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ORIGINAL ARTICLE

Incidence and predictors of heart failure with improved ejection fraction category in a HFrEF patient population

Balázs Solymossi[1], Balázs Muk[1], Róbert Sepp[2], Tamás Habon[3], Attila Borbély[4], Krisztina Heltai[5], Zsuzsanna Majoros[6], Zoltán Járai[7], Dénes Vágány[6], Ákos Szatmári[8], Erzsébet Sziliczei[9], Fanni Bánfi-Bacsárdi[1] and Noémi Nyolczas[1]*

[1]*Gottsegen National Cardiovascular Center, Budapest, Hungary;* [2]*Division of Non-Invasive Cardiology, Department of Internal Medicine, University of Szeged, Szeged, Hungary;* [3]*Division of Cardiology, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary;* [4]*Division of Cardiology, Department of Cardiology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary;* [5]*Heart and Vascular Center, Semmelweis University, Budapest, Hungary;* [6]*Department of Cardiology, Central Hospital of Northern Pest—Military Hospital, Budapest, Hungary;* [7]*South-Buda Center Hospital, St Imre University Teaching Hospital, Budapest, Hungary;* [8]*Cardiology Outpatient Clinic, Institute for Aviation Medicine, Military Fitness, and Medicine, Hungarian Defence Forces, Kecskemét, Hungary; and* [9]*Fejér County Szent György University Teaching Hospital, Székesfehérvár, Hungary*

Abstract

Aims The aim of the study was to assess the incidence and predictive factors of the development of heart failure with improved ejection fraction (HFimpEF) category during a 1 year follow-up period in a heart failure with reduced ejection fraction (HFrEF) patient population managed in a heart failure outpatient clinic.

Methods and results The study evaluated data from patients enrolled in the Hungarian Heart Failure Registry (HHFR). The incidence and predictive factors of the development of the HFimpEF category after 1 year follow-up were assessed in the group of patients who had HFrEF at baseline. We evaluated the incidence and predictors of the development of HFimpEF after a 1 year follow-up in relation to time since diagnosis of HFrEF in patients diagnosed within 3 months, between 3 months and 1 year, and beyond 1 year. The predictive factors of the development of HFimpEF were analysed using univariate and multivariate logistic regression analysis. Of the 833 HFrEF patients enrolled in the HHFR, the development of HFimpEF was observed in 162 patients (19.5%) during 1 year follow-up. In the whole patient population, independent predictors of the development of HFimpEF were female gender [odds ratio (OR): 1.73; 95% confidence interval (CI): 1.01–2.96; $P < 0.05$], non-ischaemic aetiology (OR: 1.95; 95% CI: 1.15–3.30; $P < 0.05$), and left ventricular end-diastolic diameter (LVEDD) <60 mm (OR: 2.04; 95% CI: 1.18–3.51; $P < 0.05$). The 1 year incidence of HFimpEF decreased in relation to time since diagnosis of HFrEF. The incidence of HFimpEF was 27.1% in patients diagnosed within 3 months, 18.4% in patients diagnosed between 3 months and 1 year, and 12.2% in patients diagnosed beyond 1 year. Non-ischaemic aetiology (OR: 4.76; 95% CI: 1.83–12.4; $P < 0.01$) and QRS width (OR: 0.81; 95% CI: 0.71–0.94; $P < 0.01$) for patients diagnosed within 3 months, LVEDD (OR: 0.54; 95% CI: 0.32–0.90; $P < 0.05$) and left atrial diameter ≤45 mm (OR: 5.44; 95% CI: 1.45–20.4; $P < 0.05$) for patients diagnosed between 3 months and 1 year, and LVEDD < 67 mm (OR: 2.71; 95% CI: 1.07–6.88; $P < 0.05$) for patients diagnosed beyond 1 year were found to be independent predictive factors.

Conclusions In our study, in this HFrEF patient population managed in a heart failure outpatient clinic, the 1 year incidence of HFimpEF was found to be ~20%. The 1 year incidence of HFimpEF decreased in relation to time since diagnosis of HFrEF. The most important predictors of the development of HFimpEF were female sex, non-ischaemic aetiology, narrower QRS width, and smaller diameter of the left ventricle and left atrium.

Keywords Heart failure with improved ejection fraction; Incidence; Predictive factors; Reverse remodelling

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**Correspondence to: Noémi Nyolczas, Gottsegen National Cardiovascular Center, Haller u. 29, Budapest 1096, Hungary. Tel: +36209451201; Fax: +3612157067. Email: nyolczasnoemi@gmail.com*

Introduction

In 2021, the Heart Failure Association of the European Society of Cardiology, the Heart Failure Society of America, and the Japanese Heart Failure Society published the Universal Definition and Classification of Heart Failure Consensus Statement,[1] introducing a new category of heart failure, called heart failure with improved ejection fraction (HFimpEF) in addition to the three well-known categories of heart failure—heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and heart failure with mildly reduced ejection fraction (HFmrEF). According to this new classification, the definition of HFimpEF is heart failure with a baseline left ventricular ejection fraction (LVEF) of ≤40%, a ≥10 percentage points increase from baseline LVEF, and a second measurement of LVEF of >40%.

The introduction of this new heart failure category is of paramount importance for many clinical aspects. As we know from previous data, LVEF may change during the course of the disease. Accordingly, patients can move from one heart failure category to another, which can fundamentally change their prognosis.[2,3] Patients remaining in the HFrEF category during follow-up and those previously belonging to the HFmrEF or HFpEF category but who shift to HFrEF during the disease trajectory have the worst prognosis among heart failure patients.[2] The clinical outcome is much more favourable for patients initially presenting with HFrEF but who (owing to treatment or the natural course of the disease) later shift to HFmrEF or HFpEF.[2] The introduction of this new category is also important for treatment, as we treat HFpEF patients differently if they have always been in this category or started their disease as HFrEF patients, for example.[4]

Given the recent introduction of this new heart failure category, knowledge is scarce regarding the incidence and predictive factors of the development of HFimpEF.

The aim of our study was (i) to examine the prevalence of different heart failure categories (HFrEF, HFmrEF, and HFpEF) and their changes during 1 year follow-up, (ii) to assess the incidence of the HFimpEF category after a 1 year follow-up of HFrEF patients, (iii) to examine the incidence of the HFimpEF category after 1 year follow-up in relation to time since diagnosis of HFrEF, (iv) to determine the factors that predict the development of the HFimpEF category overall, and (v) in relation to time since diagnosis of HFrEF in a heart failure patient population managed in a heart failure outpatient clinic.

Patients and methods

Patient population and study setting

Our study evaluated data from patients entered in the Hungarian Heart Failure Registry.[5] This registry contains data on heart failure patients managed in Hungarian outpatient heart failure clinics. The first patient was enrolled in the registry in March 2015 and the last patient in June 2018. Currently, the long-term follow-up of the 1573 patients is in process. Nineteen Hungarian cardiology centres are taking part in the development of the registry. Demographic, disease aetiology and comorbidities, clinical, laboratory, electrocardiogram (ECG), echocardiography, and patients' morbidity and mortality data were recorded in the registry in addition to data on diagnosis and therapy.

The Hungarian Heart Failure Registry was implemented in accordance with the Declaration of Helsinki and approved by the Medical Research Council, Committee of Science and Research Ethics, and the ethics committees of each participant institution (Medical Research Council, Committee of Science and Research Ethics Licence 55363-1/2013/EKU). Written informed consent was obtained from all patients before data collection.

In the present study, we evaluated the prevalence of different heart failure categories (HFrEF, HFmrEF, and HFpEF) and their changes during 1 year follow-up in patients who had adequate echocardiographic parameters, including appropriate LVEF measurements at the time of enrolment in the registry and after 1 year follow-up (*Figure 1*). LVEF was measured using the Simpson method. In defining the categories of HFrEF, HFmrEF, and HFpEF, we used definitions from the previously mentioned 'Universal Definition and Classification of Heart Failure' Consensus Statement[1] and the 'Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure'[6] published by the European Society of Cardiology in 2021. According to these recommendations, we allocated patients in the HFrEF, HFmrEF, and HFpEF categories with an LVEF ≤ 40%, 40% < LVEF < 50%, and LVEF ≥ 50%, respectively. HFimpEF was defined as baseline LVEF ≤ 40%, and baseline LVEF increased by at least 10 percentage points and exceeded 40% at the second LVEF measurement.

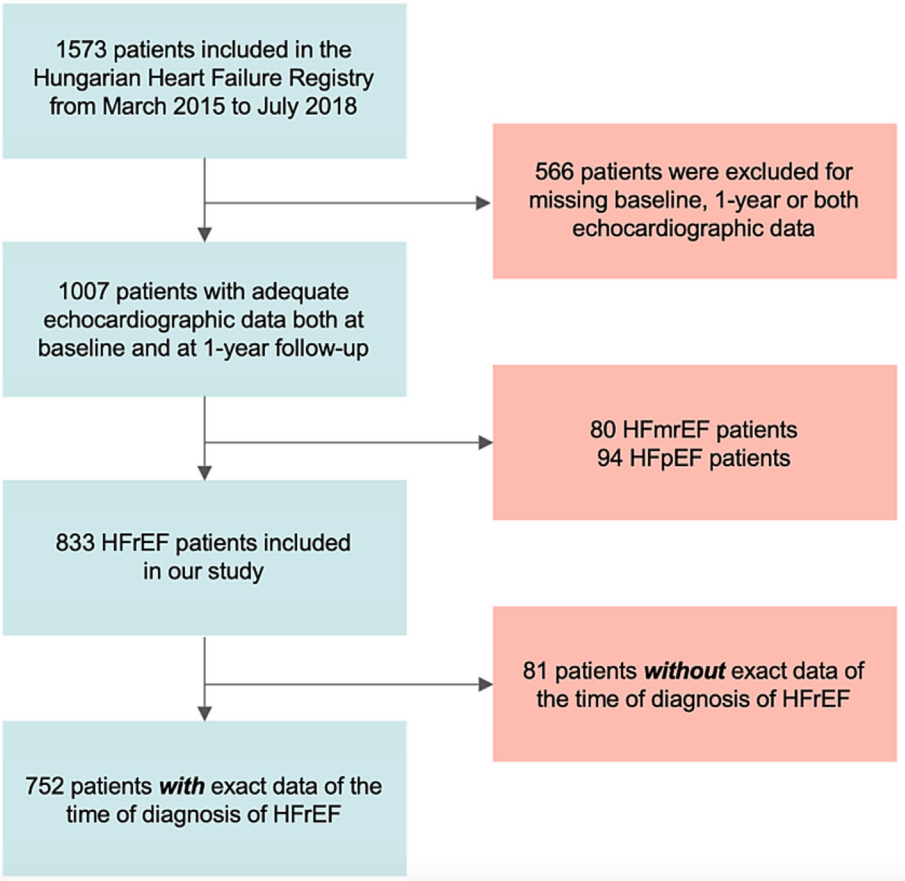
The incidence and predictive factors of the development of the HFimpEF category after 1 year follow-up were assessed in the group of patients who had HFrEF at baseline (*Figure 1*).

Further, we examined the incidence and predictive factors of the development of the HFimpEF category after a 1 year follow-up in relation to time since diagnosis of HFrEF in patients for whom we had accurate data on the time of HFrEF diagnosis (*Figure 1*).

Statistics

The recording of data was anonymized, and statistical analysis was undertaken using STATISTICA v.10 software. Normally distributed continuous variables are represented as mean ± standard deviation (SD), and the groups were compared using independent samples *t*-tests. The median

Figure 1 Flow chart of our study. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



and inter-quartile range (IQR) of continuous variables with non-normal distribution are reported, and the groups are compared using the Mann–Whitney test. The absolute and percentage values of the discrete variables are used, and groups are compared using the χ^2 test. *P* values <0.05 are considered statistically significant.

The predictive factors of the development of HFimpEF were analysed using univariate and multivariate logistic regression analysis. The optimal cut-point selection of dichotomous variables was based on significant area under the curve (AUC) results of receiver operating characteristic (ROC) curve analysis.

Results

Among the 1573 patients in the Hungarian Heart Failure Registry, 1007 patients had an LVEF measurement at enrolment and 1 year thereafter (of the 566 patients with missing echocardiographic parameters, 108 patients died). The baseline clinical characteristics of these 1007 patients are shown in *Table 1*.

The prevalence of different heart failure categories (heart failure with reduced ejection fraction, heart failure with mildly reduced ejection fraction, and heart failure with preserved ejection fraction) and their changes during 1 year follow-up

At the time of enrolment in the registry, of the 1007 patients, 833 (83%), 80 (8%), and 94 (9%) patients were classified as HFrEF, HFmrEF, and HFpEF, respectively. After a 1 year follow-up, there were 650 (64%), 168 (17%), and 189 (19%) patients in the HFrEF, HFmrEF, and HFpEF categories, respectively. The changes between categories over the 1 year follow-up are shown in *Figure 2*. Of the HFrEF phenotype,

Table 1 Baseline clinical characteristics of patients included in the study

Parameter	*n* = 1007 patients
Age (years), mean ± SD	62.6 ± 16.7
Female sex, absolute value (%)	268 (26.6%)
Ischaemic aetiology, absolute value (%)	389 (38.6%)
Hypertension, absolute value (%)	582 (57.8%)
Diabetes mellitus, absolute value (%)	300 (29.8%)
Bundle branch block, absolute value (%)	310 (30.8%)
SBP (mmHg), mean ± SD	123.8 ± 20.9
DBP (mmHg), mean ± SD	76.8 ± 34.0
HR (min^{-1}), mean ± SD	75.9 ± 15.3
PQ interval (ms), mean ± SD	174.0 ± 40.8
QRS width (ms), mean ± SD	116.9 ± 45.0
LVEF (%), mean ± SD	33.0 ± 11.4
LVEDD (mm), mean ± SD	65.2 ± 9.5
LVESD (mm), mean ± SD	54.1 ± 11.0
LV PW (mm), mean ± SD	11.4 ± 4.9
IVS (mm), mean ± SD	11.0 ± 1.7
LA diameter (mm), mean ± SD	52.9 ± 9.5
Na (mmol/L), mean ± SD	139.9 ± 3.5
K (mmol/L), mean ± SD	4.6 ± 0.5
BUN (mmol/L), mean ± SD	9.7 ± 7.6
Creatinine (μmol/L), mean ± SD	112.1 ± 50.5
eGFR (mL/min/1.73 m^2), mean ± SD	62.3 ± 21.0
Bilirubin (mmol/L), mean ± SD	14.5 ± 12.5
Haemoglobin (g/L), mean ± SD	136.8 ± 52.8
GOT (IU/L), median; IQR	23.0; 18.0–30.0
GPT (IU/L), median; IQR	22.0; 16.0–33.0
GGT (IU/L), median; IQR	49.5; 29.0–102.0
NT-proBNP (pg/mL), median; IQR	1600.5; 547.9–3560.3
BMI (kg/m^2), mean ± SD	29.4 ± 5.7
BB therapy, absolute value (%)	971 (96.4%)
RASi therapy, absolute value (%)	954 (94.7%)
MRA therapy, absolute value (%)	798 (79.2%)
Triple therapy (RASi + BB + MRA), absolute value (%)	748 (74.3%)
ICD, absolute value (%)	309 (30.7%)
CRT, absolute value (%)	139 (13.8%)

BB, beta-blocker; BMI, body mass index; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HR, heart rate; ICD, implantable cardioverter defibrillator; IQR, inter-quartile range; IVS, interventricular septum; LA, left atrial; LV PW, left ventricular posterior wall; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RASi, renin–angiotensin system inhibitor (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor); SBP, systolic blood pressure; SD, standard deviation.

75% of patients remained in the HFrEF category and 14% shifted to the HFmrEF category and 11% to the HFpEF category. Forty-four per cent of HFmrEF patients remained in this category and 26% belonged to the HFrEF category and 30% to the HFpEF category after 1 year. Finally, 81% of HFpEF patients did not change category after 1 year of follow-up, but 4% were in the HFrEF category and 15% in the HFmrEF category after 1 year.

The incidence of the heart failure with improved ejection fraction category after 1 year follow-up of heart failure with reduced ejection fraction patients

Of those originally HFrEF patients, 625 (75.0%) remained in the HFrEF category, whereas 119 (14.3%) and 89 (10.7%) patients were classified into the HFmrEF and HFpEF categories, respectively, after a 1 year follow-up. Patients who were shifted to the HFpEF category after 1 year, by definition, meet the criteria for the HFimpEF category. Among the patients in the HFmrEF category at 1 year, improvement of LVEF by at least 10 percentage points was observed in 73 (8.8%). Accordingly, after a 1 year follow-up period, 162 patients were in the HFimpEF category, resulting in an HFimpEF incidence of 19.5% in our patient population (*Figure 3*).

Several significant differences in baseline parameters were observed in patients classified as HFimpEF or non-HFimpEF after 1 year follow-up. In the HFimpEF category, patients were significantly younger, with a larger proportion of female patients and non-ischaemic aetiology and a smaller proportion of diabetes mellitus. In addition, HFimpEF patients had significantly smaller left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) as well as left atrial (LA) diameter, thicker left ventricular wall, higher heart rate, narrower QRS, lower potassium levels, more favourable renal function, and lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at baseline. There was no difference in pharmacological therapy between the two groups. The HFimpEF group included a smaller proportion of patients with implantable cardioverter defibrillator (ICD) (*Table 2*).

Predictive factors of the development of the heart failure with improved ejection fraction category

Evaluating the above parameters using univariate logistic regression analysis, we found that female sex, age younger than 65 years, non-ischaemic aetiology, heart rate below 90 min^{-1}, and higher estimated glomerular filtration rate (eGFR) were the predictive parameters that significantly increased the likelihood of the development of the HFimpEF category. A wider QRS, larger LVESD and LVEDD, and larger LA diameter were predictive factors that significantly reduced the likelihood of the development of HFimpEF (*Table 3*).

Based on the multivariate logistic regression analysis, female sex, non-ischaemic aetiology, and LVEDD of 60 mm or less proved to be independent predictive factors that significantly increased the likelihood of the development of HFimpEF (*Table 3*).

Figure 2 Prevalence of different heart failure categories [heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF)] at enrolment and after 1 year follow-up in the patient population of the Hungarian Heart Failure Registry.

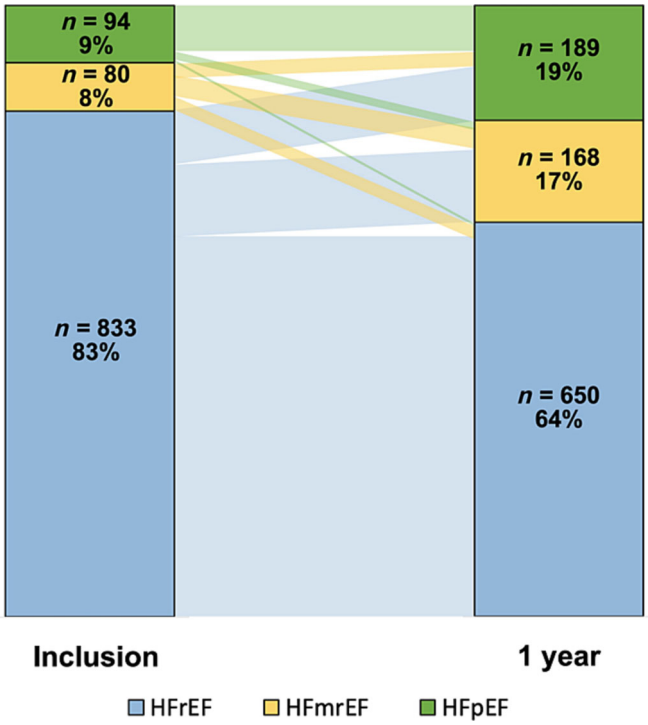


Figure 3 Number of patients in the heart failure with improved ejection fraction (HFimpEF) category after 1 year follow-up of heart failure with reduced ejection fraction (HFrEF) patients. HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

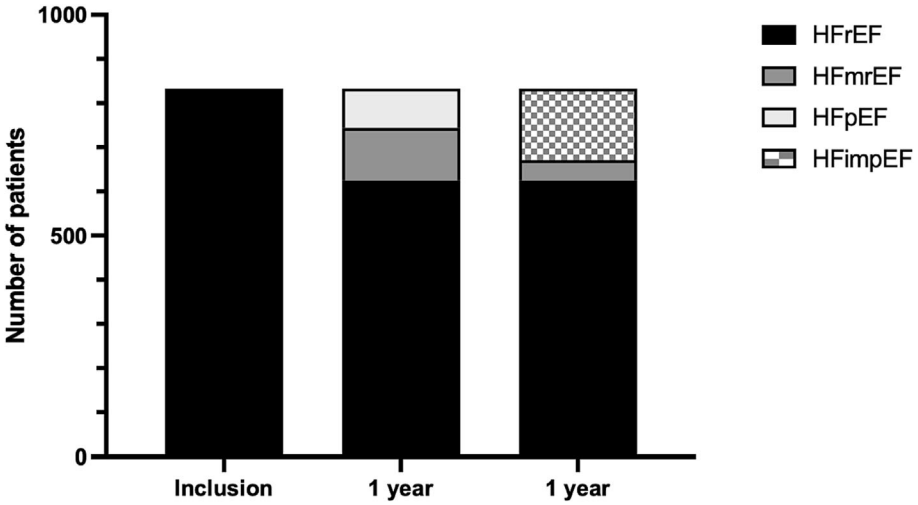


Table 2 Baseline clinical characteristics of HFimpEF and non-HFimpEF patients

Parameter	HFimpEF (n = 162)	Non-HFimpEF (n = 671)	P value
Age (years), mean ± SD	59.9 ± 12.7	62.2 ± 12.0	<0.05
Female sex, absolute value (%)	54 (33.3%)	130 (19.4%)	<0.05
Ischaemic aetiology, absolute value (%)	44 (27.2%)	291 (43.4%)	<0.05
Hypertension, absolute value (%)	88 (54.3%)	365 (51.4%)	0.98
Diabetes mellitus, absolute value (%)	34 (21.0%)	201 (30.0%)	<0.05
Bundle branch block, absolute value (%)	57 (35.2%)	289 (43.1%)	0.07
SBP (mmHg), mean ± SD	123.6 ± 23.0	122.9 ± 19.7	0.68
DBP (mmHg), mean ± SD	76.3 ± 13.2	75.4 ± 12.5	0.43
HR (min^{-1}), mean ± SD	78.3 ± 18.0	75.7 ± 14.3	<0.05
PQ interval (ms), mean ± SD	166.0 ± 27.3	175.0 ± 39.1	0.08
QRS width (ms), mean ± SD	109.4 ± 31.5	117.1 ± 34.1	<0.05
LVEF (%), mean ± SD	29.0 ± 7.0	29.0 ± 6.8	0.55
LVEDD (mm), mean ± SD	65.1 ± 9.6	67.7 ± 8.3	<0.01
LVESD (mm), mean ± SD	54.9 ± 9.0	57.4 ± 8.9	<0.01
LV PW (mm), mean ± SD	11.2 ± 1.8	10.7 ± 1.5	<0.05
IVS (mm), mean ± SD	11.7 ± 2.5	10.7 ± 1.1	<0.001
LA diameter (mm), mean ± SD	50.4 ± 8.6	54.0 ± 9.8	<0.01
Na (mmol/L), mean ± SD	139.1 ± 3.1	139.9 ± 3.5	0.064
K (mmol/L), mean ± SD	4.5 ± 0.6	4.6 ± 0.5	<0.05
BUN (mmol/L), mean ± SD	7.9 ± 3.7	10.3 ± 9.0	<0.05
Creatinine (μmol/L), mean ± SD	104.5 ± 50.6	116.0 ± 52.5	0.08
eGFR (mL/min/1.73 m^2), mean ± SD	68.1 ± 21.7	61.5 ± 21.5	<0.05
Bilirubin (mmol/L), mean ± SD	15.2 ± 10.8	14.6 ± 12.9	0.78
Haemoglobin (g/L), mean ± SD	140.0 ± 26.2	135.1 ± 24.9	0.15
NT-proBNP (pg/mL), median; IQR	1017; 419–2194	1986; 802–4174	<0.05
BMI (kg/m^2), mean ± SD	29.2 ± 5.4	28.5 ± 6.1	0.42
BB therapy, absolute value (%)	160 (98.8%)	647 (96.3%)	0.12
RASi therapy, absolute value (%)	154 (95.1%)	644 (96.0%)	0.6
MRA therapy, absolute value (%)	130 (80.2%)	568 (84.5%)	0.17
Triple therapy (RASi + BB + MRA), absolute value (%)	124 (76.5%)	534 (79.5%)	0.39
ICD, absolute value (%)	38 (23.5%)	243 (36.2%)	<0.05
CRT, absolute value (%)	19 (11.7%)	103 (15.3%)	0.24

BB, beta-blocker; BMI, body mass index; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HFimpEF, heart failure with improved ejection fraction; HR, heart rate; ICD, implantable cardioverter defibrillator; IQR, inter-quartile range; IVS, interventricular septum; LA, left atrial; LV PW, left ventricular posterior wall; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RASi, renin–angiotensin system inhibitor (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor); SBP, systolic blood pressure; SD, standard deviation.

Table 3 Factors predicting the development of the HFimpEF category in the whole study population (833 patients)—univariate and multivariate logistic regression analysis

	OR	95% CI	P value
Parameters of univariate logistic regression analysis			
Female sex	2.08	1.42–3.04	<0.001
<65 years of age	1.50	1.05–2.14	0.026
Non-ischaemic aetiology	2.05	1.41–3.00	<0.001
HR < 90 min^{-1}	1.68	1.11–2.54	0.015
eGFR (increase of 5 mL/min/1.73 m^2)	1.08	1.01–1.15	0.016
QRS (increase of 10 ms)	0.93	0.87–0.99	0.023
LVESD (increase of 5 mm)	0.85	0.76–0.96	<0.01
LVEDD (increase of 5 mm)	0.82	0.73–0.93	<0.01
LA diameter (increase of 5 mm)	0.80	0.69–0.93	<0.01
Parameters of multivariate logistic regression analysis			
Female sex	1.73	1.01–2.96	0.045
Non-ischaemic aetiology	1.95	1.15–3.30	0.013
LVEDD ≤ 60 mm	2.04	1.18–3.51	0.011

CI, confidence interval; eGFR, estimated glomerular filtration rate; HFimpEF, heart failure with improved ejection fraction; HR, heart rate; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; OR, odds ratio.

Incidence of the heart failure with improved ejection fraction category in relation to time since diagnosis of heart failure with reduced ejection fraction

Given that patients had been enrolled in the Hungarian Heart Failure Registry at different times after the diagnosis of HFrEF, we evaluated the incidence of the HFimpEF category in relation to time since diagnosis of HFrEF. Of the originally assessed 833 HFrEF patients, exact data for 81 patients were missing regarding the time that had passed between the diagnosis of heart failure and enrolment in the registry; hence, this issue could be adequately evaluated in the case of 752 patients.

Of the total of 752 HFrEF patients, 24 patients were enrolled in the registry at the time of the diagnosis of HFrEF, 275 patients between diagnosis and 3 months, 70 patients between 3 and 6 months, 55 patients between 6 and

12 months, 69 patients between 1 and 2 years, 41 patients between 2 and 3 years, and 218 patients more than 3 years following the initial diagnosis of HFrEF. Of these patients, we observed the development of the HFimpEF category in 41.7% (10 patients), 25.8% (71 patients), 17.1% (12 patients), 20.0% (11 patients), 14.5% (10 patients), 14.6% (6 patients), and 11.0% (24 patients), respectively, after 1 year follow-up (*Figure 4*). As our results depict, the development of the HFimpEF category decreases from time since diagnosis of HFrEF.

Factors predicting the development of the heart failure with improved ejection fraction category in relation to time since diagnosis of heart failure with reduced ejection fraction

Predictors of the development of HFimpEF were assessed for patients enrolled in the registry within 3 months, between 3 months and 1 year, and beyond 1 year after HFrEF diagnosis.

Of the 299 patients enrolled in the registry within 3 months after HFrEF diagnosis, 81 (27.1%) developed HFimpEF during the 1 year follow-up. In this group, baseline parameters of HFimpEF and non-HFimpEF patients differed significantly. HFimpEF patients were younger (57.9 ± 12.3 vs. 61.6 ± 12.3 years; $P < 0.05$) and had a larger proportion of women (35.8% vs. 20.2%; $P < 0.01$) and patients with non-ischaemic aetiology (76.5% vs. 58.7%; $P < 0.01$), a smaller proportion of hypertension (51.9% vs. 59.6%; $P < 0.05$) and prevalence of bundle branch block (27.2% vs. 41.7%; $P < 0.05$), narrower QRS (103.6 ± 27.4 vs. 114.5 ± 32.7 ms; $P < 0.05$), and a lower serum potassium (4.4 ± 0.6 vs. 4.6 ± 0.6 mmol/L; $P = 0.03$) and NT-proBNP [480 (101–1962) vs. 2282 (735–4386) pg/mL] level than the group of patients not classified as HFimpEF at 1 year follow-up.

Univariate logistic regression analysis indicated that female sex, non-ischaemic aetiology, absence of diabetes, and bundle branch block were the predictive parameters that significantly increased the likelihood of the development of the HFimpEF category. Increasing age, wider QRS, and higher serum potassium level were the predictive factors that significantly decreased the likelihood of the development of HFimpEF (*Table 4*).

Multivariate logistic regression analysis showed the independent predictive value of non-ischaemic aetiology and QRS width. While non-ischaemic aetiology increased the likelihood of the development of HFimpEF, an increase in QRS width decreased it (*Table 4*).

Of the 125 patients enrolled in the registry between 3 months and 1 year after HFrEF diagnosis, 23 (18.4%) developed HFimpEF during the 1 year follow-up period. HFimpEF patients were associated with a higher prevalence of female sex (39.1% vs. 17.6%; $P < 0.05$) and non-ischaemic aetiology (91.3% vs. 57.8%; $P < 0.01$), lower diastolic blood pressure (69.9 ± 10.9 vs. 76.1 ± 12.4 mmHg; $P < 0.05$), smaller LVEDD (61.2 ± 7.6 vs. 65.3 ± 6.9 mm; $P < 0.05$), and greater wall thickness parameters [interventricular septum (IVS): 11.3 ± 2.2 vs. 10.4 ± 0.7 mm; $P < 0.01$ and posterior wall (PW): 11.4 ± 2.0 vs. 10.4 ± 0.7 mm; $P < 0.001$].

Figure 4 Incidence of the heart failure with improved ejection fraction (HFimpEF) category at 1 year follow-up in relation to time since diagnosis of heart failure with reduced ejection fraction.

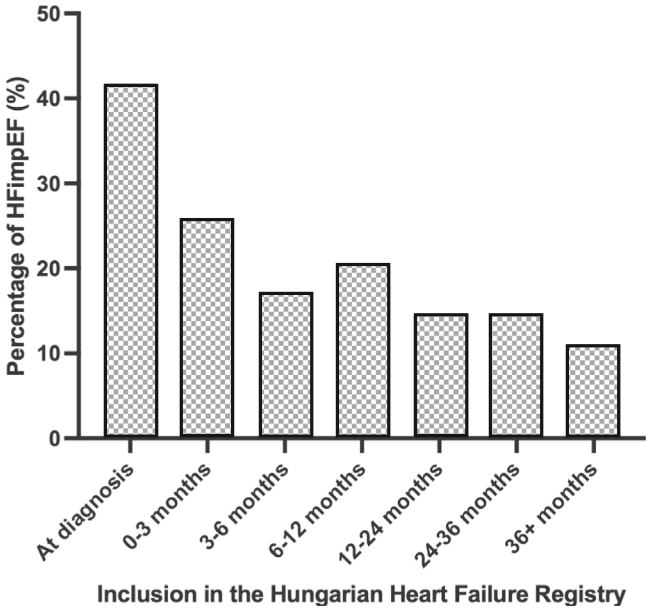


Table 4 Factors predicting the development of the HFimpEF category in patients enrolled in the registry within 3 months, between 3 months and 1 year, and beyond 1 year after HFrEF diagnosis—univariate and multivariate logistic regression analysis

Patients enrolled in the registry within 3 months			
	OR	95% CI	*P* value
Parameters of univariate logistic regression analysis			
Age (increase of 10 years)	0.82	0.67–0.99	0.044
Female sex	2.21	1.26–3.87	<0.01
Non-ischaemic aetiology	2.29	1.28–4.10	<0.01
Absence of diabetes mellitus	1.84	1.01–3.32	0.045
Absence of bundle branch block	1.92	1.10–3.36	0.022
QRS width (increase of 10 ms)	0.88	0.80–0.98	0.021
K (increase of 0.5 mmol/L)	0.71	0.52–0.97	0.030
Parameters of multivariate logistic regression analysis			
Non-ischaemic aetiology	4.76	1.83–12.4	<0.01
QRS width (increase of 10 ms)	0.81	0.71–0.94	<0.01
Patients enrolled in the registry between 3 months and 1 year			
	OR	95% CI	*P* value
Parameters of univariate logistic regression analysis			
Female sex	3.00	1.13–7.99	0.028
Non-ischaemic aetiology	7.65	1.70–34.4	<0.01
DBP (increase of 5 mmHg)	0.80	0.65–0.98	0.031
LVEDD (increase of 5 mm)	0.64	0.42–0.96	0.037
IVS (increase of 1 mm)	1.74	1.03–2.95	0.039
LV PW (increase of 1 mm)	1.99	1.15–3.46	0.014
LA diameter ≤45 mm	5.03	1.48–17.1	<0.01
Parameters of multivariate logistic regression analysis			
LVEDD (increase of 5 mm)	0.54	0.32–0.90	0.018
LA diameter ≤45 mm	5.44	1.45–20.4	0.012
Patients enrolled in the registry beyond 1 year			
	OR	95% CI	*P* value
Parameters of univariate logistic regression analysis			
Female sex	2.33	1.16–4.70	0.018
SBP (increase of 5 mmHg)	1.11	1.02–1.20	0.018
QRS width ≤95 ms	2.43	1.11–5.31	0.026
LVEDD < 67 mm	3.10	1.32–7.28	<0.01
LA diameter <55 mm	3.85	1.06–13.9	0.04
Parameters of multivariate logistic regression analysis			
LVEDD < 67 mm	2.71	1.07–6.88	0.036

CI, confidence interval; DBP, diastolic blood pressure; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IVS, interventricular septum; LA, left atrial; LV PW, left ventricular posterior wall; LVEDD, left ventricular end-diastolic diameter; OR, odds ratio; SBP, systolic blood pressure.

Univariate logistic regression analysis identified that female sex, non-ischaemic aetiology, greater wall thickness, and smaller LA diameter were the predictive parameters that significantly increased the likelihood of the development of the HFimpEF category. Increasing diastolic blood pressure and LVEDD were the predictive factors that significantly decreased the likelihood of the development of HFimpEF (*Table 4*).

Multivariate logistic regression analysis identified that LVEDD and LA diameter were independent predictive factors. While smaller LA diameter increased the likelihood of the development of HFimpEF, an increase in LVEDD decreased it (*Table 4*).

Of the 328 patients enrolled in the registry beyond 1 year after HFrEF diagnosis, 40 (12.2%) were observed to develop HFimpEF at the end of the 1 year follow-up period. In this group of patients, we found significant differences in baseline parameters between HFimpEF and non-HFimpEF patients only in the prevalence of female sex and systolic blood pressure values. In the HFimpEF group, a significantly greater prevalence of females (37.5% vs. 20.5%; $P < 0.05$) and a higher systolic blood pressure value were observed (127.5 ± 22.5 vs. 119.6 ± 19.0 mmHg; $P < 0.05$).

In univariate logistic regression analysis, female sex, higher systolic blood pressure, narrower QRS, and smaller LVEDD and LA diameter were found to be predictive factors that significantly increased the likelihood of the development of HFimpEF (*Table 4*).

Multivariate logistic regression analysis confirmed the independent predictive value of smaller left ventricular size (LVEDD) (*Table 4*).

Discussion

Our results showed that the incidence of the HFimpEF category was 19.5% in an HFrEF patient population managed in a heart failure outpatient clinic during a 1 year follow-up period. This incidence depends significantly on the time since diagnosis of HFrEF. In the months following the diagnosis, it surpassed 25%; however, beyond 3 years after the diagnosis of HFrEF, the incidence of HFimpEF was approximately only 10%.

Female gender, non-ischaemic aetiology, and LVEDD smaller than 60 mm were found to be independent clinical predictors of the development of HFimpEF in the overall patient population.

Regarding the predictive factors related to time since diagnosis of HFrEF, we found that non-ischaemic aetiology and narrower QRS have significant predictive value for the development of HFimpEF within 3 months of diagnosis, while beyond 3 months of diagnosis, smaller left ventricular and LA size have a significant predictive value for the development of HFimpEF.

Incidence of the heart failure with improved ejection fraction category

In the past few years, several studies[2,7–13] have examined the incidence of the 'improved LVEF' in HFrEF. However, these publications were rather heterogeneous and used different nomenclature and classifications [e.g. besides HFimpEF, heart failure with recovered ejection fraction (HFrecEF) terminology was also used]. Until the Consensus Statement published by Bozkurt *et al*. in 2021,[1] major differences could be

observed in the definitions of HFimpEF and HFrecEF. Furthermore, in these previous studies, the baseline demographic data, the aetiology of heart failure, the treatment regimen, and the follow-up time also showed great variation. Consequently, significant differences in HFimpEF incidence data could be seen in these publications.

Zamora *et al*.[9] found an HFimpEF incidence of 34.7% in a patient population of 1040 originally HFrEF patients in a 1 year follow-up period, using the criteria of the Universal Definition and Classification of Heart Failure.[1] Savarese *et al*.,[7] evaluating data from 4942 patients from the Swedish Heart Failure Registry, found that of 3113 originally HFrEF patients, 10% shifted to the HFpEF category and 26% to the HFmrEF category during a median follow-up of 1.4 years.[7] In the meta-analysis of He *et al*. published in 2021,[11] the pooled incidence of the HFimpEF category was found to be 22.64% in a 3.8 year follow-up period. However, none of the nine publications in the meta-analysis used the definitions of HFimpEF included in the Universal Definition and Classification of Heart Failure Consensus Statement. The HFimpEF incidence is between 10% and 52% in the studies included in the meta-analysis.

In our study, the observed HFimpEF incidence of 19.5% at 1 year follow-up fits with the results of Savarese *et al*. and He *et al*.[7,11]

Incidence of the heart failure with improved ejection fraction category in relation to time since diagnosis of heart failure with reduced ejection fraction

A significant result of our study is that it shows that the change in HFimpEF incidence depends on the time since diagnosis of HFrEF. We found that the shorter the time from the diagnosis of HFrEF, the greater the likelihood of the development of the HFimpEF category during a 1 year follow-up time. While this incidence is 27.1% within 3 months from diagnosis, it is 11.0% after 3 years.

Predictive factors of the heart failure with improved ejection fraction category

Recently, several studies have investigated the predictors of the development of the HFimpEF category.

Nallamshetty *et al*.,[14] using a cohort of 106 414 US veterans with HFrEF, found the 5 year incidence of the HFimpEF category to be 37.6%. Consistent with our study, younger age, female sex, higher systolic blood pressure, lower baseline creatinine levels, and higher body mass index (BMI) were identified as predictors of HFimpEF development. In the presence of ischaemic heart disease, the likelihood of developing HFimpEF was reduced. Of note, the former study was the first to investigate the predictive role of race and demonstrated the lower incidence of HFimpEF in patient groups of African American and Hispanic origin.

Su *et al*.,[10] in a study of a Chinese cohort published in March 2022, also found that HFimpEF patients are typically younger and less likely to have ischaemic heart disease as an aetiological factor. Higher systolic and diastolic blood pressure values at baseline, higher baseline LVEF, lower New York Heart Association (NYHA) functional class, smaller LVEDD, and beta-blocker (BB) and mineralocorticoid receptor antagonist (MRA) use were found to be predictors of the development of the HFimpEF category. In the study, the prognosis of HFimpEF was found to be more favourable than that of HFrEF and HFpEF patients. The results of this study are in good agreement with the results of our present study in terms of the predictive value of younger age, non-ischaemic HFrEF aetiology, and smaller left ventricular dimensions for the development of the HFimpEF category.

In a recent review on left ventricular reverse remodelling, Chudý and Goncalvesová[15] reviewed the predictive factors for reverse remodelling and HFimpEF, highlighting that the definition of HFimpEF in the literature and the patient populations studied are rather heterogeneous. In addition, the improvement of LVEF and the development of HFimpEF do not always imply left ventricular reverse remodelling. The review assessed the predictive value of aetiological, clinical, and imaging parameters, pharmacological and device therapy, and biomarkers. According to the results of the studies evaluated in the review, younger age, female sex, non-ischaemic aetiology, shorter duration of disease course, higher systolic blood pressure, absence of left bundle branch block, shorter QRS duration, lower NT-proBNP and troponin levels, higher absolute value of global longitudinal strain (GLS) measured by speckle tracking echocardiography, and optimized drug therapy proved to be predictors of reverse remodelling. The predictive factors identified in the review are in good agreement with the results of the present study.

Our results, the data from the literature presented above, and additional publications[16–19] consistently show that female gender is an important positive predictive factor for LVEF improvement and development of the HFimpEF category. A recently published meta-analysis[20] that evaluated the results of 18 studies that addressed this issue and data from 12 270 patients found that female sex was associated with a greater likelihood of LVEF improvement. This association, if LVEF improvement is defined as LVEF $>$ 40%, was found to be statistically significant. Why female sex is preferential for LVEF improvement in HFrEF is not precisely known. However, a large body of human and animal data demonstrates that there are differences in left ventricular remodelling and reverse remodelling between the two sexes. For example, in women with the same left ventricular dysfunction, chronic pressure overload increases left ventricular

dimensions and wall thickness to a lesser extent and also results in differences in renin activity and levels of natriuretic peptides.[21,22] The results of several studies have also identified gender differences in cardiomyocyte death and apoptosis.[23–25] In addition, the lower incidence of ischaemic heart disease in female patients is certainly a factor in the higher incidence of HFimpEF than in male patients.

Also, close correlation between non-ischaemic HFrEF aetiology and left ventricular reverse remodelling, LVEF improvement, and the development of the HFimpEF category has been generally observed.[7,16–18,26,27] This phenomenon may be explained by the fact that the hearts of patients with HFrEF of ischaemic aetiology may have less viable myocardium and more extensive scar tissue, in which the favourable haemodynamic changes associated with the disease-modifying treatment of HFrEF are unable to induce reverse remodelling similar to that in patients with non-ischaemic aetiology. Regarding the irreversible tissue lesions that occur due to myocardial infarction, recent autologous bone marrow stem cell therapy has not achieved a genuine breakthrough.[28–32]

In our study, in line with other publications,[10,33] we found that smaller left ventricular and LA dimensions are strongly associated with a higher likelihood of developing HFimpEF. Left ventricular dilatation and left ventricular dimensions and volumes reflect the extent of structural damage to the left ventricle resulting from underlying intracellular and molecular processes. Several experimental studies have evaluated this issue,[34–36] demonstrating that significant molecular damage may result in significant left ventricular dilatation, which may be an obstacle to improving LVEF and reverse remodelling. An increase in left ventricular dimensions, resulting in increased wall stress, may be a further trigger for pathological left ventricular remodelling.

It is now known that not only left ventricular remodelling but also LA remodelling has prognostic significance. A recent publication suggests that an improved LVEF in HFrEF is associated with a higher rate of LA remodelling.[37] Further, LA remodelling, like left ventricular remodelling, predicts a better prognosis and lower mortality and morbidity.

Similar to our results, several studies have demonstrated that narrow QRS is a predictive factor for left ventricular reverse remodelling.[38] In these studies, improvement of LVEF and the development of left ventricular reverse remodelling were more frequent for narrow QRS than for wide QRS without cardiac resynchronization therapy (CRT).[39,40] Although the reason for this phenomenon is not fully known, it is assumed that the electromechanical dyssynchrony observed in wide QRS is less influenced by medical therapy.

Surprisingly, in our study, unlike many others, pharmacological therapy was not shown to be predictive of HFimpEF. However, Savarese *et al*. came to a similar conclusion as us.[7] Our results may be explained by the very large proportion of patients in both the HFimpEF and non-HFimpEF groups who received renin–angiotensin system inhibitor (RASi), BB, MRA, and triple therapy.

Limitations

Members of the patient population evaluated in the study were treated and regularly followed up at dedicated, high-volume heart failure outpatient clinics. Hence, high-quality complex drug and device therapy was implemented for most of them. Thus, the data from this study may not be generalizable to other groups of heart failure patients.

The development of HFimpEF was assessed after a 1 year follow-up period. Further studies are needed to evaluate the long-term development of HFimpEF and its prognostic factors.

When patients were enrolled in the registry, evidence of the beneficial effects of sodium–glucose cotransporter-2 (SGLT2) inhibitors and the guidelines pertaining them were not yet available. Consequently, this class of drugs was not evaluated in the study.

Conclusions

In summary, in this HFrEF patient population managed in heart failure clinics, the 1 year incidence of HFimpEF was found to be ~20%. The 1 year incidence of HFimpEF decreased depending on the time since diagnosis of HFrEF. In our study, the most important favourable predictive factors for the development of HFimpEF were female sex, non-ischaemic aetiology, narrower QRS, and smaller size of the left ventricle and left atrium. Non-ischaemic aetiology and narrower QRS in the months following diagnosis and left ventricular and LA dimensions thereafter are essential in predicting the development of HFimpEF.

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Conflict of interest

None declared.

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