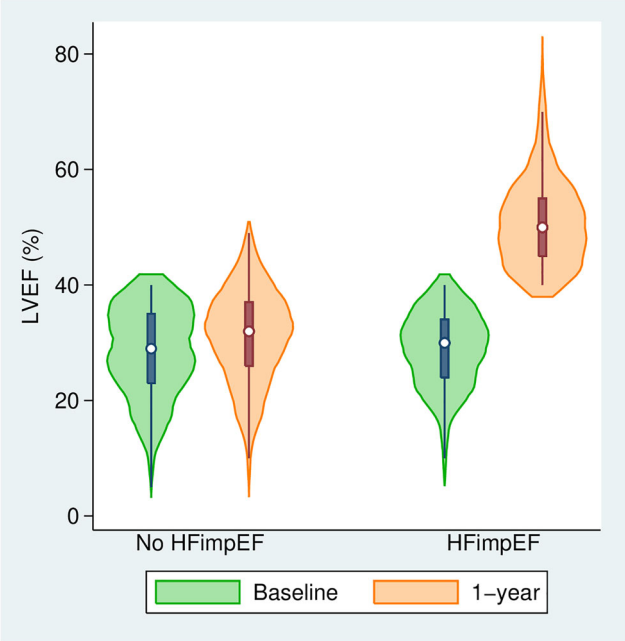
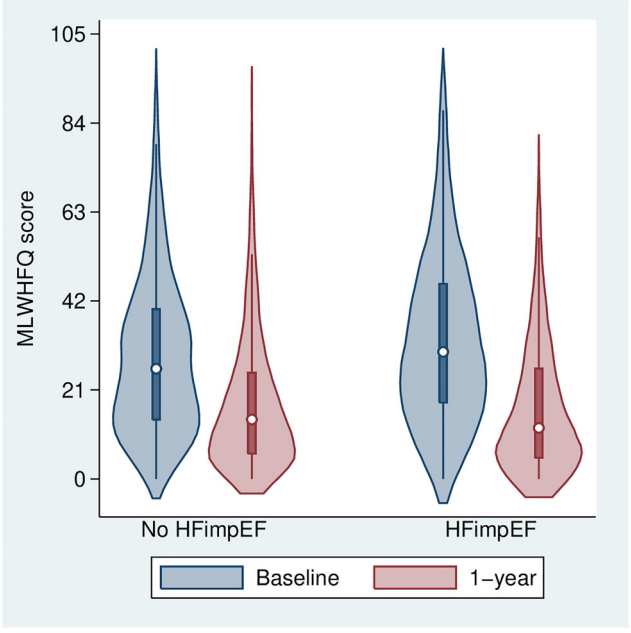


Figure 2 Violin plots of baseline and one-year MLWHFQ scores. The violin plot illustrates the kernel probability density (i.e. the width of the shaded area represents the proportion of the data located there). Inside the violin plots, boxplots indicate the median and interquartile range; the whiskers indicate 1.5 times the interquartile range. Blue violin plots represent the baseline scores. Red violin plots represent the 1-year scores.



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 symptoms[35] and QoL[36] 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, we[25] and others[5,38] 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 symptoms[39] 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,

Table 2 Characteristics associated with QoL improvement

	QoL improvement[a]					
	Univariable			Multivariable		
Characteristic	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 duration[b]	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.
[a]Improvement in the MLWHF score by ≥5 points.
[b]Months, Log(2) transformed.

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

	Composite of all-cause death or HF hospitalization					
	Univariable			Multivariable		
Characteristic	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	2.25	1.62–3.12	<0.001	1.47	0.97–2.22	0.07
HF hospitalizations in previous year	4.04	2.75–5.91	<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.

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 baseline QoL than patients with non-HFimpEF. 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 had 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.[2–10] 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.[26] Previous studies revealed that an improvement in the NYHA functional class translated into a favourable impact on QoL.[2,8] 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[15–23]; but that was not the objective of the present study. Moreover, QoL was previously associated with outcomes in patients with HF.[25–30] However, no study had investigated how QoL might influence the prognosis of patients with HFimpEF. Based on our results, we concluded that

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.

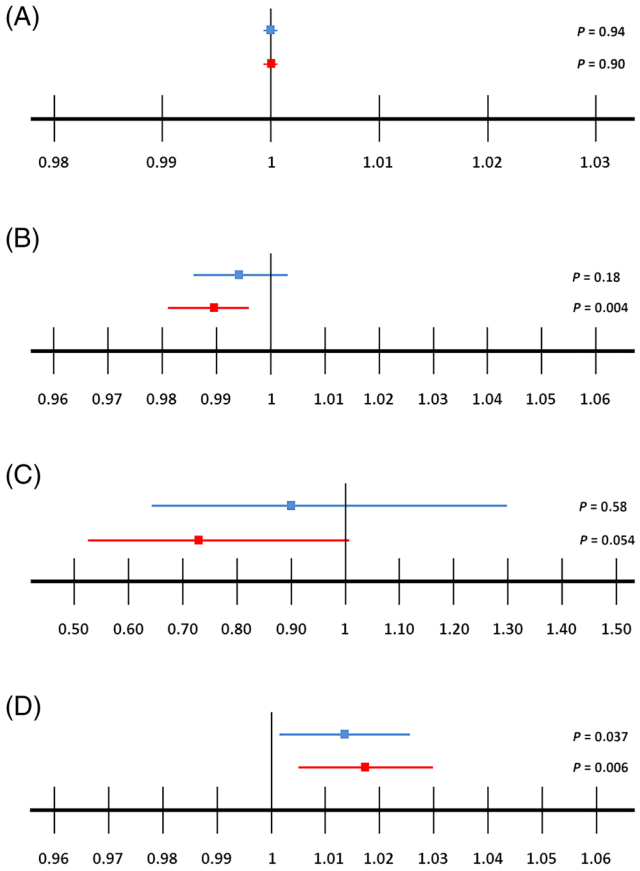


Table 4 Characteristics associated with all-cause death in patients with HFimpEF

	All-cause death					
	Univariable			Multivariable		
Characteristic	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[a]	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.
[a]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.

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