Transient versus persistent improved ejection fraction in non-ischaemic dilated cardiomyopathy

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Aims The recent definition of heart failure with improved ejection fraction outlined the importance of the longitudinal assessment of left ventricular ejection fraction (LVEF). However, long-term progression and outcomes of this subgroup are poorly explored. We sought to assess the LVEF trajectories and their correlations with outcome in non-ischaemic dilated cardiomyopathy (NICM) with improved ejection fraction (impEF).

Methods and results Consecutive NICM patients with baseline LVEF ≤40% enrolled in the Trieste Heart Muscle Disease Registry with ≥1 LVEF assessment after baseline were included. ImpEF was defined as a baseline LVEF ≤40%, and second evaluation showing both a ≥10% point increase from baseline LVEF and LVEF >40%. Transient impEF was defined by the documentation of recurrent LVEF ≤40% during follow-up. The primary endpoint was a composite of all-cause death, heart transplantation and left ventricular assist device (D/HT/LVAD). Among 800 patients, 460 (57%) had impEF (median time to improvement 13 months). Transient impEF was observed in 189 patients (41% of the overall impEF group) and was associated with higher risk of D/HT/LVAD compared with persistent impEF at multivariable analysis (hazard ratio 2.54; 95% confidence interval 1.60–4.04). The association of declining LVEF with the risk of D/HT/LVAD was non-linear, with a steep increase up to 8% points reduction, then remaining stable.

Conclusions In NICM, a 57% rate of impEF was observed. However, recurrent decline in LVEF was observed in ≈40% of impEF patients and it was associated with an increased risk of D/HT/LVAD.

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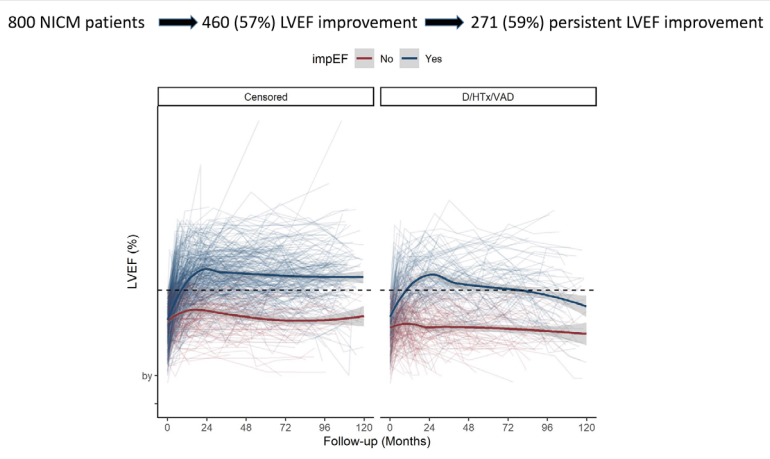
Graphical Abstract



Among the 460 patients with improved ejection fraction (impEF) (57% of the overall cohort), 271 (59%) exhibited a persistent impEF. Longitudinal trends of left ventricular ejection fraction (LVEF) clearly diverged according to outcome in patients with impEF. Patients who experienced the primary outcome (all-cause death/heart transplantation/left ventricular assist device [D/HTx/VAD]) had a larger deterioration in LVEF (median nadir of LVEF 32%, interquartile range 25–42) compared to patients alive free from heart transplantation/left ventricular assist device (median nadir of LVEF 41%, interquartile range 35–49). NICM, non-ischaemic cardiomyopathy.

Keywords Non-ischaemic cardiomyopathy • Heart failure with improved ejection fraction • Left ventricular ejection fraction • Prognosis • Follow-up

Introduction

In patients with heart failure with reduced ejection fraction (HFrEF), left ventricular (LV) reverse remodelling, intended as the improvement or recovery of LV ejection fraction (LVEF) promoted by guideline-directed medical therapy (GDMT), is associated with a positive outcome.[1–5] In former studies, different definitions of LV reverse remodelling/recovery have been proposed.[1–4] Furthermore, the re-assessment of LVEF was generally limited to a single evaluation rather than the serial determination of the whole longitudinal trajectory during follow-up, potentially leading to a general underestimation of the prevalence of LV reverse remodelling.[2,3,4,6] The revised Universal Definition of Heart Failure (HF) recently introduced the subgroup of 'HF with improved ejection fraction' (HFimpEF) in order to provide a standard definition of LVEF improvement and to highlight the importance of the longitudinal assessment of LVEF in HF.[7]

In addition, in patients with HFimpEF, LVEF can deteriorate again after a variable period of stability, suggesting the persistence of structural myocardial abnormalities.[4,6,8,9] When the recurrent decline in LVEF results from the discontinuation of GDMT it is associated with poor prognosis,[9] but it can occur despite the continuation of treatments.

In non-ischaemic dilated cardiomyopathy (NICM) the likelihood of LV reverse remodelling is higher compared to ischaemic aetiology.[2,3,10] Moreover, NICM is generally characterized by a prolonged clinical course in which recurrent LV dysfunction may occur as the result of the natural progression of the disease or the advent of new incipient factors.[7,8,10]

Nevertheless, the recent definition of improved ejection fraction (impEF) and the prognostic implications of recurrent decline of LVEF in patients with NICM and impEF have not been specifically evaluated.

In the present study we adopted the recent definition of impEF in a large cohort of NICM with serial longitudinal assessment of LVEF in order to (i) define the overall incidence, (ii) provide a comprehensive characterization, and (iii) explore the prognostic correlates of transient versus persistent impEF.

Methods

All the consecutive NICM patients enrolled between 1991 and March 2018 in the Trieste Heart Muscle Disease Registry[11] were retrospectively analysed. Patients with baseline LVEF ≤40% and ≥1 echocardiographic evaluation during follow-up in addition to baseline assessment were included. NICM was defined according to the current criteria as a decline of LVEF in absence of coronary artery disease or abnormal loading conditions.[12] The absence of a significant (i.e. >50%) stenosis in

a major coronary artery branch was systematically ruled out by coronary angiography or computed tomography according to the pre-test likelihood. Advanced systemic diseases affecting short-term prognosis, pericardial diseases, congenital heart diseases, cor pulmonale, persistent supraventricular tachyarrhythmias, severe organic valve diseases and a clinical presentation concordant with acute coronary syndrome, including stress cardiomyopathy,[13] were considered as exclusion criteria. Active myocarditis was excluded based on clinical criteria, and, when suspected, by cardiac magnetic resonance and/or endomyocardial biopsy according to our internal protocol and current international recommendations.[14]

The longitudinal trajectory of LVEF was analysed at every time-point during follow-up. ImpEF was defined as the documentation of a baseline LVEF ≤40% and a second measurement of LVEF >40% with a ≥10% points increase from baseline LVEF at the same echocardiographic follow-up.[7] Then, impEF was defined persistent if LVEF was >40% in all the subsequent available evaluations following the first one with documented improvement, and transient if a recurrent decline (≤40%) of LVEF was documented at ≥1 evaluation following the first that attested the impEF. Patients without further assessment of LVEF after the one documenting the impEF were considered as persistent impEF.

Guideline-directed medical therapy (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists) was introduced and systematically titrated at each follow-up as tolerated according to current guidelines.[15] Implantable cardioverter defibrillators and cardiac resynchronization therapy were implanted if indicated.[16]

In order to analyse the possible influence of aetiology on the trajectories of LVEF, a separate analysis was performed in a subset of patients enrolled between 2005 and 2018, as from 2005 the registry was implemented with in-depth aetiological characterization of NICM. The following groups were considered: (1) idiopathic NICM, (2) genetically determined NICM, (3) chemotherapy-induced, (4) post-myocarditis, (5) alcohol-induced, and (6) NICM with associated hypertension (see online supplementary *Appendix S1* for complete definitions).[17]

Echocardiographic analysis

Left ventricular dimensions and function were assessed according to the international guidelines.[18] LV volumes were indexed according to patients' body surface areas. LVEF was calculated by Simpson's biplane method. Diastolic function was assessed according to current recommendatons.[19] A right ventricular fractional area change <35% or tricuspid annular plane systolic excursion <17 mm defined right ventricular dysfunction. Mitral regurgitation was considered only if moderate/severe (>2+). Echocardiographic evaluations were performed per protocol at baseline, 6 months, 12 months, 24 months, and then every second year, or more frequently as for clinical need. All available evaluations were considered for the present analysis.

Outcome measure

The outcome measure was a composite of all-cause death, heart transplantation and left ventricular assist device implantation as destination therapy (D/HT/LVAD). Information regarding the outcome was obtained from official reports drawn up by hospitals, direct contact with patients, their families or general practitioners, queries of regional healthcare data warehouse and registers of death of the municipalities of residence. The enrolment date was considered the first evaluation at our centre and the end of follow-up was set on 30 September 2020 or at the time of D/HT/LVAD, so that potentially all patients had ≥30 months of evaluation. Outcome information was available for all the included patients. The institutional ethics board approved the study, and informed consent was obtained under the institutional review board policies of the hospital administration. This study complies with the Declaration of Helsinki and with the local legal requirements.

Statistical analysis

Clinical and laboratory statistics are reported as means and standard deviation, medians and interquartile ranges, or counts and percentages, as appropriate. Cross-sectional comparisons between groups were made by the ANOVA test on continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances did not hold, or the non-parametric Mann–Whitney U test when necessary. The chi-square or Fisher exact tests were calculated for discrete variables. An extended Kaplan–Meier estimator[20] was used to compare survival curves stratified by incident impEF during follow-up versus patients who never experienced impEF. Thus, the dataset was organized in a counting process format and patients can contribute to different curves at different times during follow-up. The cumulative incidence function of impEF was also estimated taking into account the competing risk of D/HT/LVAD and compared between groups with Gray's test. To identify variables associated with impEF, in the overall population, and with transient impEF (in the subgroup with impEF), uni- and multivariable cause-specific Cox regression models were fitted.[21] A multivariable Cox model was then estimated for the composite study outcome, treating impEF as time-dependent covariate. Non-linearity of model covariates was excluded by graphical diagnostics of the martingale residuals. Variables previously associated with prognosis in NICM,[3,6,10,17,22–24] avoiding collinearity, were included as model covariates. In the subgroup of patients with impEF, a multivariable Cox regression model was used to estimate the association between transient impEF and the outcome, adjusting for both fixed and time-dependent variables. Time zero was considered the time of documented LVEF worsening. For the latter, a sensitivity analysis that considered only patients with at least one echocardiographic evaluation after the documentation of impEF was performed.

Moreover, an additional sensitivity analysis was performed using a dichotomous threshold of LVEF decline, thus considering transient impEF as an absolute LVEF ≤40% plus a reduction of LVEF >5% points. Finally, we also assessed the association between the reduction of LVEF and the primary outcome by considering LVEF decline as a continuous variable and modelling it using a restricted cubic spline with 4° of freedom to allow for a non-linear effect. Non-linearity was tested with the likelihood ratio test by comparing the model with a linear effect and the model without it. All statistical analyses were performed with IBM-SPSS (New York, NY, USA) 25 and R statistical package 3.6.2 (R Foundation, Vienna, Austria), with libraries 'survival', 'cmprsk', 'ggplot2'.

Results

Study population

Among the 1233 NICM patients enrolled in the Trieste Heart Muscle Registry during the study period, 433 were excluded (282 with baseline LVEF >40% and 151 owing to lacking echocardiographic follow-up), thus in total 800 patients with NICM were considered for the analysis (online supplementary *Figure S1* and *Table S1*). During a median follow-up of 11 (interquartile range [IQR] 6–14) years, the median number of LVEF evaluations per patients was 5 (IQR 3–8). The number of patients with available echocardiographic evaluations at each time-point is shown in online supplementry *Figure S2*. *Table 1* summarizes the main baseline clinical and echocardiographic characteristics of the study population.

Improved ejection fraction in non-ischaemic dilated cardiomyopathy

In total 460 patients had impEF (57% of the overall cohort), with a median time to impEF of 13 (IQR 7–25) months. In a substantial number of patients (n = 122, 27%), impEF was observed beyond the first 24 months (*Figure 1*).

The potential influence of aetiology on the cumulative incidence of impEF was assessed starting from 2005 (number of patients = 453): impEF was less likely in primary aetiologies (idiopathic and genetically determined NICM) compared to secondary aetiologies (chemotherapy-induced, post-myocarditis, alcohol-induced, with associated hypertension) (online supplementary *Figure S3*). The baseline factors independently associated with impEF are summarized in online supplementary *Table S2*.

Table 1 Baseline characteristics of the study population

Characteristics	All population (n = 800)	Non-impEF (n = 340; 43%)	ImpEF (n = 460; 57%)	Missing rate	p-value
Age (years)[a]	51 ± 14	51.8 ± 15	50.8 ± 13	0 (0%)	0.336
Male sex[a]	569 (71.1%)	243 (71.5%)	326 (70.9%)	0 (0%)	0.875
SBP (mmHg)[a]	125 ± 19	122 ± 19	126 ± 19	16/800 (2%)	**0.007**
HR (bpm)[a]	76 ± 17	73 ± 15	78 ± 18	48/800 (6%)	**<0.001**
NYHA class III–IV[a]	233 (29.1%)	96 (30%)	137 (30.8%)	32/800 (4%)	0.873
Creatinine (mg/dl)	1.01 ± 0.20	1.02 ± 0.21	0.99 ± 0.19	248/800 (31%)	0.381
Hb (g/dl)	14.4 ± 1.5	14.4 ± 1.4	14.3 ± 1.8	208/800 (26%)	0.914
Early disease onset (i.e. <6 months)[a]	356 (44.5%)	110 (32.4%)	246 (53.1%)	0 (0%)	**<0.001**
Periods of enrolment					
1991–2000[a]	262 (32.8%)	94 (27.6%)	168 (36.5%)		**0.010**
2001–2010[a]	301 (37.6%)	127 (37.4%)	174 (37.8%)		0.941
2011–2018[a]	237 (29.6%)	119 (35%)	118 (25.7%)		**0.005**
Treatments					
ACEI/ARBs/ARNI	781 (97.6%)	329 (96.8%)	452 (98.3%)	0 (0%)	0.240
Beta-blockers	724 (90.5%)	296 (87.1%)	428 (93%)	0 (0%)	**0.005**
Loop diuretics	591 (74%)	258 (75.9%)	333 (72.4%)	0 (0%)	0.290
MRAs	346 (43.3%)	159 (46.8%)	187 (40.7%)	0 (0%)	0.097
CRT (during follow-up)	125 (15.6%)	59 (17.4%)	66 (14.3%)	0 (0%)	0.279
ICD (during follow-up)	252 (31.5%)	129 (37.9%)	123 (26.7%)	0 (0%)	**0.001**
ECG					
QRS length (ms)	119 ± 33	123 ± 32	115 ± 32	224/800 (28%)	**0.003**
LBBB[a]	271 (33.9%)	127 (37.9%)	144 (31.7%)	8/800 (1%)	0.081
AF	58 (7.3%)	23 (6.9%)	35 (7.7%)	8/800 (1%)	0.075
Echocardiography					
LVEF (%)[a]	27.8 ± 7	27.8 ± 7	27.8 ± 6	0 (0%)	0.884
iLVEDV (ml/m^2)	97 ± 38	101 ± 41	94 ± 35	40/800 (5%)	**0.020**
iLVESV (ml/m^2)	71 ± 32	74 ± 36	69 ± 29	44/800 (5.5%)	**0.032**
LAESA (cm^2)	27 ± 8	28.5 ± 8	26.3 ± 7	32/800 (4%)	**<0.001**
RFP[a]	230 (28.8%)	102 (30%)	128 (27.8%)	0 (0%)	0.528
RV dysfunction[a]	192 (24%)	86 (25.3%)	106 (23%)	0 (0%)	0.503
Moderate-severe MR[a]	354 (44.3%)	164 (48.2%)	190 (41.3%)	0 (0%)	0.052

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; Hb, haemoglobin; HR, heart rate; ICD, implantable cardioverter defibrillator; iLVEDV, indexed left ventricular end-diastolic volume; iLVESV, indexed left ventricular end-systolic volume; impEF, improved ejection fraction; LAESA, left atrial end-systolic area; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RFP, restrictive filling pattern; RV, right ventricular; SBP, systolic blood pressure.

[a]Variables included in the Cox multivariable model for the study outcome.

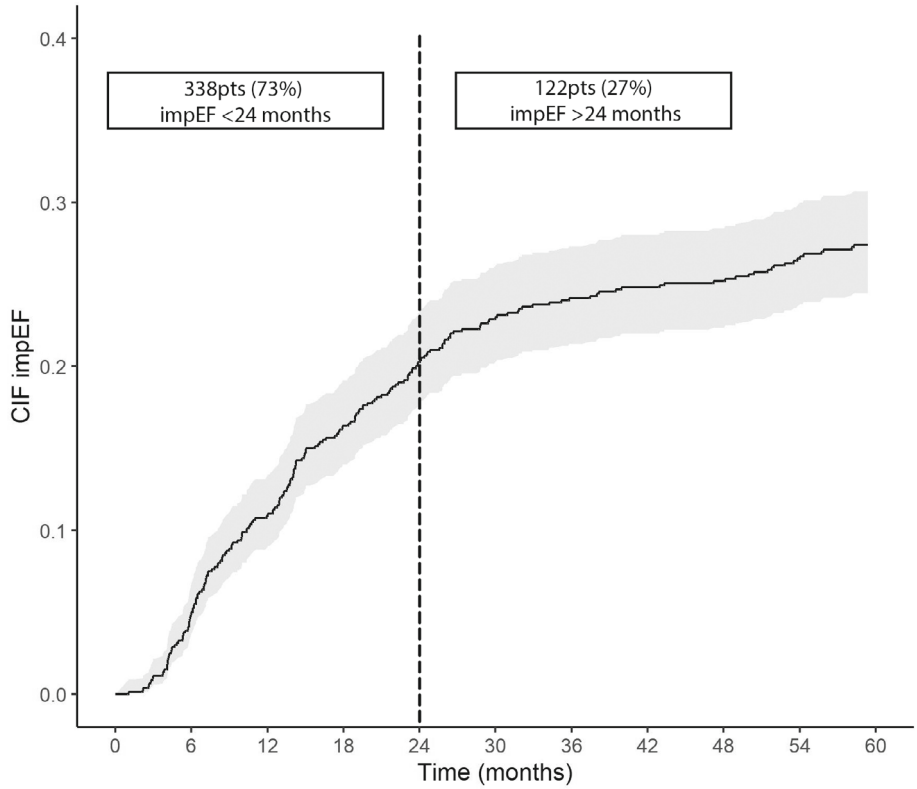


Figure 1 Cumulative incidence of improved ejection fraction (impEF) in the study population. The probability of impEF increased overtime. While most of patients (73% of the improved patients) improved the ejection fraction within 24 months (median time to impEF 13 months, interquartile range 7–25), a substantial number of patients (27% of the improved patients) improved ejection fraction beyond 24 months. CIF, cumulative incidence function.

Over a median follow-up of 122 (IQR 62–138) months, the outcome measure of D/HT/LVAD occurred in 273 patients (34% of the total population; 192 deaths, 69 HT, 12 LVAD). Patients with impEF had an unadjusted (online supplementary *Figure S4*) and adjusted (hazard ratio [HR] 0.36; 95% confidence interval [CI] 0.27–0.48; $p < 0.001$; online supplementary *Table S3*) lower risk of D/HT/LVAD compared to non-improved patients.

Transient versus persistent improved ejection fraction

ImpEF was transient in 189 patients (41% of patients with impEF) and persistent in 271 (59%). The median time to LVEF worsening in patients with impEF was 62 (IQR 34–102) months and the median absolute decline in LVEF was 11% (IQR 7–15). Clinical and echocardiographic characteristics of patients with transient versus persistent impEF at the time of documented impEF are summarized in *Table 2*. In patients with transient impEF, 97 (51%) were asymptomatic (New York Heart Association [NYHA] class I) at the time of impEF. Among them, 35% had recurrent symptoms in concomitance with recurrent LV dysfunction. An apparent complete remission of HF (NYHA class I and LVEF >50%) was instead observed in 162/460 patients (35%) of which 30 experienced recurrent LV dysfunction without symptoms and 10 experienced both recurrent LVEF ≤40% and recurrent symptoms (online supplementary *Figure S5*).

At baseline, no characteristics were independently associated with transient impEF, whereas at the time of impEF, older age (HR for every year increase 1.06; 95% CI 1.03–1.09; $p < 0.001$), lower LVEF (HR for every point increase 0.93; 95% CI 0.89–0.97; $p = 0.002$) and duration of disease longer than 6 months (HR 4.76; CI 1.54–16.77; $p = 0.007$) were independently associated with transient impEF at multivariable Cox regression analysis (*Table 3*). A clear divergence in the trajectories of LVEF after impEF was documented according to the outcome (*Graphical Abstract*). In patients alive free from D/HT/LVAD, we observed a steady trend of LVEF above 40%, while in patients who died or were transplanted/implanted with LVAD, LVEF deteriorated over time. The nadir value of LVEF after the initial improvement, indeed, was significantly lower in patients that experienced D/HT/LVAD (nadir LVEF 32%, IQR 25–42) versus patients alive free from HT/LVAD (nadir LVEF 41%, IQR 35–49).

There was a non-linear relationship between the decline in LVEF and the risk of D/HT/LVAD with a progressive increase in risk up to 8% points of decline, that remained stable for higher values (*Figure 2*). At multivariable analysis, patients with transient impEF

Table 2 Characteristics of patients with transient versus persistent improved ejection fraction at the time of improved left ventricular ejection fraction

Characteristics	Transient impEF (n = 189; 41%)	Persistent impEF (n = 271; 59%)	p-value
Age (years)	53 ± 13	50 ± 14	**0.002**
SBP (mmHg)	129 ± 17	126 ± 17	0.056
HR (bpm)	68 ± 12	67 ± 12	0.452
NYHA class III–IV	63 (33.9%)	74 (28.6%)	0.253
Treatments			
ACEI/ARBs/ARNI	173 (91.5%)	249 (91.8%)	0.680
Beta-blockers	166 (92.7%)	223 (90.7%)	0.281
Loop diuretics	89 (54.3%)	126 (57.3%)	0.314
MRAs	43 (24.2%)	80 (32.7%)	0.065
CRT (during follow-up)	36 (19%)	30 (11.1%)	**0.021**
ICD (during follow-up)	78 (41.3%)	45 (16.6%)	**<0.001**
ECG			
QRS length (ms)	115 ± 33	114 ± 31	0.860
LBBB	44 (25.7%)	47 (20.8%)	0.150
AF	2 (1.2%)	8 (3.5%)	0.147
Echocardiograhy			
LVEF (%)	43 ± 8	48 ± 8	**<0.001**
iLVEDV(ml/m^2)	73 ± 26	63 ± 21	**<0.001**
iLVESV (ml/m^2)	42 ± 18	33 ± 14	**<0.001**
LAESA (cm^2)	23 ± 6	22 ± 5	**0.014**
RFP	11 (8%)	8 (7.3%)	0.833
RV dysfunction	20 (10.5%)	18 (6%)	0.132
Moderate-severe MR	34 (18%)	21 (7.7%)	**0.001**

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; HR, heart rate; impEF, improved ejection fraction; ICD, implantable cardioverter defibrillator; iLVEDV, indexed left ventricular end-diastolic volume; iLVESV, indexed left ventricular end-systolic volume; LAESA, left atrial end-systolic area; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MR, mitral regurgitation; NYHA , New York Heart Association; RFP, restrictive filling pattern; RV, right ventricular; SBP, systolic blood pressure.

Table 3 Factors associated with the risk of recurrent left ventricular dysfunction at Cox multivariable regression analysis in patients with improved ejection fraction

Characteristic	HR[a]	95% CI	p-value
Age (years)	1.06	1.03–1.09	**<0.001**
Male sex	1.87	0.90–3.88	0.092
HR (bpm)	1.02	0.99–1.05	0.13
SBP (mmHg)	0.98	0.95–1.01	0.12
Late disease onset (i.e. >6 months)	4.76	1.54–16.67	**0.007**
Periods of enrolment			
1991–2000	–	–	–
2001–2010	0.68	0.31–1.49	0.3
2011–2018	0.41	0.15–1.09	0.075
LBBB	2.22	0.88–5.61	0.092
LAESA (cm^2)	0.99	0–94-1.05	0.8
LVEF (%)	0.93	0.89–0-97	**0.002**
RFP	0.36	0.11–1.18	0.09
Moderate-severe MR	1.10	0.70–1.71	0.7
RV dysfunction	1.45	0.44–4.75	0.5

Baseline is intended at the time of documented improved ejection fraction.
424 patients with complete data out of 460 patients with improved ejection fraction were included in the model.
CI, confidence interval; HR, hazard ratio/heart rate; LAESA, left atrial end-systolic area; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; RFP, restrictive filling pattern; RV, right ventricular; SBP, systolic blood pressure.
[a]HRs for continuous variable are expressed for increase of every unit of measure.

had an almost three-fold increased risk of D/HT/LVAD compared to patients with persistent impEF (HR 2.54; 95% CI 1.60–4.04; $p < 0.001$) (*Table 4*).

In the sensitivity analysis that included only patients with at least one echocardiographic assessment after the documentation of impEF, 79 impEF patients were excluded. Accordingly, the proportion of transient impEF increased up to 49% (189 of the 381 patients with impEF). However, transient impEF remained strongly associated with the risk of D/HT/LVAD (online supplementary *Table S4*). Finally, including the 5% points threshold of LVEF decline in the definition of transient impEF, the overall number of patients with transient impEF decreased to 175 (39% of the total impEF cohort), but the association with the risk of D/HT/LVAD was unchanged (online supplementary *Table S5*).

Discussion

The recovery of LVEF is a major therapeutic goal in HFrEF that leads to a definite prognostic benefit. Several definitions of LVEF recovery/LV reverse remodelling were proposed and these have influenced the incidence estimation and the magnitude of benefit determined by improved LV function. Furthermore, the structural and molecular abnormalities of the diseased myocardium underlying reduced contractility persist despite the improvement of systolic function and potentially expose the left ventricle to a late new decline of LVEF.

The recent definition of HFimpEF provided a standard definition for the entity of LVEF improvement.[7] However, some aspects, including the incidence of impEF in specific setting such as NICM, the risk of recurrent LV dysfunction and its impact on prognosis, remain partially unexplored.

In this study we adopted the recently proposed definition of impEF in a large cohort of NICM patients recruited in a single tertiary care centre for HF and cardiomyopathies with serial longitudinal re-evaluations (median 5) over a median follow-up of ≈10 years. The main findings were that (i) the incidence of impEF in NICM patients during long-term follow-up was ≈60%, (ii) although the median time to impEF was 13 months, in 21% of cases impEF occurred beyond the second year of follow-up, and (iii) across the whole observation period, ≈40% of patients with impEF experienced recurrent LV dysfunction with an almost three-fold increased risk of D/HT/LVAD compared to patients with persistent impEF.

Improved ejection fraction in non-ischaemic dilated cardiomyopathy: the importance of longitudinal assessment

Non-ischaemic dilated cardiomyopathy represents a subgroup of HFrEF with, in general, good response to GDMT. In retrospective studies, the prevalence of LVEF improvement ranged between 10% and 38%, according to the adopted definitions,[2–4,25–27] and it was

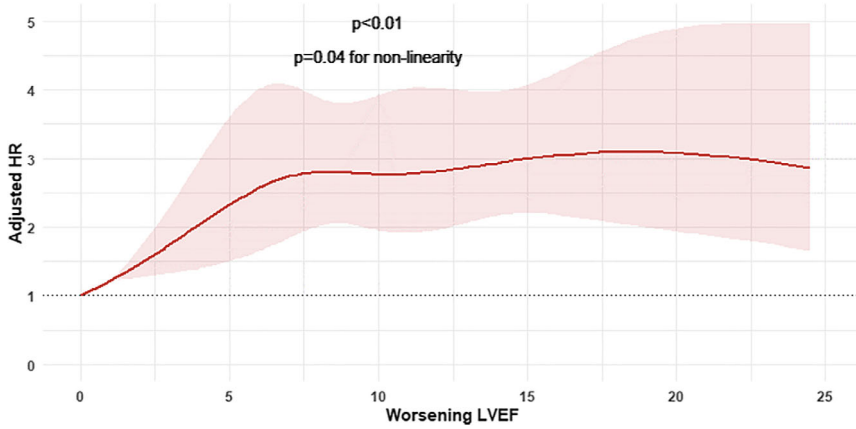


Figure 2 Association between left ventricular ejection fraction (LVEF) worsening and the risk of all-cause death/heart transplant/left ventricular assist device implantation for each point of LVEF worsening in patients reaching LVEF ≤40% after improvement. LVEF worsening is treated as a continuous variable. The light painted area indicate 95% confidence interval (CI). A worsening of 0 points was considered as reference value. Hazard ratio (HR) between 0 and 5 points: 2.33 (95% CI 1.50–3.61); HR between 0 and 7 points: 2.74 (95% CI 1.84–4.08); HR between 0 and 10 points: 2.78 (95% CI 1.95–3.92). impEF, improved ejection fraction; NYHA, New York Heart Association.

Table 4 Cox multivariable regression model for all-cause death/heart transplant/left ventricular assist device (only patients with improved ejection fraction)

Characteristic	HR	95% CI	*p*-value
Transient versus persistent impEF	2.54	1.60–4.04	**<0.001**
Age	1.04	1.02–1.06	**<0.001**
Male sex	1.60	0.97–2.64	0.2
HR	1.00	0.99–1.01	0.9
SBP	0.99	0.98–1.00	0.2
Early disease onset (i.e. <6 months)	0.89	0.57–1.39	0.6
NYHA class III–IV	1.42	0.89–2.25	0.14
Periods of enrolment			
1991–2000	–	–	–
2001–2010	0.42	0.24–0.74	**0.003**
2011–2018	0.41	0.15–1.09	0.075
LBBB	0.63	0.39–1.03	0.068
LVEF	0.99	0.96–1.02	0.6
LAESA	0.99	0.94–1.05	0.8
RFP	0.98	0.58–1.65	0.9
Moderate-severe MR	1.38	0.90–2.12	0.14
RV dysfunction	1.52	0.86–2.70	0.15

420 patients with complete data out of 460 patients with impEF were included in the model.
CI, confidence interval; HR, hazard ratio/heart rate; impEF, improved ejection fraction; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; RFP, restrictive filling pattern; RV, right ventricular; SBP, systolic blood pressure.

lower in clinical trials.[10] However, the timing of LV response to therapies is not completely established, and in most of the previous studies it was evaluated at single timelines,[2–4,25,26] while longitudinal reassessment of LVEF over longer period of follow-up has rarely been reported.[5,6,8]

In our study, that encompassed a >10-year follow-up and included only NICM, the rate of impEF was 57%, which is higher compared to previous experiences. This is likely due to the serial longitudinal assessment adopted in our study (median of five LVEF evaluations per patient) rather than an arbitrarily established single timing for the reassessment of LVEF. Noteworthy, we observed a 21% of impEF beyond the first 2 years of observation, supporting the concept that impEF can occur in the late course of disease. Indeed, serial implementation of treatments or, alternatively, a delayed response to GDMT might not be rare in these patients. Secondary aetiologies had higher likelihood of impEF compared to primary aetiologies (i.e. idiopathic and genetic dilated cardiomyopathy).

The prognostic advantage of recovered/improved LVEF on therapy has been demonstrated in our analysis even after extensive adjustment confirming data from previous studies.[1–6,25,26]

Transient versus persistent improved ejection fraction

The natural history of patients with HFimpEF remains unexplored. Data are limited to patients with complete normalization (>50%) of LVEF and showed that patients with normalized LVEF remained at increased risk of events compared to the general population regardless of therapy.[4] This is further supported by the fact that, despite LVEF normalization, recurrent LV dysfunction during follow-up has been reported in 20%–40% of cases in the setting of NICM,[6,28] and a single open-label randomized study on a small sample of patients with dilated cardiomyopathy demonstrated >40% disease relapse in the arm of treatment withdrawal.[9]

More recently, the trajectory of LVEF was serially assessed over a 15-year period in a HF cohort confirming, after the initial improvement, the tendency to a slow decline of LVEF very late during follow-up.[8] The more reliable explanation is that reverse

remodelling is the adaptation of the left ventricle to the abnormal condition promoted by therapy, but persisting molecular and structural abnormalities make the failing heart more prone to recurrent LV dysfunction when exposed to triggering factors such as therapeutic withdrawal or super-imposed external injuries.[27,29]

In our series including ≈1000 NICM patients with a median of five LVEF reassessments per patient over a median 11-year follow-up, we documented a 41% rate of recurrent LV dysfunction (i.e. LVEF ≤40%) in patients with previous impEF, with a median time to recurrent LV dysfunction of ≈5 years. Compared to previous reports, the rate of recurrent LV dysfunction was higher.[6,28] This difference might be partially explained by the longer period of observation and by the serial longitudinal reassessment during follow-up.[6] While no parameters at baseline were independently associated with transient impEF, at the time of improvement lower LVEF, older age and longer duration of disease were associated with increased risk of recurrent deterioration of LVEF and might aid to stratify patients requiring closer follow-up.

The prognostic implications of recurrent LV dysfunction in patients with impEF were largely unknown. In a previous descriptive report from our group, we reported higher mortality/HT in patients with a decline in LVEF after an initial normalization.[6] In the current study, the decline in LVEF was paired with a greater exposure to the risk of D/HT/LVAD as attested by the clear divergence in the trajectories of LVEF according to outcome (*Graphical Abstract*). Moreover, in the adjusted analysis, patients with transient versus persistent impEF had an almost three-fold increased risk of D/HT/LVAD. In this sense, our findings overcome the limitations of previous reports, suggesting the strong independent prognostic role of recurrent LVEF worsening, and tracing a more reliable incidence of this phenomenon in NICM. Of note, we observed a steep increase in the risk of D/HT/LVAD for each point of LVEF decline up to 8% points, that remained instead stable for values beyond 8%. This suggests that strategies of treatment implementation should be carefully considered for any decline in LVEF observed during the follow-up of patients with impEF.

Unfortunately, in the present study information about therapies and dosages was partial, thus we were not able to explore the interactions between therapeutic escalation/de-escalation, trends in LVEF and outcomes. In general, indefinite continuation of GDMT is advocated in our Centre for every patient unless contraindicated, including those with complete LVEF recovery. However, future dedicated investigations are strongly warranted to better define these aspects.

Study limitations

Some limitations need to be acknowledged. As all observational studies on long-term registries, this study suffers from the common bias due to its retrospective design. The current study population was enrolled in a single third-level centre for HF and cardiomyopathies and included only NICM patients, limiting the generalizability of results.

The exclusion of patients without echocardiographic re-evaluation during follow-up might have generated a selection bias. However, the main characteristics and the rate of D/HT/LVAD of these patients did not differ from the study cohort. Patients with impEF and no additional echocardiographic assessment after the documentation of impEF were considered as persistent impEF, as in our experience patients deferring the follow-up or that decide to be followed at the referring clinic are in general those more stable and without warnings of forthcoming deterioration. However, a sensitivity analysis that considered only patients with available imaging after impEF was performed and largely confirmed the results of the primary analysis.

Several parameters included in the multivariable models could be biased due to the exclusion of patients with missing data. However, the low missing rate of our population partially overcame this limitation.

Despite the limited interval between consecutive assessments of ejection fraction, the exact timing of ejection fraction improvement or deterioration could not be defined and, thus, must be considered an estimation.

Cardiac magnetic resonance data and deformation echocardiographic imaging, which might provide further insights into this setting, were not systematically available and thus were not part of this study.

Although we showed a higher probability of impEF in patients affected by modifiable NICM aetiologies compared to those with idiopathic or genetically determined NICM, we did not include aetiologies in the Cox regression model, as a precise aetiological characterization was available only since 2005.

The wide timeline of enrolment might have determined a heterogeneity in treatment between former and more recent patients. For this reason, period of enrolment was included as a confounder in adjusted analyses.

Data on brain natriuretic peptides were not systematically available for all the patients and were not included in the analyses.

Intra and inter-observer variability in the estimation of LVEF could have determined the misclassification of some patients with LVEF values around 40%.

Finally, novel HF therapies such as angiotensin receptor–neprilysin inhibitors and sodium–glucose contransporter 2 inhibitors were used in a minority of patients. We cannot exclude that future implementation of such drugs would further increase the proportion of patients with impEF or modify the rates of recurrent LV dysfunction.[30]

Conclusions

We found that almost 60% of patients with NICM improved LVEF during follow-up even beyond the traditional 12-month timeline, with associated more favourable outcomes. However, through the observation of the long-term trajectories of LVEF we documented in patients with impEF a ≈40% rate of recurrent LV dysfunction, with potential negative impact on survival. Regular follow-up should not be abandoned in patients with impEF and the late deterioration of LVEF should be strongly considered in the definition of treatment implementation in order to counteract its negative prognostic implications.

Supplementary Information

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

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