

Association Between Left Ventricular Ejection Fraction and 1-Year Outcomes in Patients with Heart Failure with Reduced Ejection Fraction

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Abstract:

Background: Left ventricular ejection fraction (LVEF) is the backbone of the classification and management of heart failure with reduced ejection fraction (HFrEF) and the prognostic gradient across the reduced-EF range is clinically heterogeneous. Study Hypothesis: Baseline LVEF is associated with 1-year mortality and heart failure hospitalization in adults with HFrEF.

Methods: This was a prospective observational cohort of 312 consecutive adults with symptomatic HFrEF and LVEF $\leq 40\%$. Participants were categorized as LVEF $\leq 25\%$, 26–30%, 31–35%, and 36–40%. The main outcome was a composite of all-cause mortality or unplanned heart-failure hospitalization at 1 year. Cox proportional-hazards models were used to identify independent predictors.

Results: Mean age was 61.8 ± 11.4 years, 71.5% were men, and mean LVEF was $29.7 \pm 6.1\%$. The primary endpoint occurred in 107 patients (34.3%). Event rates decreased progressively across LVEF categories: 48.8%, 38.9%, 25.6%, and 17.2%, respectively ($p < 0.001$). The rate of one-year mortality was 14.4%, and 27.2% had at least one hospitalization for heart failure. For every 5 percentage-point increase in LVEF, the risk of the primary endpoint was reduced by 26% (adjusted hazard ratio 0.74, 95% CI 0.62–0.88; $p = 0.001$) after accounting for age, systolic blood pressure, renal function, natriuretic peptide concentration, New York Heart Association functional class, ischemic etiology, and guideline-directed therapy. Higher risk was identified independently by LVEF $\leq 25\%$, eGFR < 60 mL/min/1.73 m² and NYHA class III–IV.

Conclusion: In HFrEF, LVEF was gradedly associated with worse 1-year outcomes and was an independent predictor of outcomes over major clinical covariates.

Keywords: Heart Failure; Reduced Ejection Fraction; Left Ventricular Ejection Fraction; Hospitalization; Mortality; Prognosis.

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Introduction

HF with reduced EF (HFrEF) is a significant contributor to early death, re-hospitalization, and decreased quality of life. Modern recommendations focus on LVEF $< 40\%$ as the main criterion for HFrEF, and suggest that multidrug disease-modifying therapy can significantly reduce the risk of cardiovascular death and progression of heart failure [1]. European guidance also focuses on LVEF phenotyping, but the prognosis is also affected by age, renal function, congestion, blood pressure, functional class, comorbidity and treatment intensity [2]. Despite these advances, the use of LVEF continues as a quick summary indicator of systolic performance and for the eligibility criteria for a number of pharmacologic and device therapies.

LVEF value does not have a consistent prognostic significance over the entire range. In stable heart-failure cohorts, mortality increases with decreasing LVEF, but this is more strongly seen when LVEF is clearly below the normal or mildly reduced range [3]. Individual-patient analyses have also demonstrated significant survival differences between reduced and preserved EF phenotypes and indicated a clinically meaningful cut-point at $\sim 40\%$ [4]. Therefore, it is important to recognize that all patients with LVEF $\leq 40\%$ are not the same, and that this may be masked by grouping them together.

With the advent of heart failure risk stratification, LVEF is increasingly combined with other commonly available parameters. The MAGGIC risk model demonstrated that the combination of age,

LVEF, creatinine, blood pressure, diabetes, chronic obstructive pulmonary disease, symptom severity, smoking, body mass index, and treatment variables are independent factors that contribute to the estimation of mortality [5]. However, LVEF is especially valuable because it can be repeated during follow-up, it influences decisions about ICD and CRT placement, and it can be altered by reverse remodeling following optimal treatment.

Another question that is relevant to the modern therapeutic era is whether baseline LVEF remains an independent prognostic marker in the era of contemporary guideline-directed therapy. Sacubitril/valsartan has been shown to lower cardiovascular mortality and heart-failure hospitalization in symptomatic HFrEF [6] and dapagliflozin [7] and empagliflozin [8] have been shown to reduce worsening heart-failure events in large HFrEF populations. The absolute event rates in these therapies may not reflect current clinical practice as these estimates are adjusted for these therapies.

This study sought therefore to investigate the relationship between baseline LVEF and clinical outcomes at 1 year in adults with HFrEF treated with modern therapy. The main goal was to see if there was a higher risk of death from any cause or unplanned heart-failure hospitalization with progressively lower LVEF. Secondary objectives included comparing individual outcomes components between LVEF categories, and assessing whether LVEF was independently associated with events, after adjusting for clinical, biochemical, and treatment-related variables.

Materials and Methods

Study Design and Participants: A prospective, observational cohort study was conducted. Consecutive adults (18 years or older) who received a clinical diagnosis of chronic HFrEF in a cardiology service were screened. Symptoms or signs of heart failure, LVEF $\leq 40\%$ (confirmed by transthoracic echocardiogram within 30 days of enrollment), and clinically stable at the index assessment. Patients with acute myocarditis, congenital heart disease requiring intervention, severe primary valvular disease planned for surgery, hypertrophic cardiomyopathy, active malignancy with less than 1 year prognosis, and inability to complete follow-up were excluded. A total of 312 participants formed the analytic cohort.

Clinical evaluation and echo: Baseline data were age, sex, BMI, duration of heart failure, ischemic or non-ischemic etiology, previous myocardial infarction, hypertension, diabetes mellitus, atrial fibrillation, smoking status, NYHA functional class, resting heart rate, and blood pressure. Hemoglobin, serum sodium, potassium, creatinine, estimated

glomerular filtration rate (eGFR), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were obtained. Medications used were angiotensin receptor-neprilysin inhibitor or ACE inhibitor/ARB, evidence-based beta-blocker, mineralocorticoid receptor antagonist, sodium-glucose cotransporter-2 inhibitor, and loop diuretic. Standard 2D transthoracic echocardiograms were used. If technically possible, LVEF was calculated using the biplane Simpson method and confirmed by an experienced cardiologist. Participants were categorized into four prespecified groups: $\leq 25\%$, 26–30%, 31–35%, and 36–40%.

Outcomes and Follow-up: The participants were followed for 12 months after the index assessment. The main outcome was the first hospitalization for worsening heart failure or death from any cause. The outcome of hospitalization for heart failure was defined as an unplanned admission of ≥ 24 hours and the presence of the typical signs or symptoms of congestion and/or increased use of intravenous diuretics and/or vasoactive therapy. Secondary outcomes were all-cause mortality, cardiovascular mortality, heart-failure hospitalization, and the number of recurrent heart-failure admissions. Data on outcomes was collected from clinical records, structured telephone follow-up and hospital databases. Adjudications were made without using the study's LVEF category comparisons.

Statistical Analysis: Continuous variables were summarized as mean $\pm$ standard deviation or median (interquartile range) depending on the distribution of the data, and categorical variables were summarized as number and percentage. One-way analysis of variance and Kruskal-Wallis testing were used for continuous variables, and chi-square testing was used for categorical variables, when comparing across LVEF categories. Event-free survival was described using Kaplan-Meier methods and compared between LVEF groups by log rank testing. The associations with the primary outcome were examined using Cox proportional-hazards regression. All variables with clinical relevance and those with univariable $p < 0.10$ were considered for multivariable modeling. LVEF was examined both as continuous variable (per 5 percentage-point increase) and as categorical variable. The proportional-hazards assumptions were evaluated graphically and using Schoenfeld residuals. A two-sided $p < 0.05$ was deemed statistically significant.

Results

The cohort included 312 patients with a mean age of 61.8 ± 11.4 years; 223 (71.5%) were men. Mean LVEF was $29.7 \pm 6.1\%$, and 176 patients (56.4%) had ischemic cardiomyopathy. Diabetes mellitus was present in 126 (40.4%), hypertension in 197 (63.1%), and atrial fibrillation in 82 (26.3%). At baseline, 132 patients (42.3%) were in NYHA class

III–IV. Use of beta-blockers was 89.4%, renin-angiotensin system inhibition or angiotensin receptor-neprilysin inhibition 85.6%, mineralocorticoid receptor antagonists 71.2%, and SGLT2 inhibitors 68.9%.

Patients with the lowest LVEF had a less favorable clinical profile. Those with LVEF $\leq 25\%$ had higher

median NT-proBNP, lower systolic blood pressure, more frequent NYHA III–IV symptoms, and a greater prevalence of ischemic etiology than those with LVEF 36–40%. Renal function and diabetes prevalence also differed across groups, although age and sex distribution were broadly comparable.

Table 1: Baseline characteristics according to LVEF category

Characteristic	$\leq 25\%$ (n=86)	26–30% (n=90)	31–35% (n=78)	36–40% (n=58)	p value
Age, years	62.9 $\pm$ 10.8	62.0 $\pm$ 11.7	61.1 $\pm$ 11.6	60.6 $\pm$ 11.7	0.66
Male sex, n (%)	64 (74.4)	65 (72.2)	55 (70.5)	39 (67.2)	0.79
Ischemic etiology, n (%)	57 (66.3)	54 (60.0)	41 (52.6)	24 (41.4)	0.018
NYHA III–IV, n (%)	48 (55.8)	42 (46.7)	27 (34.6)	15 (25.9)	0.001
Systolic BP, mmHg	108.6 $\pm$ 15.8	112.9 $\pm$ 16.4	116.7 $\pm$ 15.1	120.4 $\pm$ 14.8	<0.001
eGFR, mL/min/1.73 m ²	61.7 $\pm$ 20.4	65.5 $\pm$ 19.1	69.8 $\pm$ 18.0	72.9 $\pm$ 17.6	0.004
NT-proBNP, pg/mL, median (IQR)	2480 (1420–4010)	1960 (1120–3250)	1510 (870–2620)	1120 (690–1910)	<0.001
SGLT2 inhibitor, n (%)	56 (65.1)	60 (66.7)	55 (70.5)	44 (75.9)	0.50

Data are mean $\pm$ SD, n (%), or median (IQR). BP: blood pressure; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association.

Table 2: One-year clinical outcomes according to LVEF category

Outcome	$\leq 25\%$	26–30%	31–35%	36–40%	Overall	p value
Death or HF hospitalization, n (%)	42 (48.8)	35 (38.9)	20 (25.6)	10 (17.2)	107 (34.3)	<0.001
All-cause death, n (%)	19 (22.1)	14 (15.6)	8 (10.3)	4 (6.9)	45 (14.4)	0.031
Cardiovascular death, n (%)	15 (17.4)	11 (12.2)	6 (7.7)	3 (5.2)	35 (11.2)	0.048
≥ 1 HF hospitalization, n (%)	33 (38.4)	28 (31.1)	17 (21.8)	7 (12.1)	85 (27.2)	0.002
Recurrent HF admissions, mean $\pm$ SD	0.63 $\pm$ 0.92	0.47 $\pm$ 0.76	0.31 $\pm$ 0.61	0.17 $\pm$ 0.42	0.42 $\pm$ 0.75	<0.001

HF: heart failure. Percentages are calculated within each LVEF category.

Table 3. Multivariable Cox regression for the primary 1-year endpoint

Variable	Adjusted HR	95% CI	p value
LVEF, per 5% increase	0.74	0.62–0.88	0.001
LVEF $\leq 25\%$ vs 36–40%	2.42	1.30–4.50	0.005
Age, per 10 years	1.23	1.04–1.45	0.016
NYHA III–IV	1.71	1.16–2.52	0.007
eGFR < 60 mL/min/1.73 m ²	1.58	1.08–2.31	0.019
Log NT-proBNP, per unit	1.34	1.10–1.64	0.004
SGLT2 inhibitor use	0.71	0.49–1.04	0.078

HR: hazard ratio; CI: confidence interval. The model additionally adjusted for sex, ischemic etiology, diabetes, systolic blood pressure, beta-blocker use, renin-angiotensin system inhibition/ARNI, and mineralocorticoid receptor antagonist use.

During 12 months, 107 patients (34.3%) reached the primary composite outcome. A clear graded pattern was observed, with the event rate falling from 48.8% in the LVEF $\leq 25\%$ group to 17.2% in the 36–40% group. All-cause mortality occurred in 45 patients (14.4%), and 85 patients (27.2%) had at least one heart-failure hospitalization. Recurrent admissions were also concentrated among patients with the lowest LVEF.

In adjusted analysis, LVEF retained an independent association with the primary endpoint. Each 5-percentage-point increase in LVEF was associated with an adjusted hazard ratio of 0.74. When LVEF was modeled categorically, the $\leq 25\%$ group had more than twice the adjusted hazard of the 36–40% reference group. NYHA class III–IV, reduced renal function, older age, and higher NT-proBNP were also independently associated with worse outcome.

Discussion

The main result of this study is that LVEF was independently and strongly associated with 1-year clinical outcomes in a population with a limited range of LVEF (HFrEF). The highest mortality and heart failure hospitalization rates were seen in patients with LVEF $\leq 25\%$, and the lowest rates were seen in patients with LVEF 36–40%. This association persisted following adjustment for age, renal function, blood pressure, symptom severity, natriuretic peptide concentration, etiology and major guideline-directed therapies. The observations underscore the clinical importance of LVEF beyond simply the classification of heart failure, and the fact that there is prognostic heterogeneity within the group of patients who fulfil the traditional definition of HFrEF.

The association is in the same direction as previously observed in CHF. Curtis et al. showed that there was a non-linear relationship between LVEF and mortality, and that the risk of death increased as systolic function declined [3]. The survival was also shown to differ between EF phenotypes in the MAGGIC individual-patient meta-analysis and to increase significantly when EF was below about 40% [4]. In our study, we extend this idea by specifically looking at the reduced-EF spectrum and by showing a graded event pattern over relatively narrow LVEF categories for 1 year.

LVEF should not be used as a single risk marker, importantly. The MAGGIC model showed that prognosis is the result of a combination of demographic, clinical, renal, hemodynamic and treatment factors [5]. In this analysis, impaired renal

function, NYHA III–IV symptoms, higher NT-proBNP, and older age were independent predictors of the primary endpoint. This is a practical lesson: a stable patient with an LVEF of 25% and normal renal function and optimized therapy is not at the same absolute risk as a patient with an LVEF of 25% who is congested, has renal dysfunction, hypotension and markedly elevated natriuretic peptides.

The event rates observed also must be considered in relation to current treatment. In PARADIGM-HF, angiotensin receptor-neprilysin inhibition was associated with better cardiovascular outcomes than enalapril [6] and in DAPA-HF and EMPEROR-Reduced, SGLT2 inhibition was associated with reduced worsening heart failure and cardiovascular events [7, 8]. These therapies work in ways that are not reflected in a single baseline LVEF and can lower the absolute risk, even with severe systolic dysfunction. Even though the use of disease-modifying therapy has been widely adopted, LVEF remained a prognostic factor in the current cohort, with high use of beta-blockers and significant use of mineralocorticoid receptor antagonists and SGLT2 inhibitors.

There are a number of possible mechanisms that could account for the increased risk with very low LVEF. When systolic dysfunction is severe, there is usually a decrease in forward stroke volume, an increase in neurohormonal activation, increase in filling pressures, increase in adverse ventricular remodeling, and increase in vulnerability to functional mitral regurgitation and ventricular arrhythmias. It could also be a sign of greater scar size due to ischemia or more severe non-ischemic myocardial disease. These pathophysiological characteristics can lead to greater risk of pump failure and sudden death, and reduce the hemodynamic reserve in the event of infection, arrhythmia, ischemia, or renal failure.

There are a number of clinical implications of our data. Patients with very low LVEF should be followed closely in the early stages, treatment of basic HFrEF therapy should be completed quickly, adherence and tolerability should be assessed and monitored for continued congestion. Second, it is still important to repeat the assessment of LVEF after a suitable period of optimized medical therapy, as LVEF may improve and this may impact device eligibility and may provide information about reverse remodeling. Third, LVEF should be combined with other markers, including eGFR, NT-proBNP, blood pressure, rhythm, functional status and previous hospitalization, and not used as a single predictor.

There are some limitations to the study. It is observational and is unable to prove that low LVEF is the cause of bad outcomes. Multivariable

adjustment can't rule out the possibility of residual confounding. There are image quality, loading condition, and reader interpretation-related measurement variability issues with LVEF, and a single baseline measurement will not reflect longitudinal recovery or deterioration. The treatment doses and changes in treatment during follow-up were not modeled as time-dependent exposures. The size of the cohort did not allow for detailed subgroup analysis and results may not be applicable to patients with advanced infiltrative, congenital or valvular disease. Last, the composite endpoint is a combination of mortality and hospitalization, which are of varying clinical severity, but the component analyses were directionally similar.

Although these are limitations, the consistency of the graded outcome pattern, continuous LVEF analysis and adjusted categorical analysis support the conclusion that LVEF continues to be a useful prognostic marker in HFrEF. Future studies should assess if changes in LVEF over time, myocardial strain, imaging of scars, biomarkers, and treatment trajectory further enhance risk discrimination over baseline LVEF.

Work done externally also supports the combination of ejection fraction with a wider clinical risk information. The MAGGIC score has been found to be reproducible in hospitalized patients and large national registries, and may be used with renal function, age, blood pressure, symptom burden, and comorbidity, but not alone [9,10]. Furthermore, the CHARM program showed that the association between ejection fraction and cardiovascular outcomes holds true over a wide range of heart-failure phenotypes and that risk increases with progressive decreases in LVEF into the reduced range [11].

The clinical significance of a low LVEF is also adjusted for the extent of evidence-based therapy. CHAMP-HF revealed significant deficiencies in the use and target dosing of cornerstone HFrEF therapies in the real world [12]. In EMPHASIS-HF [13] and RALES [14] the use of mineralocorticoid-receptor antagonism was associated with a decrease in mortality and heart failure hospitalization in both mildly symptomatic systolic heart failure and severe systolic heart failure, respectively. The results highlight the importance of LVEF as a marker of a high-risk substrate, but the intensity of treatment can have a meaningful impact on the absolute event rate in each LVEF category.

The advantages of early multidrug optimization are further supported by more recent evidence. A comparative analysis of the major HFrEF trials suggested significant improvements in event-free and overall survival with full disease-modifying drug therapy vs older conventional drug therapy [15]. STRONG-HF also demonstrated that

guideline-directed treatment up-titrated over a short period of time and followed up closely after acute heart failure leads to a lower risk of early death or heart-failure readmission [16]. Therefore, LVEF should be used in conjunction with active monitoring of congestion, renal function, natriuretic peptides and attainment of recommended therapy in follow-up.

Conclusion

In adults with HFrEF, lower baseline LVEF was associated with higher 1-year mortality and heart failure hospitalization rates, in a progressive fashion. This association continued to be present when clinical and laboratory risk factors and modern treatment were taken into account. LVEF is thus still able to offer practical prognostic information in the reduced-EF range, especially when combined with functional class, renal function, natriuretic peptide concentration, and treatment status. Very low LVEF patients are a clinically vulnerable group and early optimization of evidence-based therapy and close follow-up is crucial.

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