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Heart Failure

Predictors of Left Ventricular Ejection Fraction Improvement in Patients with Early-Stage Heart Failure with Reduced Ejection Fraction

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Objectives: To identify the predictors of left ventricular ejection fraction (LVEF) recovery in patients with heart failure with reduced ejection fraction (HFrEF) and compare the mortality rate between patients with HFrEF and heart failure with improved ejection fraction (HFimpEF).

Methods: Patients in a post-acute care program from 2018 to 2021 were enrolled. A series of echocardiograms were arranged during follow-up. Mortality, cardiovascular death and sudden cardiac death events were recorded. A total of 259 patients were enrolled and followed for at least 1 year; 158 (61%) patients fulfilled the criteria of HFimpEF, 87 (33.6%) were defined as having persistent HFrEF, and 14 (5.4%) were defined as having heart failure with mildly reduced ejection fraction. The patients with HFimpEF and persistent HFrEF were included for analysis.

Results: The mean follow-up duration was 1090 ± 414 days, and the median time to LVEF recovery was 159 days (IQR 112-289 days). Multivariate logistic regression analysis showed that beta-blocker prescription was the only independent predictor of HFimpEF [odds ratio (OR) 2.11, 95% confidence interval (CI) 1.10-4.08, p = 0.03]. Diagnosis of ischemic cardiomyopathy (ICM) and QRS duration ≥ 110 ms were negative predictors of HFimpEF (OR 0.49, 95% CI 0.27-0.88, p = 0.02, and OR 0.4, 95% CI 0.21-0.77, p = 0.005, respectively). The patients with HfimpEF had a significantly better prognosis with lower mortality (hazard ratio 0.2, 95% CI 0.08-0.50, log-rank p < 0.001) than the patients with persistent HFrEF.

Conclusions: Beta-blocker prescription was an independent predictor of HFimpEF, while the diagnosis of ICM and QRS duration ≥ 110 ms were negative predictors of HFimpEF. Patients with HfimpEF had a significantly lower mortality rate compared to those with persistent HFrEF.

Key Words: Heart failure with improved ejection fraction • Heart failure with reduced ejection fraction

INTRODUCTION

Heart failure with improved ejection fraction (HFimpEF) is defined as heart failure (HF) with a baseline left ventricular ejection fraction (LVEF) of ≤ 40%, followed by a ≥ 10-point increase from baseline LVEF, and a subsequent measurement of LVEF of > 40%.[1] A previous meta-analysis found that around 23% of patients with heart failure with reduced ejection fraction (HFrEF) were classified as having HFimpEF after treatment, and that they would then have a 56% decrease in mortality risk.[2] Current guidelines[3] suggest angiotensin-converting enzyme

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Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
BB	Beta-blocker
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronization therapy
CV	Cardiovascular
DCM	Dilated cardiomyopathy
DM	Diabetes mellitus
ECG	Electrocardiography
EF	Ejection fraction
HF	Heart failure
HFimpEF	Heart failure with improved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HTN	Hypertension
ICM	Ischemic cardiomyopathy
IQR	Interquartile range
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NHI	National health insurance
NTUH	National Taiwan University Hospital
NYHA	New York Heart Association
OR	Odds ratio
PAC	Post-acute care
SCD	Sudden cardiac death
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
TSOC	Taiwan Society of Cardiology
VHD	Valvular heart disease
VT	Ventricular tachycardia

inhibitors (ACEis), sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and dapagliflozin/empagliflozin as optimal medical treatment. The number of patients with LVEF recovery has increased over time in the sacubitril/valsartan and dapagliflozin/ empagliflozin era.[4,5]

After being discharged from the hospital for decompensated heart failure, a post-acute care (PAC) program can maximize a patient's functional progress and reduce disability. PAC programs involve the pre- and post-discharge periods for approximately 3 to 6 months. The 2019 TSOC Guidelines for the Diagnosis and Treatment of Heart Failure emphasize the importance of PAC programs.[6] At National Taiwan University Hospital (NTUH), we initiated a PAC program in 2018 for patients who were diagnosed with HFrEF and discharged from acute heart failure hospitalization. All patients enrolled in the PAC program were in New York Heart Association (NYHA) functional class II-III and had the potential for rehabilitation and clinical improvement, such as having more motivation for rehabilitation and better compliance.

Thanks to advances in medical and device treatments, the long-term mortality rates for patients with heart failure have improved over time, and this has been accompanied by an increase in the rate of LVEF recovery. A study conducted in the United Kingdom found that the 1-year mortality rate following heart failure hospitalization was approximately 19% in 2016, while the 5-year mortality rate was 52% in 2012, and the 10-year mortality rate was 74% in 2017.[7] In the past, approximately 30% to 50% of all cardiac deaths in patients with heart failure were sudden deaths.[8] However, the annual rate of sudden death has decreased over time, from 6.5% in the earliest trial (RALES, completed in 1998) to 3.3% in the most recent trial (PARADIGM-HF, completed in 2014).[9]

The aim of this study was to identify the indicators of LVEF recovery in patients enrolled in a PAC program and compare the risks of sudden cardiac death (SCD) and mortality between patients with HFrEF and HFimpEF.

METHOD

Subjects and study protocol

The PAC program at NTUH enrolled patients with HFrEF who were hospitalized due to acute decompensated heart failure, and involved post-discharge periods to optimize medical therapy and encourage rehabilitation to improve their outcomes. All of the enrolled patients were in NYHA functional class II-III and had the potential for rehabilitation and clinical improvement, such as having more motivation for rehabilitation and better compliance. These patients were regularly followed up at cardiovascular outpatient clinics at NTUH. Any cardiovascular events or mortality were recorded in charts after the patients sought medical help and/or reported to case managers.

This study prospectively enrolled patients enrolled in the PAC program at NTUH from 2018 to 2021. During the follow-up period, a series of echocardiograms were

arranged as required by clinical needs, and standard techniques were used to obtain M-mode, 2-dimensional, and Doppler measurements. The LVEF was measured using the M-mode and Simpson method. A set of relevant covariates was obtained during the study period, including age, sex, and medical comorbidities such as hypertension (HTN), diabetes mellitus (DM), dyslipidemia, coronary artery disease (CAD), valvular heart disease (VHD), atrial fibrillation (AF), chronic kidney disease (CKD), and chronic obstructive pulmonarydisease (COPD)/asthma, which were documented based on medical records.

Heart failure etiologies such as dilated cardiomyopathy (DCM), ischemic cardiomyopathy (ICM), VHD, acute myocarditis or others, medication, electrocardiography (ECG) QRS duration and morphology, and those who received cardiac interventions were all recorded. The ECG criteria for left bundle branch block (LBBB) were as follows: 1. QRS duration greater than 120 ms; 2. Lead V1 exhibiting a QS or a small r wave with a large S wave; and 3. Lead V6 showing a notched R wave and no Q wave. ICM was defined as cases where CAD was the main cause of HFrEF. If CAD was not the main etiology of HFrEF, it was coded as a comorbidity.

According to current heart failure guidelines, the triad of an ACEi, angiotensin II receptor blocker (ARB), or an angiotensin receptor-neprilysin inhibitor (ARNI), a beta-blocker (BB), and an mineralocorticoid receptor antagonist (MRA) is recommended as the cornerstone therapy for these patients, unless the drugs are contraindicated or not tolerated. The guidelines suggest that all patients with HFrEF who are already treated with an ACEi/ARNI, a BB, and an MRA, regardless of whether they have diabetes or not, should be given a sodium-glucose co-transporter 2 inhibitor (SGLT2i), dapagliflozin, and empagliflozin to reduce the risk of cardiovascular (CV) death and worsening HF. However, SGLT2is were only reimbursed by the national health insurance (NHI) in May 2022. We recorded the use of SGLT2is in patients in this cohort who had comorbid diabetes.

All follow-up echocardiographs, any changes in LVEF, as well as whether LVEF recovery had occurred and the timing of such recovery were recorded. LVEF recovery was defined as a baseline LVEF of $\leq$ 40%, with a $\geq$ 10-point increase from the baseline LVEF, and a subsequent measurement of LVEF > 40%. Patients meeting these criteria were classified as having HFimpEF. Patients whose follow-up echocardiography showed an LVEF > 40% but did not meet the $\geq$ 10-point increase from baseline LVEF criterion were classified as having heart failure with mildly reduced ejection fraction (HFmrEF). Patients with an LVEF which remained < 40% were classified as having persistent HFrEF. Patients defined as having HFimpEF and persistent HFrEF were included for analysis. Mortality, CV death and SCD, and ventricular tachycardia (VT) events were also recorded retrospectively. Patients who presented with out-of-hospital cardiac arrest without resuscitation were defined as having experienced SCD. The definition of VT occurrence was the presence of sustained VT documented on an ECG, whether cardioversion was required or not.

To avoid lead time bias, since the HFimpEF patients had to survive long enough for a second LVEF assessment, patients who died between the first and second LVEF measurements were excluded. In addition, as the PAC program enrolled patients with LVEF $\leq$ 40% at the time of enrollment, the diagnosis of HFrEF varied in terms of how long the patients had been diagnosed. As a result, some patients with pre-existing and persistent HFrEF may have been enrolled in this cohort. To avoid bias, we excluded patients who had been diagnosed with HFrEF for more than 1 year without improvement in LVEF at the time of enrollment. Therefore, all patients included in the analysis were diagnosed with early-stage HFrEF within 1 year of enrollment.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were expressed as percentages. To examine the differences in characteristics between participants with and without LVEF recovery, VT attack or death, a chi-square test was used for categorical variables, and a t-test was used for continuous variables.

Logistic regression analysis was performed to identify the predictors of LVEF recovery. Variables associated with LVEF recovery with a p-value < 0.05 were included as confounding variables in the multivariate analysis. A two-sided p-value < 0.05 was considered statistically significant. All statistical tests were performed using MedCalc Version 20.112 and R.

Power analysis used input data according to the latest KorAHF registry[10] in Asia: 23% patients with an ini-

tial diagnosis of HFrEF had an improvement in LVEF and were diagnosed with HFimpEF; the all-cause mortality rates in the persistent HFrEF and HFimpEF groups were 34% and 16%, respectively; with a type I error of 0.05 and type II error of 0.2. The estimated sample size was 306, including 248 in the HFrEF group and 58 in the HfimpEF group.

RESULTS

Demographic and clinical characteristics

A total of 329 patients from the PAC cohort during 2018-2021 were enrolled and followed up for at least 1 year to evaluate the prevalence of LVEF recovery and the incidence of SCD and all-cause mortality. Among these patients, 62 were diagnosed with HFrEF before 2017 and were excluded from the analysis, and 8 patients died before the second LVEF measurement, leaving a final sample of 259 patients with an initial diagnosis of HFrEF (Figure 1).

We recorded every follow-up echocardiograph and ensured that every patient had follow-up data within 6 months post-diagnosis. Of the 259 patients, 158 (61%) met the criteria for HFimpEF (≥ 10-point increase from baseline LVEF and a second measurement of LVEF of > 40%), 87 (33.6%) were defined as having persistent HFrEF, and 14 (5.4%) were defined as having HFmrEF. The patients defined as having HFimpEF and persistent HFrEF were included for analysis. The mean follow-up duration was 1090 ± 414 days, and the median time to LVEF recovery was 159 days (IQR 112-289 days), with a mean of 234 ± 214 days.

Table 1 presents the clinical characteristics of the patients with HFimpEF and persistent HFrEF. The mean age of the HFimpEF group was younger than that of the persistent HFrEF group (60.1 ± 15.6 vs. 66.6 ± 14.1 years, p < 0.001), with male predominance in both groups. With regards to the etiology of the initial HFrEF, fewer patients had an etiology of ICM in the HFimpEF group compared to the persistent HFrEF group (36.1% vs. 52.9%, p = 0.01), and more patients had an etiology of acute

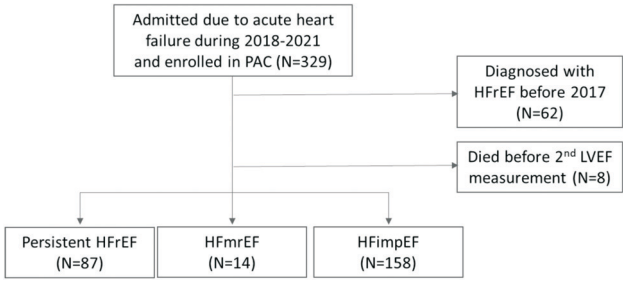

Figure 1. *Flow chart of patient enrollment. HFimpEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PAC, post-acute care.*

Table 1. Clinical characteristics of patients with HFimpEF and persistent HFrEF

	HFimpEF (n = 158)	Persistent HFrEF (n = 87)	p value
Demographic data			
Age	60.1 ± 15.6	66.6 ± 14.1	< 0.001*
Men	118 (74.7%)	69 (79.3%)	0.05
Etiology			
ICM	57 (36.1%)	46 (52.9%)	0.01*
DCM	66 (41.8%)	28 (32.2%)	0.62
VHD	20 (12.7%)	11 (12.6%)	0.55
Acute myocarditis	10 (6.3%)	0 (0%)	0.02*
Others (CHD, TCM)	5 (3.2%)	2 (2.3%)	0.70
Past medical history			
HTN	67 (42.4%)	43 (49.4%)	0.07
DM	44 (27.8%)	34 (39%)	0.07
CAD	70 (44.3%)	49 (56.3%)	0.07
VHD	33 (20.9%)	19 (21.8%)	0.86
AF	38 (24%)	22 (25.3%)	0.83
COPD/asthma	8 (5%)	6 (6.9%)	0.56
ECG			
LBBB	11 (7%)	15 (17.2%)	0.01*
QRS	106.83 ± 26.1	120.76 ± 34.2	< 0.001*
CRT implantation	6 (3.8%)	4 (4.6%)	0.76
Medication			
RASi	120 (75.9%)	63 (72.4%)	0.54
ARNI	58 (36.7%)	40 (46%)	0.15
BB	129 (81.6%)	58 (66.7%)	0.01*
MRA	86 (54.4%)	48 (55.1%)	0.91
SGLT2i	24 (15.2%)	17 (19.5%)	0.38

AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CAD, coronary artery disease; CHD, congenital heart disease; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; DM, diabetes mellitus; ECG, electrocardiography; HfimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced EF; HTN, hypertension; ICM, ischemic cardiomyopathy; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose co-transporter 2 inhibitors; TCM, tachycardia-mediated cardiomyopathy; VHD, valvular heart disease.

myocarditis in the HFimpEF group (6.3% vs. 0%, p = 0.017). ECG analysis showed a lower rate of LBBB pattern in the HFimpEF group compared to the persistent HFrEF group (7% vs. 17.2%, p = 0.013), but the cardiac resynchronization therapy (CRT) implantation rate was similar in both groups (3.8% vs. 4.6%, p = 0.762). A shorter QRS duration was observed in the HFimpEF group (106.8 ± 26.1 ms vs. 120.8 ± 34.2 ms, p < 0.001). The prescription rate of beta-blockers was higher in the HFimpEF group (81.6% vs. 66.7%, p = 0.01). However, the prescription rates of RASis, ARNIs, and MRAs were similar in both groups (75.9% vs. 72.4%, p = 0.54; 36.7% vs. 46%, p = 0.15; and 54.4% vs. 55.1%, p = 0.91, respectively).

Predictors of HFimpEF

Multivariate logistic regression analysis was performed with factors that were significant in univariate analysis. The results showed that beta-blocker prescription was the only independent predictor of HFimpEF [odds ratio (OR) 2.11, 95% confidence interval (CI) 1.10-4.08, p = 0.03]. The diagnosis of ICM and QRS duration ≥ 110 ms were negative predictors of HFimpEF (OR 0.49, 95% CI 0.27-0.88, p = 0.02, and OR 0.21, 95% CI 0.21-0.77, p = 0.005, respectively). To determine the optimal cutoff point for QRS duration to predict LVEF improvement, automatic bootstrapping was implemented to maximize the Youden index, which was found to be 106 ms (Figure 2). Therefore, a cutoff point of 110 ms was set for QRS duration to predict LVEF improvement. The independent predictors of HFimpEF are summarized in Table 2.

Clinical outcomes

Fifteen (17.2%) patients with persistent HFrEF died during follow-up, with 7 deaths resulting from advanced heart failure, 3 due to sudden cardiac death, and the others from non-cardiac causes. Two patients experienced SCD but survived. In the HFimpEF group, 6 (3.8%) patients died during the follow-up period, with none of the deaths being due to heart failure, 1 due to SCD, and the others from non-cardiac causes. One patient also experienced SCD but survived. VT developed in 14 (16%) HFrEF patients and 13 (8.2%) HFimpEF patients. The patients with HFimpEF had a significantly better prognosis with lower mortality [hazard ratio (HR) 0.2, 95% CI 0.08-0.5, log-rank p < 0.001] and lower cardiovascular death (HR 0.07, 95% CI 0.02-0.26, log-rank p < 0.001) rates compared to the patients with persistent HFrEF. Although there was a trend towards a lower SCD rate in the patients with HFimpEF compared to those with HFrEF, the difference was not statistically significant (HR 0.22, 95% CI 0.04-1.12, log-rank p = 0.07) (Figure 3). After adjusting for other covariates in Table 2 using a Cox regression model, only HFimpEF was found to be an independent predictor of all-cause mortality and cardiovascular death.

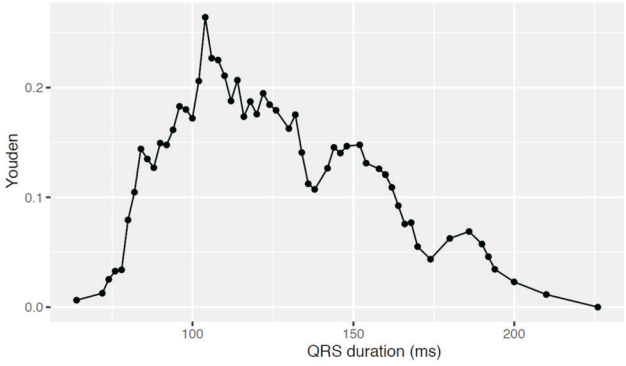

Figure 2. *Optimal cutoff point was obtained by automatic bootstrap to maximize the Youden index.*

DISCUSSION

The 2013 American College of Cardiology/American Heart Association guidelines introduced a new classification of heart failure, named "HFpEF, improved".[11] This was in recognition that a subset of patients with HFpEF may previously have had HFrEF, and that patients with an improvement or recovery in ejection fraction (EF) may be clinically distinct from those with persistently preserved or reduced EF. Later, several terms were introduced to describe similar entities but with different defi-

Table 2. Independent predictors of LVEF recovery

Variable	Odds ratio	95% CI	p value
Age	0.99	0.97-1.01	0.28
ICM	0.49	0.27-0.88	0.02*
LBBB	0.65	0.23-1.79	0.41
QRS ≥ 110	0.4	0.21-0.77	0.005*
BB	2.11	1.10-4.08	0.03*

BB, beta-blocker; CI, confidence interval; ICM, ischemic cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

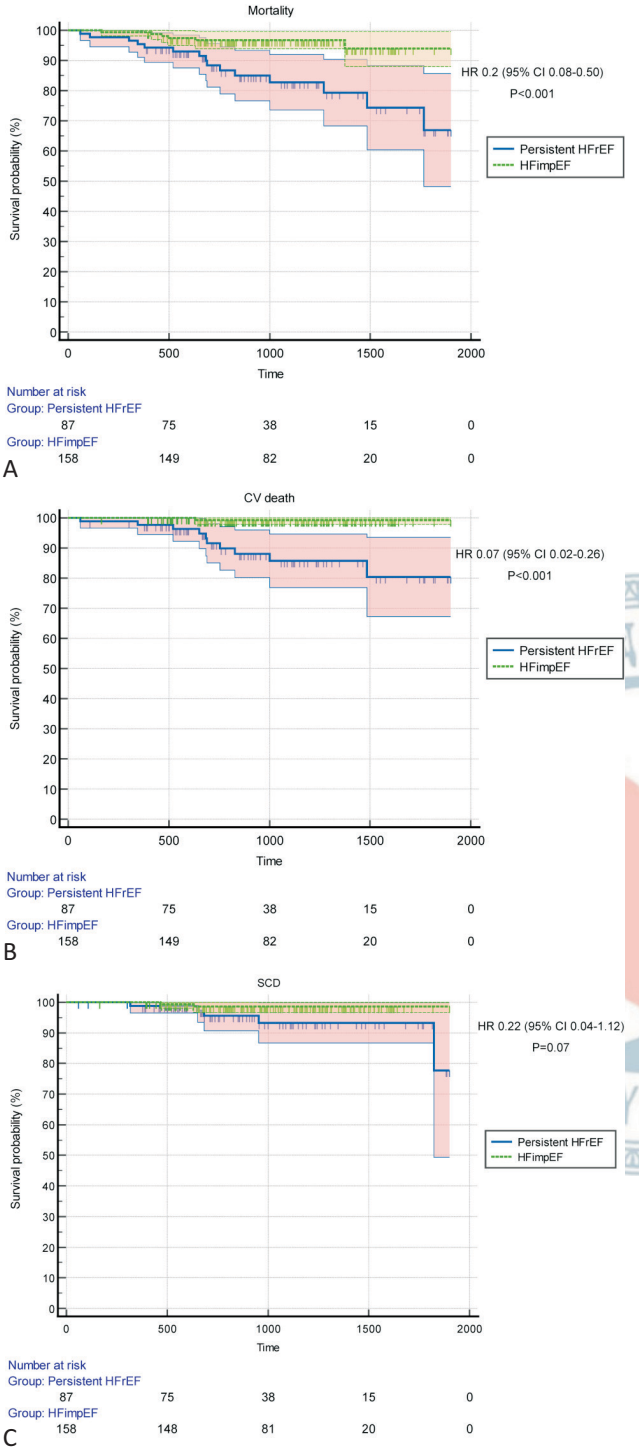

Figure 3. *Clinical outcomes of patients with HFimpEF and persistent HFrEF patients with HFimpEF showed significantly better prognosis with lower mortality (A), lower CV death (B) than patients with persistent HFrEF. There was no significant difference in SCD rate (C). CV death, cardiovascular death; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SCD, sudden cardiac death.*

nitions of LVEF improvement. The Heart Failure Society of America (HFSA), Heart Failure Association of the European Society of Cardiology (HFA/ESC), and the Japanese Heart Failure Society (JHFS) published the latest consensus statement of a universal definition for HF. Subsequently, HF with a second measurement of LVEF > 40% and a ≥ 10% increase from a baseline LVEF of ≤ 40% was defined as HfimpEF.[1]

LVEF is an important prognostic indicator in patients with HF. Previous studies have shown better outcomes in patients with improved EF. A meta-analysis of 9 studies with 9,491 heart failure patients showed that 22.64% of patients with HFrEF would be classified as HFimpEF after treatment. In addition, HFimpEF was associated with a 56% decrease in mortality and a 60% decrease in cardiac hospitalization compared with HFrEF patients.[2] Not all patients diagnosed with HFrEF were included in our study, as the PAC program only enrolled patients with functional class II-III who had the potential for rehabilitation and clinical improvement. Consequently, the patients in this cohort were more likely to have the potential for LVEF improvement following treatment. Our results demonstrated that the patients with HFimpEF had a significantly better prognosis with lower mortality and lower cardiovascular death rates than the patients with persistent HFrEF.

Several studies have reported that female sex, non-ischemic cause of HF, shorter duration of HF, less severe adverse cardiac remodeling at the initial evaluation, presence of hypertension, and the use of beta-blockers at discharge were associated with a greater likelihood of improved LVEF.[12,13] In the present study, all of the patients were diagnosed with HFrEF within 1 year, so the characteristics of our patient population may differ from those in previous studies. It is possible that the higher rate of LVEF improvement observed in our study is due to the fact that these patients tended to be in better functional class, with more motivation for rehabilitation and better compliance. Our findings that beta-blocker use was a predictor and ICM was a negative predictor of LVEF improvement are consistent with findings from other studies.

We also found that QRS duration was associated with LVEF improvement, and a shorter QRS duration (< 110 ms) was a predictor of LVEF recovery. An inverse correlation has been shown between QRS prolongation and LVEF.[14] Previous studies have reported that a longer QRS

duration was a risk indicator of adverse outcomes in patients with HFrEF. In addition, Kalra et al. found that patients with a QRS ≥ 120 ms had a 3-fold increased risk of death or transplantation.[15] Sam et al. reported that in the absence of CRT, patients with a wide QRS (≥ 120 ms) had less LV reverse remodeling compared to those with a narrow QRS (< 120 ms).[16] In a recent Taiwan local study, Huang et al. also found that wide QRS durations were associated with a lower degree of left ventricular improvement compared to narrow QRS durations in HFrEF patients even under ARNI treatment.[17] A wide QRS complex reflects left-sided intraventricular conduction delay in patients with HFrEF, and is associated with more advanced myocardial disease.

In the present study, we identified a new cutoff point for QRS duration that was found to be a better predictor of LVEF improvement. The reason for this may be that all of our patients were diagnosed with HFrEF at an early stage (within 1 year). Therefore, a QRS duration of ≥ 110 ms may indicate the early stages of LV remodeling and be associated with less reverse remodeling after medical treatment.

The rate of LBBB was higher in the patients with persistent HFrEF (17.2%) than in those with HFimpEF (7%) in this study. However, the rate of CRT implantation was similar in both groups (3.8% in the HFimpEF group and 4.6% in the persistent HFrEF group). The CRT implantation rate for CRT candidates was higher in the patients with HFimpEF. There was no significant difference in the CRT implantation rate for CRT candidates between the two groups, which may be due to the small number of patients (only 26 patients). Increasing the CRT implantation rate for CRT candidates may enhance left ventricular reverse remodeling and improve the LVEF recovery rate.

In this study, the median time to LVEF recovery was 159 days (IQR 112-289 days). Thus, if a patient is diagnosed with HFrEF within 1 year, has an initial QRS duration of less than 110 ms, has a non-ICM etiology, and receives beta-blockers, there is a higher likelihood of LVEF improvement after 3-6 months of guideline-directed medical treatment, and a decrease in mortality rate.

NEW KNOWLEDGE GAINED

Shorter QRS duration (< 110 ms) was a predictor of LVEF recovery in patients with early-stage HFrEF.

CONCLUSIONS

Beta-blocker prescription was an independent predictor of HFimpEF, while a diagnosis of ICM and QRS duration of ≥ 110 ms were negative predictors of HFimpEF. Patients with HfimpEF had a significantly lower mortality rate compared to those with persistent HFrEF.

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ETHICAL APPROVAL

The study was approved by the Institutional Review Board of the National Taiwan University Hospital Ethics Committee as number 202005126RIND.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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