Serum Levels of Irisin Are Positively Associated with Improved Cardiac Function in Patients with Heart Failure with Reduced Ejection Fraction

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Article

Serum Levels of Irisin Are Positively Associated with Improved Cardiac Function in Patients with Heart Failure with Reduced Ejection Fraction

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Abstract: The role of irisin in predicting functional cardiac recovery in patients with heart failure with reduced ejection fraction (HFrEF) retains not fully understood. The aim of the study is to determine discriminative value of irisin for improved left ventricular ejection fraction (LVEF) in discharged patients with HFrEF. We included in the study 313 patients who were discharge with HFrEF (at admission LVEF < 40%) and followed them for 3 months. HF with improved EF (HFimpEF) was defined as an increase in LVEF of more than 40% on transthoracic B-mode echocardiography within 3 months of follow-up. All individuals gave their informed consent to participate in the study and obtained optimal guideline-based management. Serum concentrations of NT-proBNP, high-sensitivity cardiac troponin T, tumor necrosis factor-alpha (TNF-alpha), high-sensitivity C-reactive protein (hs-CRP), interleukin-6, galectine-3, soluble suppression of tumorigenicity-2 and irisin were determined using commercially available enzyme-linked immunosorbent assay kits. At 3rd months 117 (37.4%) patients had improved LVEF, whereas 196 individuals were categorized as having persistent HFrEF. The proportions of current stable coronary artery disease, atrial fibrillation, chronic kidney disease grade 1-3, and percutaneous coronary intervention history were significantly higher in patients with persistent HFrEF compared with HFimpEF. We found that HFimpEF was associated with lower left ventricular end-diastolic dimension, serum levels of NT-proBNP and higher left atrial volume index (LAVI), irisin concentrations than those with persistent HFrEF, whereas the levels of other biomarkers did not significantly differ between groups. The most balanced cut-off value of irisin and NT-proBNP (improved LVEF versus non-improved LVEF) were 10.8 ng/mL (area under curve [AUC] = 0.96, sensitivity = 81.0%, specificity = 88.0%; P = 0.0001) and 1540 pmol/L (AUC = 0.79; sensitivity = 73.1%, specificity 78.5%, p = 0.0001), respectively. Using multivariate comparative analysis we established that the irisin levels ≥ 10.8 ng/mL (odds ration [OR] = 1.73; P = 0.001) and NT-proBNP < 1540 pmol/mL (OR = 1.47; P = 0.001), LAVI < 39 mL/m2 (OR = 1.23; P = 0.001), atrial fibrillation (OR = 0.95; P = 0.010) independently predicted HFimpEF. The discriminative value of irisin ≥10.8 ng/mL was better than NT-proBNP <1540 pmol/mL, but the combined model (irisin added to NT-proBNP) did not improve the predictive modality of irisin alone. In conclusion, serum irisin ≥10.8 ng/mL predicted improved LVEF in patients with HFrEF independently of NT-proBNP.

Keywords: heart failure with reduced ejection fraction; heart failure with improved ejection fraction; cardiac function; irisin; biomarkers

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1. Introduction

Heart failure (HF) remains a highly prevalent condition ranged from 0.2% to 17.7% in the general population with unacceptably high mortality rates, despite the implementation of new diagnostic, preventive and treatment options in routine clinical practice [1,2]. Several population-representative studies have shown that one-year mortality from heart failure varied from 4% to 45%, with an average of 33% overall and 24% depending on the presentation of HF phenotypes, concomitant comorbidities across all adult age groups and were categorized by left ventricular ejection fraction (LVEF) [3,4]. Interestingly, cardiovascular (CV) and HF readmission rates were markedly higher in patients with HF with reduced ejection fraction (HFrEF) and mildly reduced ejection fraction (HFmrEF) compared with those with HF with preserved ejection fraction (HFpEF), whereas the composite endpoint (all-cause mortality, cardiovascular death and re-hospitalization) was similar in all subgroups [5–7].

A substantial proportion of patients with HFrEF show improvement in LVEF (known as HF with improved EF [HFimpEF]) when treated with guideline-directed medical therapy (GDMT) [8]. Recovery of systolic function in patients with HFrEF is associated with improved short- and long clinical outcomes including mortality and hospital re-admission [9,10]. Despite the presence of several factors as positive predictors of HFimpHF, i.e., younger age, female sex, de novo HF, hypertension, atrial fibrillation, sodium-glucose cotransporter-2 (SGLT2) inhibitors and beta-blockers, and as negative predictors such as NYHA class III/IV, anaemia, diabetes mellitus and ischaemic heart disease, the role of conventionally used circulating biomarkers in the management of HFimpHF is still not clearly understood [10,11]. Moreover, the clinical benefit of contemporary management in terms of HFimpHF was present regardless of baseline N-terminal brain natriuretic pro-peptide (NT-proBNP) concentration, while higher NT-proBNP levels were linearly associated with a greater risk of the poor outcome [12]. However, post-discharge monitoring of NT-proBNP levels showed no clear benefit in predicting re-admission rate or non-HF adverse clinical events, but was significantly associated with a lower risk of CV death [13]. Another aspect is a determination of non-HF mortality in HFimpHF after discharge from hospital, because non-cardiac causes accounted for more 60% of deaths, which are not completely predicted with biomarkers of mechanical stress (NT-proBNP), myocardial damage (high-sensitivity troponin T/I), inflammation (galectin-3, interleukin-6, high-sensitivity C-reactive protein, growth differential factor-15) and fibrosis (soluble suppression of tumorigenicity 2 [sST2]) [14–18]. In addition, the improvement in LV systolic function is accompanied by a decrease in serum natriuretic peptide levels [19]. A significant proportion of these patients frequently determined as having euvolumic status may have low/near-normal levels of NT-proBNP (<300 pg/mL), which severely limit its ability to discriminate clinical outcomes in HFimpEF, so that a large part of these patients maybe underestimated at the risk of adverse outcomes [20]. In this context, the discovery of new approaches based on circulating biomarkers for predicting of HFimpEF could be considered to be promising.

In recent years, there has been numerous evidence that the intensity of systemic inflammation may be associated with severity and poor prognosis in any HF phenotypes [21,22]. In this context, CV risk factors (age, smoking), metabolic comorbidities (diabetes mellitus, dyslipidaemia, obesity, thyroid dysfunction), cardiac cachexia, rheumatic and respiratory diseases, acute and chronic kidney disease, altered microbiota contribute to the pathogenesis and progression of HF through modulating inadequate immune response, mediating synthesis and releasing inflammatory mediators, which consequently induce adipose tissue and skeletal muscle dysfunctions, and intervene in vascular and cardiac remodelling [23].

Irisin is the membrane-associated component of fibronectin type III domain-containing 5 protein (FNDC5), which is activated by peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) after stretching in skeletal muscle [24]. Several forms of physical exercise, i.e., aerobic, anaerobic, interval training, have been identified as primary causes of an increase in irisin levels. In physiological conditions, irisin acts as a regulator of insulin receptor phosphorylation in tyrosine residues that increase the activity of the phosphatidylinositol 3-kinases pathway, thereby attenuating

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insulin sensitivity, inflammatory response and cognitive function [25]. FNDC5/irisin stimulates the transcriptional potency RUNX1/2 factors through a focal adhesion kinase-dependent pathway in brain and peripheral tissues including bone and subcutaneous white adipose tissue (WAT) and consequently plays a pivotal role in thermogenesis, energy metabolism and browning WAT [26,27]. In pathophysiological conditions irisin is not only produced by skeletal myocytes, but also adipocytes, cardiac myocytes, hepatocytes, astrocytes [28,29]. Irisin prevents ischemia-reperfusion injury, cell necrosis / apoptosis / pyroptosis, protects autophagy and mitochondrial dysfunction, as well as reduce extracellular matrix accumulation, fibrosis, oxidative stress and inflammation via the AKT/mTOR signalling, ERK1/2 and the Sirtuin-1-p53-SLC7A11/GPX4 pathways [30–32].

Low levels of circulating irisin were not only associated with cardio- and cerebrovascular conditions and diseases (myocardial infarction, HF, hypertension, atherosclerosis, vascular dementia, stroke), osteoporosis, diabetes mellitus, obesity, chronic kidney disease, but also demonstrated its discriminative ability for prognosis of their natural evolution [33–38]. Finally, predictive potency of irisin concentrations were better than NT-proBNP in HF in patients with metabolic comorbidities, such as obesity and diabetes mellitus [39]. However, the possible role of irisin in predicting functional cardiac recovery in HFrEF patients retains not fully understood. The aim of the study is to determine discriminative value of irisin for improved LVEF in discharged patients with HFrEF.

2. Materials and Methods

2.1. Patient Population and Study Design

We selected 356 patients, who were admitted with a diagnosis of HFrEF and had hemodynamically stable status with the levels of NT-proBNP > 300 pmol/mL. Among whom 313 individuals had no the inclusion criteria and were consecutively enrolled from October 2020 to November 2024. The subjects were then evaluated during a subsequent inpatient stay at the private hospital "Vita Center" (Zaporozhye, Ukraine), and the inclusion and exclusion criteria, in addition to the study procedures and the determination of clinical outcomes, are outlined in Figure 1.

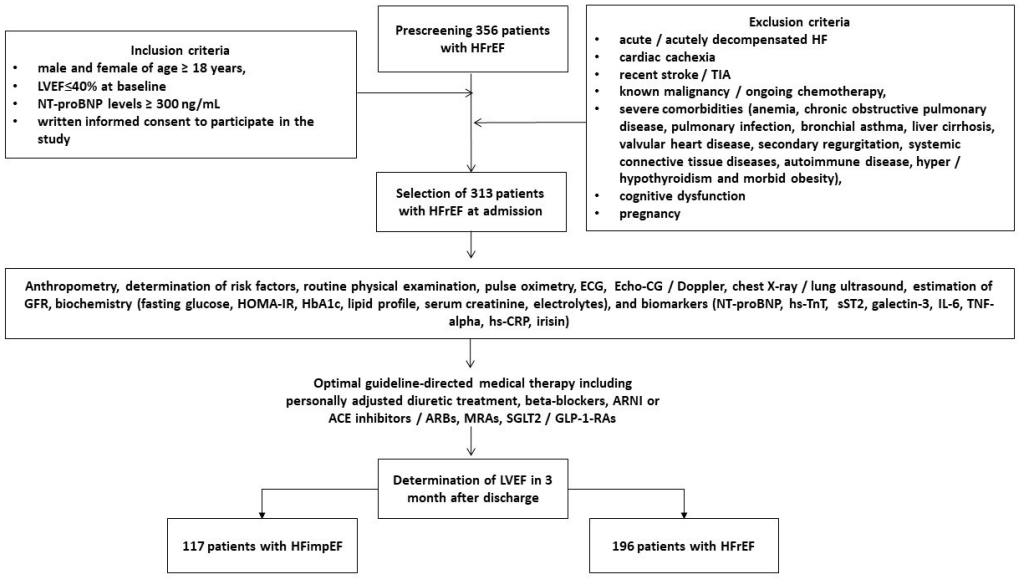

Figure 1. Flow chart of study design. Abbreviations: ACE, angiotensin-converting enzyme; ARBs, Angiotensin-II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; Echo-CG, echocardiography; ECG, electrocardiography; GLP-1-RAs, glucagon-like peptide-1 receptor agonists; IL, interleukin; LVEF, left ventricular ejection fraction; hs-CRP, high-sensitivity C-reactive protein; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal brain natriuretic pro-peptide; TNF-alpha, tumor necrosis factor-

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alpha; sST2, soluble suppression of tumorigenicity-2; SGLT2, sodium-glucose co-transporter-2; TIA, transient ischemic attack.

All patients were administered optimal, guideline-based therapy, including personalised doses of diuretics, renin-angiotensin-aldosterone system inhibitors, beta-blockers, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists. At 3 months post-discharge, patients meeting the criteria for HFimpHF were enrolled in the first cohort (n=117), whereas those without improvement in LVEF were categorised as having persistent HFrEF and enrolled in the second cohort (n=196).

2.2. The Evaluation of Participants' Demographics, Anthropometry Parameters and Concomitant Diseases / Conditions

The study collected detailed information about the participants' demographics (age, gender) and anthropometry parameters including weight, height, waist circumference, body surface area, and body mass index (BMI). The evaluation involved an assessment of conventional cardiovascular risk factors and concomitant diseases / conditions such as hypertension, smoking, dyslipidemia, obesity, atrial fibrillation, coronary artery disease (CAD), type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).

2.3. Determination of HFimpEF

HFimpEF has been defined as LVEF of ≤40% at baseline, with an improvement of up to 40% and a ≥10% decrease in LVEF recorded over a period of one 3 month after discharge from hospital [11].

2.4. Echocardiography Examination

In the study, each participant underwent a standard transthoracic B-mode ultrasound examination administered by high-qualified assessors. The ultrasound examination was performed in apical 2- and 4-chamber views using a GE Healthcare Vivid E95 scanner (General Electric Company, Horton, Norway). The conventional hemodynamic parameters were evaluated in accordance with the 2018 Guideline of the American Society of Echocardiography [40]. This encompassed cardiac dimensions, left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes, left atrial volum index (LAVI), and tricuspid annular plane systolic excursion (TAPSE). LVEF was determined by Simpson's method. Doppler examination was performed to determine the presence of mitral and tricuspid regurgitation, and to measure early diastolic mitral blood filling (E), medial and lateral e` velocities.The estimated E/e` ratio was expressed as the ratio of the E wave velocity to the averaged medial and lateral e` velocities. Left ventricular hypertrophy was defined as a left ventricular mass index (LVMI) of ≥95 g/m2 in women or ≥115 g/m2 in men [40].

2.5. Glomerular Filtration Rate and Insulin Resistance Determination

The conventional CKD-EPI formula was utilised to estimate the glomerular filtration rate (eGFR) [41]. The Homeostatic Assessment Model of Insulin Resistance (HOMA-IR) was employed to assess insulin resistance [42].

2.6. Blood Sampling and Biomarker Analysis

Peripheral blood samples were obtained via venipuncture and collected in BD Vacutainer serum tubes. Following centrifugation at 3000 rpm for a period of 10 minutes, the serum was harvested and stored in a temperature of -70°C until analysis. Conventional haematological and biochemical parameters were determined using a Roche P800 analyser (Basel, Switzerland) in the local laboratory of the Vita Centre (Zaporozhye, Ukraine). Circulating biomarkers (NT-proBNP, tumor necrosis factor [TNF]-alpha, high-sensitive C-reactive protein [hs-CRP], high-sensitive troponin T [hs-TnT], interleukin [IL]-6, galectin-3, soluble suppression of tumorigenicity-2 [sST2], irisin) were measured

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in serum using ELISA kits (Elabscience, Houston, Texas, USA) at the baseline. Analyses were performed according to the manufacturer's instructions, with standard curve analysis being performed on the data obtained from the ELISA analysis. Each sample was analysed on two separate occasions, and the mean of these measurements was used for the final evaluation. The intra- and inter-assay coefficients of variability for each marker were both found to be less than 10%.

2.7. Statistics

Statistical analysis of the data was conducted utilising SPSS Statistics 29 (IBM, Armonk, NY, USA) and Prism v.10 (GraphPad, San Diego, CA, USA) software. Variables are reported as mean and standard deviation, median and interquartile range (IQR), or absolute numbers and percentages (%), as appropriate. The Anderson-Darling test was employed to verify the data distribution. Continuous variables were compared using paired t-test or Mann-Whitney test when appropriate, whereas categorical variables were compared using Fisher's exact test. Possible predictors of HFimpEF were identified using univariate logistic regression and backward stepwise multivariate logistic regression, and an odds ratio (OR) and 95% confidence interval (CI) were calculated for each predictor. Predictors with a P-value of less than 0.05 in the univariate log regression analysis were included in the multivariate log regression model. The reliability of the predictive models was determined by Receiver Operating Curve (ROC) analysis, with further calculation of area under the curve (AUC), its confidence interval (CI), sensitivity (Se), and specificity (Sp) for each predictor. The Youden test was used to estimate the cut-off points for irisin. The integrated discrimination indices (IDI) and the net reclassification improvement (NRI) were also calculated to assess the potential value of irisin in predicting HFimpHF. Statistically significant results were defined as those with a P-value less than 0.05.

3. Results

3.1. Basic Clinical Characteristics, Echocardiographic Parameters and Laboratory Findings

The study included 117 patients with HFimpEF and 196 individuals with persistent HFrEF. The basic characteristics of the patients was presented in Table 1. The mean age of the patients in this study was 69 years, and 58.9% were male. The patients had comorbidity profile that included smoking (43.1%), obesity (24.0%), dyslipidemia (74.8%), hypertension (56.2%), coronary artery disease (51.8%), dilated cardiomyopathy (18.2%), atrial fibrillation (29.7%), chronic kidney disease 1-3 grades (21.7%), and type 2 diabetes mellitus (32.6%). Percutaneous coronary intervention was provided about 31.0% of the patients from entire group. Along with it, NYHA HF classes II, III and IV were detected in 23.0%, 58.9% and 18.1%, respectively. All patients had stable hemodynamic, increased both left ventricular diastolic and systolic volumes, and LVEF less 40% at baseline. Mean value of LAVI was 41 mL/m2, E/e` ratio was 17 and LVMI was 148 g/m2. The patients had dyslipidaemia, mild an increase in HOMA-IR, circulating creatinine, inflammatory biomarkers (hs-CRP, TNF-alpha, IL-6), as well as indicators of fibrosis (galectin-3 and sST2). The mean serum levels of NT-proBNP and irisin were 1810 pmol/mL and 5.75 ng/mL, respectively. Concomitant medications included RAAS inhibitors, SGLT-2 inhibitors, mineralocorticoid receptor antagonists, beta-blockers, ivabradine (for those with sinus rhythm and uncontrolled heart rate on beta-blocker therapy), diuretics, statins, and anticoagulants/antiplatelet agents. Patients with concomitant T2DM or obesity were treated with a personalised diet, metformin and glucagon-like peptide-1 receptor agonists.

There were no significant differences in age, gender, body mass index, waist circumference, smoking, obesity, dyslipidaemia, hypertension, dilated cardiomyopathy, left ventricular hypertrophy and T2DM. The proportions of current stable coronary artery disease, atrial fibrillation, CKD grade 1-3 and PCI history were significantly higher in patients with HFrEF compared with HFimpEF. There were no differences in the presentation of NYHA HF classes between the two patient cohorts. Patients with HFimpEF had significantly lower LVEDV, LVESV and LAVI than those with

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HFrEF. TAPSE, E/e` and LVMI did not differ between the two cohorts. We did not find sufficient differences between the cohorts in baseline eGFR, creatinine, electrolytes, lipid profile, HOMA-IR, fasting glucose, HbA1c, hemoglobin, hematocrit, serum uric acid, hs-CRP, TNF-alpha, IL-6, cTnT, sST2, galectine-3. In contrast, NT-proBNP levels were higher and irisin concentrations were lower in HFimpEF compared with HFrEF. With the exception of anticoagulants, there were no differences in concomitant medications between the cohorts.

Table 1. Baseline general characteristics of eligible patients.

Variables	Entire HF patient cohort (*n* = 313)	Patients with HFimpEF (*n* = 117)	Patients with HFrEF (*n* = 196)	*P* value between cohorts
Demographics and anthropometry parameters				
Age, year	69 (61–78)	67 (60–75)	70 (62–81)	0.146
Male gender, *n* (%)	184 (58.9)	68 (58.1)	116 (59.2)	0.146
BMI, kg/m²	26.2 ± 4.26	25.3 ±3.88	26.9 ± 3.97	0.272
Waist circumference, cm	101 ± 7	99 ± 5	101 ± 8	0.690
Medical history				
Smoking history, *n* (%)	135 (43.1)	48 (41.0)	87 (44.4)	0.642
Abdominal obesity, *n* (%)	75 (24.0)	27 (23.1)	48 (24.5)	0.475
Dyslipidaemia, *n* (%)	234 (74.8)	86 (73.5)	148 (75.5)	0.344
Hypertension, *n* (%)	176 (56.2)	66 (56.4)	110 (56.1)	0.871
Stable CAD, *n* (%)	162 (51.8)	57 (48.7)	105 (53.6)	0.046
Dilated cardiomyopathy, *n* (%)	57 (18.2)	20 (17.1)	37 (18.9)	0.242
Atrial fibrillation, *n* (%)	93 (29.7)	28 (23.9)	65 (33.2)	0.048
LVH, *n* (%)	217 (69.3)	81 (69.2)	136 (69.4)	0.844
CKD 1–3 grades, *n* (%)	68 (21.7)	22 (18.8)	46 (23.5)	0.044
T2DM, *n* (%)	102 (32.6)	38 (32.5)	64 (32.7)	0.526
PCI history, *n* (%)	97 (31.0)	42 (35.9)	55 (28.1)	0.048
NYHA functional class, *n* (%)				
II	72 (23.0)	29 (24.8)	43 (21.9)	0.142
III	184 (58.9)	69 (59.0)	115 (58.7)	0.416
IV	57 (18.1)	19 (16.2)	38 (19.4)	0.144
Hemodynamic and echocardiographic parameters				
Systolic BP, mm Hg	127 ± 8	129 ± 8	126 ± 9	0.395
Diastolic BP, mm Hg	68 ± 9	69 ± 7	68 ± 7	0.462
LVEDV, mL	176 (154–197)	178 (155–201)	173 (149–193)	0.274
LVESV, mL	103 (98–106)	99 (95–103)	110 (97–119)	0.022
LVEF, %	41 (34–51)	44 (40–47)	37 (33–39)	0.024
LVMI, g/m²	148 ± 22	147 ± 19	155 ± 20	0.226
LAVI, mL/m²	44 (35–54)	42 (36–49)	47 (40–53)	0.046
TAPSE, mm	20 (15-26)	19 (14-24)	22 (15-27)	0.611
E/e`, unit	17 ± 7	16 ± 4	17 ± 5	0.355
Laboratory findings				
Baseline eGFR, mL/min/1.73 m²	64 ± 19	65 ± 15	61 ± 13	0.331
K, mmol/L	4.1 (3.3-5.3)	4.3 (3.4-5.5)	4.0 (3.1-5.10)	0.124
Na, mmol/L	139 (128-146)	139 (125-149)	137 (127-145)	0.846
HOMA-IR, units	5.11 ± 2.33	5.05 ± 2.23	5.19± 2.25	0.658
Fasting glucose, mmol/L	4.68 ± 0.57	4.59 ± 0.52	4.70 ± 0.51	0.681
HbA1c, %	5.10 ± 1.99	5.07 ± 1.65	5.11± 1.57	0.560
Haemoglobin, g/L	13.9 (12.6–15.1)	13.8 (12.5-14.7)	14.0 (12.6-15.3)	0.674
Haematocrit, %	38 (34–42)	38 (35-40)	39 (35–43)	0.644
Baseline creatinine, μmol/L	104 ± 10	97 ± 11	106 ± 9	0.128

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Serum uric acid, μmol/L	359 ± 85	352 ± 80	360 ± 88	0.672
Total cholesterol, mmol/L	5.69 ± 0.60	5.61 ± 0.68	5.73 ± 0.66	0.654
HDL-C, mmol/L	1.02 ± 0.10	1.03 ± 0.09	1.02 ± 0.10	0.748
LDL-C, mmol/L	3.60± 0.20	3.50 ± 0.18	3.60± 0.20	0.786
Triglycerides, mmol/L	2.34 ± 0.37	2.30 ± 0.29	2.41 ± 0.27	0.650
hs-CRP, mg/L	5.98 (2.24–9.70)	5.52 (2.12–8.16)	6.11 (2.80–10.56)	0.860
TNF-alpha, pg/mL	3.68 (2.10–5.23)	3.45 (2.03–4.94)	3.81 (2.19–5.21)	0.547
IL-6, ng/mL	2.91 (0.76–4.95)	2.70 (0.67–4.82)	3.20 (0.88–5.61)	0.216
cTnT, ng/mL	0.036 (0.004-0.112)	0.021 (0.001-0.110)	0.048 (0.003-0.120)	0.690
NT-proBNP, pmol/mL	1810 (980–2560)	1330 (870–1580)	2310 (1130–3580)	0.044
sST2, ng/mL	29.40 (13.90-45.70)	27.63 (11.17–41.80)	31.90 (15.82-47.54)	0.844
Galectin-3, ng/mL	27.5 (11.6 – 53.4)	24.1 (9.8 – 41.5)	32.7 (10.1 – 60.3)	0.671
Irisin, ng/mL	5.75 (2.18–9.12)	8.23 (4.26–13.50)	4.37 (1.62–7.17)	0.001
Concomitant medications and devises				
ACE inhibitors, *n* (%)	122 (39.0)	43 (36.8)	79 (40.3)	0.519
ARBs, *n* (%)	39 (12.5)	20 (17.1)	19 (9.7)	0.050
ARNI, *n* (%)	152 (48.7)	54 (46.2)	98 (50.0)	0.538
Beta-blockers, *n* (%)	285 (91.1)	105 (89.7)	180 (91.8)	0.351
Ivabradine, *n* (%)	32(10.2)	10 (8.5)	22 (11.2)	0.271
CCBs, *n* (%)	35 (11.2)	11 (9.4)	24 (12.2)	0.164
MRA, *n* (%)	231 (73.8)	86 (73.5)	145 (74.0)	0.834
Diuretics, *n* (%)	298 (98.2)	112 (95.7)	186 (94.9)	0.877
Antiplatelet agents, *n* (%)	179 (57.2)	69 (59.0)	110 (56.1)	0.048
Anticoagulants, *n* (%)	93 (29.7)	28 (23.9)	65 (33.2)	0.048
Metformin, *n* (%)	97 (31.0)	36 (30.8)	61 (31.1)	0.713
SGLT2 inhibitors, *n* (%)	227 (72.5)	86 (73.5)	141 (71.9)	0.637
GLP-1-RAs, *n* (%)	34 (10.8)	13 (11.1)	21 (10.7)	0.511
Statins, *n* (%)	234 (74.8)	86 (73.5)	148 (75.5)	0.344
RCT, *n* (%)	22 (7.0)	9 (7.7)	13 (6.6)	0.766

Notes: Variables are given as M ± SD and Me (25–75% IQR). Chi-square test was used to compare categorical variables. Abbreviations: AF, atrial fibrillation; ACE, angiotensin-converting enzyme; ARBs, Angiotensin-II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; BMI, body mass index; CAD, coronary artery disease; CCBs, calcium channel blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; E/e`, early diastolic blood filling to longitudinal strain ratio; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; GLP-1-RAs, glucagon-like peptide-1 receptor agonists; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricle myocardial mass index, LVH, left ventricular hypertrophy; MRA, mineralocorticoid receptor antagonist; RCT, resynchronized therapy; NT-proBNP, N-terminal brain natriuretic pro-peptide; TNF-alpha, tumor necrosis factor-alpha; sST2, soluble suppression of tumorigenicity-2; SGLT2, sodium-glucose co-transporter-2.

3.2. The Optimal Cut-Offs for Possible Predictors of HFimpEF: The Results of the ROC Curve Analysis

To determine the optimal cut-offs for potential predictors of HFimpEF, ROC curve analysis was performed (Table 2). The following factors for further regression analysis have been identified: LAVI

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<39 mL/m2, E/e`<17; hs-CRP <6.1 mg/L; TNF-alpha <3.7 ng/mL; NT-proBNP <1540 pmol/mL; sST2 <31 ng/mL, galectin-3 < 28 ng/mL; irisin >10.8 ng/mL.) (Table 2).

Table 2. Receiver Operating Characteristic Curve Analysis for possible predictive factors of HFimpHF.

Variables	AUC	95% CI	P value	Cut-offs	Se, %	Sp,%
LAVI	0.721	0.680 – 0.773	0.001	39 mL/m²	73.9	77.1
E/e`	0.667	0.615 – 0.718	0.001	17	63.6	70.2
hs-CRP	0.744	0.712 – 0.779	0.001	6.1 mg/L	72.3	75.4
TNF-alpha	0.602	0.543 – 0.665	0.048	3.7 pg/mL	62.4	61.8
NT-proBNP	0.855	0.811 – 0.892	0.0001	1540 pmol/mL	79.0	73.1
sST2	0.768	0.733 – 0.795	0.001	31 ng/mL	72.6	70.4
Galectin-3	0.741	0.708 – 0.795	0.001	28 ng/mL	73.5	78.1
Irisin	0.960	0.910 – 0.988	0.0001	10.8 ng/mL	81.0	88.0

Abbreviations: AUC, area under curve; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; E/e`, early diastolic blood filling to longitudinal strain ratio; LAVI, left atrial volume index; Se, sensitivity; Sp, specificity; NT-proBNP, N-terminal brain natriuretic pro-peptide; sST2, soluble suppression of tumorigenicity-2; TNF-alpha, tumor necrosis factor-alpha.

3.3. Predictive Factors for HFimpEF: Univariate and Multivariate Logistic Regression Models

Univariate logistic regression analysis showed that atrial fibrillation, CKD stages 1–3, LAVI <39 mL/m2, E/e`<17; hs-CRP <6.1 mg/L; TNF-alpha <3.7 ng/mL; NT-proBNP <1540 pmol/mL; sST2 <31 ng/mL, galectin-3 < 28 ng/mL; irisin >10.8 ng/mL were associated with improved LVEF in HF individuals (Table 3). Multivariate logistic regression analysis revealed that the presence of AF, LAVI <39 mL/m2, NT-proBNP<1540 pmol/mL and irisin≥10.8 ng/mL were independent predictors for HFimpEF.

Table 3. Predictive factors for HFimpEF: Univariate and multivariate log regression analysis.

Predictive factors	Univariate log regression		Multivariate log regression	
	OR (95% CI)	P value	OR (95% CI)	P value
T2DM (presence vs absent)	0.97 (0.91–1.02)	0.212	-	
PCI history (presence vs absent)	0.95 (0.89–1.13)	0.437	-	
AF (presence vs absent)	0.95 (0.91–0.98)	0.010	0.95 (0.90–0.98)	0.010
Stable CAD (presence vs. absent)	1.02 (0.94–1.17)	0.380	-	
CKD stages 1–3 (presence vs. absent)	0.93 (0.87–0.99)	0.048	0.95 (0.89–1.01)	0.177
Dilated CMP (presence vs absent)	0.96 (0.92–1.02)	0.422	-	
LAVI < 39 mL/m² vs. ≥39 mL/m²	1.32 (1.15–1.56)	0.001	1.23 (1.11–1.39)	0.001
E/e`<17 vs. ≥17	1.18 (1.04–1.35)	0.012	1.10 (1.00–1.27)	0.052
hs-CRP <6.1 mg/L vs. ≥6.1 mg/L	1.12 (1.06–1.20)	0.018	1.09 (1.00–1.20)	0.120
TNF-alpha <3.7 bg/mL vs. ≥3.7 ng/mL	1.06 (1.01 – 1.12)	0.044	1.05 (0.99 – 1.10)	0.206
NT-proBNP <1540 vs. ≥ 1540 pmol/mL	1.56 (1.12–2.15)	0.001	1.47 (1.11–2.12)	0.001
sST2 <31 ng/mL vs. ≥31 ng/mL	1.24 (1.02–1.65)	0.048	1.20 (1.00–1.68)	0.086
Galectin-3 <28 ng/mL vs. ≥28 ng/mL	1.17 (1.01–1.43)	0.050	1.12 (1.00–1.27)	0.064
Irisin ≥ 10.8 ng/mL vs.<10.8 ng/mL	1.75 (1.22–4.32)	0.001	1.73 (1.16–4.18)	0.001

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; CKD, chronic kidney disease; LAVI, left atrial volume index; NT-proBNP, N-terminal brain natriuretic pro-peptide; sST2, soluble suppression of tumorigenicity-2; OR, odds ratio; TNF-alpha, tumor necrosis factor-alpha; T2DM, type 2 diabetes mellitus.

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3.4. Comparison of the Predictive Models

We compared the predictive models for HFimpEF and found that the model 1 (NT-proBNP<1540 pmol/mL) and the model 2 (a presence of AF) did not markedly differ each another in prediction of HFimpEF, whereas Model 3 (LAVI <39 mL/m2) was worse than reference model (Table 4). The model 4 (irisin≥10.8 ng/mL) were significantly better than the model 1. Furthermore, the combined model 1 + 4 (NT-proBNP<1540 pmol/mL + irisin≥10.8 ng/mL) was superior to model 1 alone (NT-proBNP<1540 pmol/mL), but did not increase the discriminatory power of model 4 (irisin≥10.8 ng/mL). Other combined models showed no better benefit than model 1.

Table 4. The comparisons of predictive models for HFimpEF.

Predictive Models	Dependent Variable: AKI					
	AUC		NRI		IDI	
	M (95% CI)	*p* value	M (95% CI)	*p* value	M (95% CI)	*p* value
Model 1 (NT-proBNP<1540 pmol/mL)	0.855 (0.811 – 0.892)	-	Reference	-	Reference	-
Model 2 (a presence of AF)	0.820 (0.715 – 0.944)	0.427	0.10 (0.06– 0.15)	0.388	0.11 (0.05– 0.17)	0.481
Model 3 (LAVI <39 mL/m²)	0.721 (0.680 – 0.773)	0.044	0.03 (0.01– 0.06)	0.642	0.06 (0.02– 0.09)	0.552
Model 4 (irisin≥10.8 ng/mL)	0.960 (0.910 – 0.988)	0.001	0.36 (0.24– 0.49)	0.001	0.44 (0.38– 0.52)	0.001
Model 1+ Model 2	0.848 (0.790 – 0.910)	0.066	0.10 (0.05– 0.17)	0.249	0.12(0.06– 0.19)	0.265
Model 1+ Model 3	0.851 (0.810 – 0.912)	0.270	0.09 (0.03– 0.15)	0.338	0.11 (0.03- 0.17)	0.286
Model 1+ Model 4	0.979 (0.932 – 0.982)	0.001	0.38 (0.29– 0.50)	0.001	0.44 (0.35– 0.54)	0.001

Abbreviations: AUC, area under curve; CI, confidence interval; IDI, integrated discrimination indices; NRI, net reclassification improvement; NT-proBNP, N-terminal brain natriuretic pro-peptide. Note: p value indicates a significant difference in terms of Model 1.

4. Discussion

The study showed that positive changes in hemodynamics among optimally treated patients with HFimpEF were associated with a decline in serum levels of NT-proBNP and an increase in circulating levels of irisin, whereas the concentrations of conventionally used biomarkers reflecting inflammation (hs-CRP, IL-6, TNF-alpha), fibrosis (galectin-3, sST2) and cardiac damage (hs-TnT) remained to be comparable between the groups of the individuals with HFimpHF and persistent HFrEF. Moreover, serum levels of irisin ≥ 10.8 ng/mL added new predictive information to NT-proBNP for HFimpEF, but the combination of these two biomarkers did not demonstrate its discriminative benefit in comparison with irisin alone.

As HFimpEF is associated with a 50% greater reduction in the risk of death and hospital readmission compared with HFrEF, promoting improvement in LVEF and predicting a positive response to treatment are both sides of the same coin [43]. Indeed, the prognosis of almost a quarter of patients with HFrEF can be significantly improved in case of sustained improvement in myocardial contractility assessed as LVEF>40% [43,44]. Notably, recent clinical studies have identified a number of promising positive (NYHA Class II HF, concomitant hypertension, beta-blocker use) and negative (alcohol consumption, dilated cardiomyopathy, serum uric acid) predictors of LVEF improvement [44,45]. However, these studies did not include patients receiving optimal therapy for HFrEF based on 4 major classes of prognosis-improving drugs. In our study, despite significant comorbidity, all patients received personalized optimal GDMT for HFrEF with any RAAS inhibitor, including

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angiotensin receptor-neprilysin inhibitor, beta-blockers, MRA and SGLT2 inhibitors. This resulted in 37.4% of patients in the HFrEF group having a positive response to HF therapy, including reduction in LVEDV and LVESV, increase in LVEF and control of circulating NT-proBNP (< 2000 pmol/mL). These findings support previous evidence of clinical trials and current guideline recommendations for use of guideline-directed medical therapies in patients with HFimpEF [11,46,47].

Another aspect of the study was that atrial fibrillation and chronic kidney disease were the most significant comorbidities for prediction of HFimpEF, whereas in some studies and meta-analysis not only mentioned above conditions, but also anemia, T2DM, CAD, dyslipidemia, cerebrovascular disease, and hypertension were found to be predictive factors for recovered LVEF [48]. However, the signature of comorbidities often depends on the age and gender of the patients. In our study, age was not identified as a negative predictive factor for HFimpEF, probably because related comorbidities also did not show a high association with recovery of LV contractile function in the short term (about 3 months). It is conceivable that the profile of comorbid factors with plausible predictive values for HFimpEF may change as patient follow-up is extended to one year or even longer.

Nevertheless, the results open one of the most important aspects of the debate around whether NT-proBNP retains its prognostic value in patients with HFimpEF. It has previously been shown that low or near-normal NT-proBNP levels are unlikely to accurately discriminate clinical outcomes in patients with HFpEF [50]. This should not necessarily mean that well controlled levels of natriuretic peptides lose their importance in HF patients with recovery of systolic function during guideline-based treatment. However, there is evidence that alternative biomarkers such as irisin can significantly increase the discriminatory potency of NT-proBNP [51]. Our data clearly show that irisin not only adds prognostic information to NT-proBNP, but also outperforms NT-proBNP in its ability to predict HFimpEF.

Previous studies have shown that irisin has various influences on key points of the pathogenesis of HF, such as mitochondrial and endothelial dysfunction, vasoconstriction, oxidative stress, immune and inflammatory reactions, metabolic imbalance, skeletal muscle dystrophy, altered energy expenditure and tissue reparation [29,52,53]. Therefore, low levels of irisin were found to be a negative predictive factor for any HF phenotype [54–56]. However, it has remained unclear whether guideline-directed HF therapy is able to modulate serum irisin levels and whether HFimpEF is associated with restoration of circulating irisin.

First, we have clearly shown that optimal therapy in HFrEF is related to a higher likelihood of improvement in LVEF and that control of NT-proBNP in HFrEF may be associated with restoration of irisin levels. It seems particularly valuable that the positive response in the form of improved LVEF with GDMT was not accompanied by significant changes in biomarkers reflecting myocardial injury (hs-TnT), inflammation (hs-CRP, IL-6, TNF-alpha), and fibrosis (sST2, galectin-3). Previously, the possibility of serially measuring these biomarkers to predict response to heart failure therapy and assess the risk of adverse complications has been widely debated. Nevertheless, as observed, no major differences were found between HFimpEF and persistent HFrEF groups at 3 months in our study. This may be partly due to the fact that the study included hemodynamically stable patients who did not require inotropic and mechanical support. It is for these groups of patients with HFrEF and acute or acutely decompensated HF that the predictive role of these biomarkers seems particularly relevant [57]. Although irisin and inflammatory biomarker concentrations are inversely correlated in untreated HFrEF patients or patients with acute HF, this relationship is apparently less pronounced in patients with HFimpEF. In any case, the mechanisms by which irisin may interfere with the recovery of myocardial systolic function need to be studied in detail in the future.

Therefore, irisin levels should not only be considered as a plausible predictive biomarker, but also as an additional target for the therapy of HF. Finally, these findings support the further integration of these advances into clinical practice and highlight the need for ongoing research to fully realize their potential to change the landscape of HFrEF management.

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The lack of assessment of patients' metabolic and nutritional status and the inclusion of HF patients with optimal guideline-based therapy are the main limitations of this study. However, we believe that these limitations do not affect the interpretation of the results.

5. Conclusions

We found that an improvement of LVEF in patients with HFrEF is associated with a restoration of serum irisin levels and a decrease in NT-proBNP. Serum irisin >10.8 ng/mL predicted improved LVEF in patients with HFrEF independently of NT-proBNP, whereas combined predictive model (irisin ≥ 10.8 ng/mL + NT-proBNP< 1540 pmol/mL) did not improve a discriminative value of irisin alone.

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