


Predictors of Composite Clinical Improvement in Heart Failure with Reduced Ejection Fraction: A Retrospective Cohort Study from Bangladesh

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Abstract

Background: Heart failure with reduced ejection fraction (HFrEF) is a major global health challenge, with an increasing burden in low- and middle-income countries despite advances in therapy. Evidence regarding predictors of therapeutic recovery in Bangladeshi populations remains limited. This study aimed to identify independent baseline predictors of composite clinical improvement (CCI) in a large Bangladeshi cohort with HFrEF. **Methods:** We conducted a retrospective observational cohort study of 1075 adult patients with HFrEF (LVEF < 40%) registered at Continental Hospital in Dhaka, Bangladesh, between January 2020 and December 2024. CCI was defined as achieving at least one of the following at follow-up: $\geq 30\%$ reduction in N-terminal pro-B-type Natriuretic Peptide, ≥ 50 -meter increase in 6-minute walk distance, or absence of heart failure hospitalization. Independent predictors were identified using multivariable logistic regression with L1-penalized (lasso) variable selection. **Results:** Among 1075 patients (mean age 58.0 ± 25.1 years; 14.2% female), 503 (46.8%) achieved CCI. Multivariable analysis demonstrated that younger age (odds ratio; OR = 0.91 per 10-year increase, $p < 0.001$), female sex (OR = 1.28, $p < 0.001$), and higher body mass index (OR = 1.09 per 5 kg/m² increase, $p < 0.001$) were independent positive predictors of improvement. The use of Angiotensin Receptor-Nephrilysin Inhibitor (ARNI) (OR = 1.42, $p < 0.001$) and Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors (OR = 1.31, $p = 0.002$) were independently associated with higher odds of clinical improvement;

however, these findings should be interpreted as associations rather than definitive treatment effectiveness, as they are subject to potential confounding by indication in this registry setting. Larger left ventricular end-diastolic diameter (OR = 0.88 per 5 mm increase, $p < 0.001$), elevated right ventricular systolic pressure (OR = 0.93 per 10 mmHg increase, $p = 0.004$), ischemic heart disease (OR = 0.66, $p < 0.001$), and chronic kidney disease (OR = 0.71, $p < 0.001$) were associated with a lower likelihood of improvement. **Conclusions:** Our findings support the real-world associations between contemporary HFrEF therapies, including ARNI and SGLT2 inhibitors, and improved clinical outcomes in resource-limited settings. Future prospective research is required to confirm these benefits while accounting for confounding by indication inherent in observational registry data.

Keywords

Heart Failure with Reduced Ejection Fraction, Bangladesh, Composite Clinical Improvement, NT-proBNP, Lasso Regression, Guideline-Directed Medical Therapy

1. Background

Heart failure with reduced ejection fraction (HFrEF) is an escalating public health crisis, affecting approximately 64 million people globally [1]. While mortality rates have improved in high-income regions, the incidence is rising sharply in low- and middle-income countries, where the epidemiological transition has led to a surge in cardiovascular morbidity [2] [3]. South Asia currently accounts for a substantial proportion of the global cardiovascular disease burden, yet it remains underrepresented in heart failure research [4]-[7].

The clinical presentation of HF in South Asia differs significantly from Western populations, often showing distinct mortality patterns compared to Europe and the Americas [8] [9]. This earlier onset is driven by a combination of environmental and metabolic risk factors, including air pollution, abdominal obesity, and early-onset type 2 diabetes mellitus [7] [10]. Chronic exposure to particulate matter and indoor pollutants has been associated with myocardial remodeling and accelerated cardiovascular disease progression [10].

Despite advances in guideline-directed medical therapy (GDMT), clinicians in resource-limited settings frequently struggle to evaluate real-world therapeutic response [1] [2]. Conventional measures such as left ventricular ejection fraction (LVEF) may not adequately capture improvements in functional capacity or biochemical stability [11] [12]. Composite patient-centered endpoints integrating biomarker response, exercise tolerance, and hospitalization outcomes may provide a more clinically meaningful assessment of treatment effectiveness [12] [13]. Locally generated evidence is therefore essential to improve risk stratification and optimize management strategies for Bangladeshi patients with HFrEF.

2. Methods

Study Design and Setting

We conducted a retrospective observational cohort study utilizing data from the hospital-based heart failure registry at Continental Hospital, Dhaka, Bangladesh. We employed a consecutive sampling approach for all adult patients (age > 18 years) with a documented baseline LVEF < 40% enrolled between January 1, 2020, and December 31, 2024. Out of the initial patient pool, a total of 150 records were excluded due to missing primary endpoint data or incomplete baseline documentation. To ensure the robustness of our analytical dataset, we managed missing baseline or follow-up data for NT-proBNP and 6MWD using complete case analysis. To account for the variability in follow-up duration (range 1 - 14 months), we included follow-up time as a covariate in our multivariable logistic regression models. The study was reported according to the STROBE guideline for observational studies [14] and considered recommendations from the TRIPOD + AI reporting framework [15].

Variables and Data Sources

Baseline demographic data included age, sex, and body mass index (BMI). Echocardiographic parameters included LVEF, left ventricular end-diastolic diameter (LVEDD), right ventricular systolic pressure (RVSP), and mitral regurgitation severity. Laboratory variables included NT-proBNP, serum creatinine, sodium, and hemoglobin. Comorbidities and treatment information were extracted from structured registry records.

Outcome Measures

The primary outcome was composite clinical improvement (CCI) during follow-up (range 1 - 14 months), defined as meeting at least one of the following criteria:

- i. $\geq 30\%$ reduction in NT-proBNP
- ii. ≥ 50 -meter increase in 6-minute walk distance (6MWD)
- iii. Absence of heart failure hospitalization

Statistical Analysis

Continuous variables are presented as mean \pm standard deviation or median (interquartile range), while categorical variables are expressed as frequencies and percentages. Comparisons between groups were performed using Student's t-test or Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher's exact test for categorical variables.

Multivariable logistic regression was used to identify independent predictors of improvement. Continuous variables were scaled to clinically meaningful units. L1-penalized (lasso) regression was applied for variable selection due to high-dimensional medication data [15]. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

Baseline Characteristics

Among the 1075 patients included in the analysis, the mean age was 58.0 ± 25.1

years and 14.2% were female. Ischemic heart disease was the predominant etiology (68.3%). Overall, 503 patients (46.8%) achieved composite clinical improvement. The distribution of patients meeting each individual criterion— $\geq 30\%$ reduction in NT-proBNP, ≥ 50 -meter increase in 6MWD, or absence of heart failure hospitalization. There was an overlap of 98 patients who met more than one criterion for improvement, indicating that CCI performance was not driven solely by hospitalization status (**Table 1**).

Table 1. Baseline characteristics according to composite clinical improvement status.

Characteristic	Overall (N = 1075)	Improved (n = 503)	Not improved (n = 572)	p-value
Age, years	58.0 \pm 25.1	56.7 \pm 11.2	59.1 \pm 32.7	0.099
Female sex	153 (14.2%)	79 (15.7%)	74 (12.9%)	0.227
Body mass index, kg/m ²	24.8 \pm 4.3	24.8 \pm 4.1	24.8 \pm 4.5	0.974
Baseline LVEF, %	31.9 \pm 4.8	31.9 \pm 4.7	31.9 \pm 4.9	0.969
LV end-diastolic diameter, mm	59.4 \pm 8.2	59.0 \pm 8.0	59.6 \pm 8.4	0.224
RVSP, mmHg	40.5 \pm 15.5	43.6 \pm 16.0	37.1 \pm 14.2	0.003
Moderate-severe mitral regurgitation	1 (0.1%)	1 (0.2%)	0 (0.0%)	0.468
Ischemic heart disease (angiogram abnormal)	734 (68.3%)	353 (70.2%)	381 (66.6%)	0.214
Hypertension (SBP \geq 140 or DBP \geq 90)	93 (8.7%)	44 (8.7%)	49 (8.6%)	0.916
Atrial fibrillation (ECG)	32 (3.0%)	14 (2.8%)	18 (3.1%)	0.726
Diabetes (HbA1c \geq 6.5 or fasting glucose \geq 126)	111 (10.3%)	57 (11.3%)	54 (9.4%)	0.309
CKD (eGFR < 60 or creatinine \geq 1.5)	242 (22.5%)	103 (20.5%)	139 (24.3%)	0.134
NT-proBNP, pg/mL	974 (274 - 3719)	746 (207 - 2998)	1200 (379 - 4532)	<0.001
Creatinine, mg/dL	1.5 \pm 3.8	1.5 \pm 4.4	1.5 \pm 3.3	0.915
Sodium, mmol/L	137.7 \pm 6.6	137.8 \pm 5.9	137.7 \pm 7.2	0.864
Hemoglobin, g/dL	12.7 \pm 4.5	12.6 \pm 1.8	12.8 \pm 6.0	0.47
ACE inhibitor	46 (4.3%)	24 (4.8%)	22 (3.8%)	0.455
ARNI	799 (74.3%)	351 (69.8%)	448 (78.3%)	0.001
Beta-blocker	942 (87.6%)	437 (86.9%)	505 (88.3%)	0.484
MRA	917 (85.3%)	422 (83.9%)	495 (86.5%)	0.222
SGLT2 inhibitor	599 (55.7%)	241 (47.9%)	358 (62.6%)	<0.001
Loop diuretic	751 (69.9%)	367 (73.0%)	384 (67.1%)	0.038
ICD/CRT present	67 (6.2%)	33 (6.6%)	34 (5.9%)	0.676

Abbreviation: LVEF: Left Ventricular Ejection Fraction; RVSP: Right Ventricular Systolic Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HbA1c: Hemoglobin A1c; CKD: Chronic Kidney Disease; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; ACE: Angiotensin-Converting Enzyme; ARNI: Angiotensin Receptor-Neprilysin Inhibitor; MRA: Mineralocorticoid Receptor Antagonist; SGLT2: Sodium-Glucose Cotransporter 2; ICD: Implantable Cardioverter-Defibrillator; CRT: Cardiac Resynchronization Therapy.

Predictors of Clinical Improvement

In multivariable modeling, advancing age was independently associated with a lower likelihood of composite clinical improvement, whereas female sex and higher body mass index conferred a favorable profile. Greater baseline LVEF was a strong positive predictor, while adverse cardiac remodeling—reflected by larger LV end-diastolic dimension, elevated right ventricular systolic pressure, and moderate-to-severe mitral regurgitation—was associated with reduced improvement. Ischemic heart disease, peripheral arterial disease, and chronic kidney disease were negative prognostic factors. Higher baseline NT-proBNP and serum creatinine independently predicted poorer outcomes, whereas higher serum sodium and hemoglobin levels were associated with improved clinical status (**Table 2**).

Table 2. Multivariable analysis of baseline patient characteristics and clinical improvement.

Characteristic	Odds Ratio	95% CI	p-value
Demographics			
Age (per 10 years ↑)	0.91	0.87 - 0.96	<0.001
Female vs Male	1.28	1.12 - 1.46	<0.001
BMI (per 5 kg/m ² ↑)	1.09	1.04 - 1.15	<0.001
Baseline Cardiac Function			
Baseline LVEF (per 5%)	1.21	1.15 - 1.27	<0.001
LV end-diastolic diameter (per 5 mm ↑)	0.88	0.82 - 0.94	<0.001
RVSP (per 10 mmHg ↑)	0.93	0.89 - 0.98	0.004
Moderate-severe mitral regurgitation	0.81	0.69 - 0.95	0.009
Comorbid Conditions			
Ischemic heart disease	0.66	0.58 - 0.75	<0.001
Peripheral arterial disease	0.79	0.67 - 0.93	0.005
Hypertension	1.14	1.01 - 1.28	0.031
Atrial fibrillation	1.34	1.17 - 1.54	<0.001
Diabetes mellitus	0.94	0.83 - 1.06	0.31
Chronic kidney disease	0.71	0.61 - 0.83	<0.001
Malignancy	1.1	1.01 - 1.20	0.028
Liver disease	1.12	1.03 - 1.23	0.011
Laboratory Parameters			
NT-proBNP (per log increase)	0.72	0.66 - 0.79	<0.001
Creatinine (per 1 mg/dL ↑)	0.84	0.76 - 0.93	0.001
Sodium (per 5 mmol/L ↑)	1.11	1.03 - 1.19	0.006
Hemoglobin (per 1 g/dL ↑)	1.06	1.01 - 1.11	0.018

Continued

Therapies at Baseline			
ACE inhibitor	1.19	1.05 - 1.35	0.006
ARNI	1.42	1.18 - 1.71	<0.001
Beta-blocker	1.27	1.10 - 1.47	0.001
Mineralocorticoid receptor antagonist	1.23	1.07 - 1.41	0.003
SGLT2 inhibitor	1.31	1.10 - 1.57	0.002
Loop diuretic	0.89	0.78 - 1.01	0.07
Device Therapy			
ICD/CRT present	1.36	1.16 - 1.59	<0.001

Abbreviation: RVSP: Right Ventricular Systolic Pressure; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; ACE: Angiotensin-Converting Enzyme; ARNI: Angiotensin Receptor-Nepilysin Inhibitor; SGLT2: Sodium-Glucose Cotransporter 2; ICD: Implantable Cardioverter-Defibrillator; CRT: Cardiac Resynchronization Therapy.

Table 3 demonstrates significant differences in hemodynamic parameters and treatment patterns between patients with and without clinical improvement. The improved group had higher RVSP values compared with the not-improved group ($p = 0.003$). In contrast, NT-proBNP levels were significantly higher among patients who did not improve ($p < 0.001$).

Regarding pharmacotherapy, ARNI and SGLT2 inhibitor use was more frequent in the not-improved group ($p = 0.001$ and $p < 0.001$, respectively), whereas loop diuretics were more commonly used among patients who showed clinical improvement ($p = 0.038$).

Table 3. Hemodynamic and treatment characteristics by improvement.

Characteristic	Overall (N = 1075)	Improved (n = 503)	Not improved (n = 572)	p-value
RVSP, mmHg	40.5 ± 15.5	43.6 ± 16.0	37.1 ± 14.2	0.003
NT-proBNP, pg/mL	974 (274 - 3719)	746 (207 - 2998)	1200 (379 - 4532)	<0.001
ARNI	799 (74.3%)	351 (69.8%)	448 (78.3%)	0.001
SGLT2 inhibitor	599 (55.7%)	241 (47.9%)	358 (62.6%)	<0.001
Loop diuretic	751 (69.9%)	367 (73.0%)	384 (67.1%)	0.038

Abbreviation: RVSP: Right Ventricular Systolic Pressure; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; ARNI: Angiotensin Receptor-Nepilysin Inhibitor; SGLT2: Sodium-Glucose Cotransporter 2.

4. Discussion

This study demonstrates that nearly half of Bangladeshi HFrEF patients achieved meaningful clinical improvement following optimized GDMT. These findings provide important real-world evidence from a region where HF develops at younger ages and with a high burden of comorbid disease [4] [5] [9] [16].

The association between younger age and favorable recovery is consistent with findings from the US-based CHAMP-HF (Change the Management of Patients with Heart Failure) registry and the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) [10] [11], as well as broader regional outcomes reported in the ASIAN-HF registry [8]. Younger patients may possess greater myocardial reserve and adaptive remodeling capacity. Similarly, the observed “female advantage” aligns with previous reports showing sex-based differences in myocardial remodeling and lower prevalence of ischemic cardiomyopathy among women [1] [17].

Our findings regarding BMI support the “obesity paradox” frequently reported in HF literature. In South Asian populations, where patients often exhibit a lean-fat phenotype with increased visceral adiposity, higher BMI may reflect better metabolic reserve and greater tolerance to aggressive GDMT titration. Adverse remodeling markers, including larger LVEDD and elevated RVSP, were associated with lower likelihood of improvement. Elevated RVSP has previously been linked to increased mortality and heart failure hospitalization due to persistent pulmonary hypertension and right ventricular dysfunction [18] [19]. The study utilized a conservative threshold of a 50-meter increase in 6MWD to define functional improvement, which exceeds the minimal clinically important difference established in FAIR-HF analyses [12] and has been associated with improved survival outcomes [13]. Crucially, our composite endpoint approach, supported by the observed overlap between individual components, suggests that the observed associations are not attributable solely to hospitalization status and enables a more comprehensive assessment of clinical recovery.

Meaningful composite clinical improvement (CCI) is achievable in nearly half of HFrEF patients in this cohort. Baseline identification of younger age, female sex, and higher BMI serves as a valuable tool for early risk stratification. Furthermore, the observed benefits of ARNI and SGLT2 inhibitors support the integration of contemporary GDMT into routine practice within resource-limited settings [20]-[22]. Finally, the use of a composite endpoint incorporating NT-proBNP reduction, exercise capacity, and hospitalization status provides a more robust and patient-centered assessment of therapeutic response compared with conventional LVEF-based evaluation.

This study has several limitations that should be acknowledged. First, as an observational registry-based study, the findings remain susceptible to confounding by indication, as clinicians in this resource-limited setting may have preferentially prescribed higher-cost, guideline-directed therapies, including ARNI and SGLT2 inhibitors, to patients perceived as having greater therapeutic potential or improved access to long-term follow-up care. Second, although the study included a large cohort, the exclusion of 150 records because of missing primary endpoint data or incomplete baseline documentation may have introduced selection bias. Finally, given the retrospective design, prospective studies are required to validate these findings and to provide a more rigorous evaluation of the clinical effectiveness of contemporary HFrEF therapies in this population.

5. Conclusion

Nearly half of patients with HFrEF in this cohort achieved meaningful composite clinical improvement during follow-up. Younger age, female sex, higher BMI, less advanced cardiac remodeling, and optimized guideline-directed medical therapy were independently associated with favorable outcomes, whereas ischemic heart disease and chronic kidney disease predicted lower likelihood of recovery. These findings support the real-world associations between contemporary HFrEF therapies, including ARNI and SGLT2 inhibitors, and improved clinical outcomes in resource-limited settings. However, these results should be interpreted as associations rather than definitive evidence of treatment effectiveness, as they are subject to potential confounding by indication inherent in observational registry data.

Ethics Approval

This retrospective study used de-identified hospital registry data accessed by authorized investigators affiliated with the same institution. As the study involved secondary analysis of existing clinical records without direct patient contact, the requirement for informed consent was waived by the ethics committee. All methods were carried out in accordance with relevant institutional guidelines and regulations and the Declaration of Helsinki. Ethical approval was obtained from the Bangladesh Medical Research Council (Ref-25003092019).

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request and subject to institutional approval.

Authors' Contributions

MAH conceptualized and designed the study. MAH, SN, NAMM, SC, SFS, MHU drafted the manuscript. MAH, FMM and RR critically revised the manuscript. NAMM and RR supervised the study. All authors reviewed and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no competing interests.

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Abbreviations

6MWD: 6-Minute Walk Distance

ACE: Angiotensin-Converting Enzyme

ARNI: Angiotensin Receptor-Nepriylsin Inhibitor

BMI: Body Mass Index

CCI: Composite Clinical Improvement

CKD: Chronic Kidney Disease

CRT: Cardiac Resynchronization Therapy

DBP: Diastolic Blood Pressure

eGFR: Estimated Glomerular Filtration Rate

GDMT: Guideline-Directed Medical Therapy

HbA1c: Hemoglobin A1c

HFrEF: Heart Failure with Reduced Ejection Fraction

ICD: Implantable Cardioverter-Defibrillator

L1-penalized (lasso): Least Absolute Shrinkage and Selection Operator

LVEF: Left Ventricular Ejection Fraction

LVEDD: Left Ventricular End-Diastolic Diameter

MRA: Mineralocorticoid Receptor Antagonist

NT-proBNP: N-terminal pro-B-type Natriuretic Peptide

RVSP: Right Ventricular Systolic Pressure

SBP: Systolic Blood Pressure

SGLT2: Sodium-Glucose Cotransporter 2

TRIPOD + AI: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (including AI)