Predictors of Poor Clinical Outcomes in Patients with Heart Failure with Preserved Ejection Fraction and Low Levels of N-Terminal Pro-B-Type Natriuretic Peptide

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Article

Predictors of Poor Clinical Outcomes in Patients with Heart Failure with Preserved Ejection Fraction and Low Levels of N-Terminal Pro-B-Type Natriuretic Peptide

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Abstract: Background: Despite existing evidence of the high predictive value of natriuretic peptides (NPs) in patients with heart failure (HF), patients treated with guideline-directed therapy who have low or near-normal NP levels are unlikely to be correctly stratified for risk of clinical outcomes. The aim of the study is to detect plausible predictors for poor one-year clinical out-comes in patients with HFpEF and low NT-proBNP treated with in accordance with conventional guideline. Methods: A total of 337 patients with HF with preserved ejection fraction (HFpEF) who had low levels of N-terminal natriuretic pro-peptide (NT-proBNP) at discharge due to optimal guideline-based therapy were enrolled in the study. The course of the observation was 3 years. Echocardiography and assessment of conventional hematological and biochemical parameters including NT-proBNP, tumor necrosis factor-alpha, high-sensitivity C-reactive protein (hs-CRP), adropin, irisin, visfatin, and fetuin-A, were performed at baseline and at the end of study. Results: Three-year cumulative clinical endpoint (cardiovascular death, myocardial infarction / unstable angina / acute coronary syndrome, HF decompensation / hospitalization due to HF, sudden cardiac death, or cardiac-related surgery and / or all-cause death) were detected in 104 patients, whereas 233 did not meet the endpoint. After adjusting for age ≥ 64 years, a presence of atrial fibrillation, diabetes mellitus, CKD stages 1–3 and dilated cardiomyopathy, the multivariable Cox regression analysis showed that irisin levels ≤7.2 ng/mL was an independent predictor of cumulative clinical endpoint. Moreover, patients with the levels of irisin >7.2 ng/mL had better the Kaplan–Meier survival rate than those with lower serum irisin levels (≤7.2 ng/mL). Conclusions: We found that age ≥ 64 years, the presence of atrial fibrillation, diabetes mellitus, CKD stages 1–3 and dilated cardiomyopathy, LAVI ≥39 mL/m2, serum levels of hs-CRP ≥6.10 mg/L, irisin ≤7.2 ng/mL and visfatin ≤1.1 ng/mL as predictors of poor clinical outcome in HFpEF. Serum levels of irisin ≤7.2 ng/mL could emerge as valuable biomarker for predicting long-term prognosis among HFpEF patients with low or near normal levels of NT-proBNP.

Keywords: heart failure with preserved ejection fraction; clinical outcomes; natriuretic peptide; circulating biomarkers

1. Introduction

Heart failure (HF) remains a high prevalent life-threatening condition in older adults that is associated with a high 1-year risk of death and hospitalization, poor functional capacity and quality of life [1]. A median prevalence rate of all HF phenotype has 11.8% (range 4.7-13.3%), but over the last decade HF with preserved ejection fraction (HFpEF) is more common [median prevalence 4.9% (range 3.8-7.4%) and 3.3% (range 2.4-5.8%), respectively] than HF reduced ejection fraction (HFrEF)

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[2]. However, HF prevalence, new incidence and survival varied widely in close connection with age, gender, ethnicity, HF phenotype, concomitant comorbidity profile, as well as certain socio-demographic factors including affordability of health system resources and guideline-directed medical therapies [3-5]. On the other hand, early-to-moderate stages of HFpEF remains more frequently under-recognized than symptomatic HFrEF / HF with mildly reduced ejection fraction (HFmrEF) in everyday practice due to a wide range of comorbidity pattern including metabolic syndrome, obesity, diabetes mellitus, chronic kidney disease, respiratory and autoimmune diseases [6, 7].

Although patients with any HF phenotypes showed a strict similarity in short-term hospitalization rate, long-term survival rate may vary sufficiently depending on age, HF etiology, comorbidity status and N-terminal natriuretic pro-peptide (NT-proBNP) levels [8]. In fact, HF patients with low (< 300 ng/L) / near normal (< 125 ng/L) NT-proBNP levels had a better prognosis than those with elevated NT-proBNP levels (>300 ng/L), regardless of HF phenotype [9]. A high proportion of the individuals with any HF phenotypes with low NT-proBNP levels exhibit a high incidence of diabetes and obesity. Aline with it, among of those who reached target levels of NT-proBNP (< 1000 ng/L) there were no significant differences in the presence of metabolic comorbidities, but many patients had better clinical status, cardiac performance including improved left ventricular ejection fraction (LVEF), quality of life and greater longevity than those with higher NT-proBNP [10, 11].

Another aspect concerns patients with HF who were discharged from hospital after decompensation with hemodynamic stability, improved LVEF and low NT-proBNP. More of them were treated with conventional guideline-based therapy, including renin-angiotensin-aldosterone system antagonists, beta-blockers, mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 (SGLT2i) inhibitors [12]. However, near normal / low levels of NT-proBNP seems not to be a significant predictive factor for further adverse clinical outcomes including mortality and HF-related outcomes when compared with elevated concentrations of this pro-peptide [13]. In fact, there are no evidence-based recommendations for clinical risk assessment in patients with HF with improved LVEF (HFimpEF) / HFpEF with low / near normal NT-proBNP [14]. Although numerous clinical studies have identified numerous plausible predictors (male sex, left atrial volume index, left ventricular end diastolic dimension, anemia, neutrophil count, the levels of myokines / hepatokines including irisin and adropin, glomerular filtration rate, creatinine, pre-existing kidney failure, atrial fibrillation, diabetes mellitus) for these patients [15-19], reliable predictors corresponding with this clinical presentation remain to be under scientific discussion. Moreover, the predictive utility of metabolic-related factors for HF outcomes, such as adipokines with inflammatory activity, myokines, hepatokines, inflammatory cytokines, are not still fully recognized [20-22].

Indeed, visceral, perivascular and epicardial adipose tissues, myocardium, skeletal muscles, liver are considered endocrine organs that synthesize and release a broad spectrum of cytokines with pro- and anti-inflammatory properties, many of which are directly and indirectly involved in the pathogenesis of adverse cardiac remodeling and are responsible for HF development and progression [23]. Apelin is an anti-inflammatory and angiopoetic adipokine, whose levels are markedly reduced in patients with chronic HF and upregulated after reversible cardiac remodeling [24]. Circulating levels of visfatin – a metabolic regulator of oxidative phosphorylation and suppressor of oxidative stress - were found to be significantly lower in patients with HF [25]. Patients with HF especially those with HFrEF and HFmrEF had sufficiently reduced serum concentrations of adipokine / myokines irisin, which has organ protective and anti-inflammatory properties, and increased levels of inflammatory cytokines such as tumor necrosis factor-alpha and C-reactive protein [26]. Fetuin-A – multifunctional adipokine / hepatokines (known as tissue chaperone) with organoprotective properties – exerted a link with liver hypoperfusion in HFrEF and inversely correlated with exercise tolerance and survival [27]. However, their discriminative abilities in patients with HFpEF with low NT-proBNP have not yet been deeply studied. The aim of the study is to detect plausible predictors for poor one-year clinical outcomes in patients with HFpEF and low NT-proBNP treated with in accordance with conventional guideline.

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2. Materials and Methods

2.1. Study Population

Using our local database, we pre-screened 1952 patients with HF who were hospitalized for HF progression and finally enrolled 337 discharged patients according to the inclusion criteria: age ≥. 18 years, hemodynamic stability and established HFpEF at hospital discharge, low levels of N-terminal natriuretic pro-peptide (NT-proBNP) due to optimal guideline-based therapy, and written informed consent to participate in the study (Figure 1). The major exclusion criteria were patients with acute HF, HF with reduced (HFrEF) and mildly reduced (HFmrEF) ejection fraction, acute myocardial infarction, unstable angina, recent stroke / transient ischemic attack, acute viral and bacterial infection, known malignancy, active chemotherapy, with severe comorbidities, including end stage renal disease (ESRD), cognitive dysfunction/dementia, pregnancy/gestation. We followed patients for 3 years and divided them into two cohorts depending on the presence of clinical combined outcome: 104 patients exhibited clinical events, whereas 233 individuals did not have them.

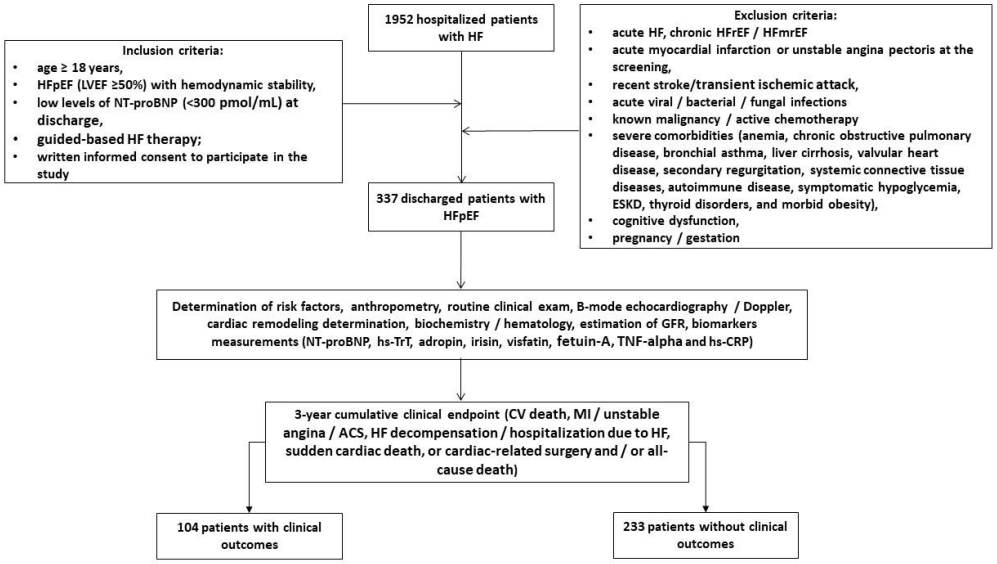

Figure 1. Flow chart of the **s**tudy design. Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; ESRD, end stage renal disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure reduced ejection fraction; HFmrEF, heart failure mildly reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarct; TNF-alpha, tumor necrosis factor-alpha; hs-CRP, high-sensitivity C-reactive protein; hs-TrT, high-sensitivity troponin T; NT-proBNP, N-terminal natriuretic pro-peptide.

2.2. Determination of Clinical Outcomes and Follow-Up

We determine 3-year cumulative clinical endpoint that included CV death, myocardial infarction / unstable angina / acute coronary syndrome, HF decompensation / hospitalization due to HF, sudden cardiac death, or cardiac-related surgery and / or all-cause death. To detect cumulative clinical endpoint we utilized direct interview with patients, their relatives, contact with general practitioners, as well as review of databases, discharge and autopsy reports. Follow-up data were collected via clinic visits at baseline (at discharge from the hospital), during 36 months after the study entry.

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2.3. Echocardiography Examination

In the study, all patents were undergone a routine transthoracic B-mode and Doppler ultrasound examination, which had been provided by experienced echo cardiographer in apical 2- and 4-chamber views using a GE Healthcare Vivid E95 scanner (General Electric Company, Horton, Norway). The conventional hemodynamic parameters included the left ventricular ejection fraction (LVEF) by using Simpson's method, the left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes, the left atrial volume index (LAVI), early diastolic blood filling (E), and the mean longitudinal strain ratio (e') were evaluated according to 2018 Guideline of the American Society of Echocardiography [28]. The estimated E/e' ratio was expressed as the ratio of the E-wave velocity to the average of the medial and lateral e' velocities. After acquisition of high-quality echocardiographic data during at least three cardiac cycles, LV GLS was obtained by 2D speckle-tracking image analysis. The data were stored in the DICOM format for subsequent analysis. Left ventricular hypertrophy was defined as a left ventricular mass index (LVMI) ≥95 g/m^2 in women or ≥115 g/m^2 in men [28].

2.4. Blood Sampling

Blood samples were obtained from all participants in fasting condition and collected in BD Vacutainer Serum Plus Tube. After centrifugation at 3000 rpm for 10 min, the supernatant was collected and stored at -70°C until analysis.

2.5. Biomarkers Assessment

Conventional hematological and biochemical parameters were determined with a Roche P800 analyzer (Basel, Switzerland) in the local laboratory of the Vita Centre (Zaporozhye, Ukraine). Data on blood routine indices glucose, total cholesterol, triglycerides, high density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) cholesterol, serum uric acid, and serum creatinine were recorded. In addition, we measured circulating biomarkers (NT-proBNP, tumor necrosis factor-alpha [TNF-alpha], high-sensitivity C-reactive protein [hs-CRP], adropin, irisin, visfatin, fetuin-A) in serum using ELISA kits (Elabscience, Houston, Texas, USA) in accordance with the instructions provided by the manufacturer at the initial baseline measurement and at the end of the study. The data obtained from the ELISA analysis were subjected to a standard curve-based evaluation. Each sample was analyzed in duplicate, and the mean value was employed for the final analysis. Both intra- and inter-assay coefficients of variability for each marker were < 10%.

2.7. Glomerular Filtration Rate Estimation

Conventional CKD-EPI formula was to estimate the glomerular filtration rate (eGFR) [29].

2.8. Statistics

All statistical analyses were conducted using SPSS 11.0 for Windows and Graph Pad Prism, version 9 (Graph Pad Software, San Diego, CA, USA). Kolmogorov-Smirnov test was used to determine whether data were normally distributed. All continues variables were expressed as mean ± standard deviation [SD] median and interquartile range [IQR] depending on whether the data were normally distributed, whereas categorical variables were presented as number (n) and percentage (%). Categorical variables were compared using the chi-squared test. The Mann-Whitey U test was used to compare differences in continuous variables between cohorts with and without combined clinical events. Receiver operating characteristic (ROC) curves were used to calculate the cutoff values of irisin for predicting combined clinical event. To determine the optimal cut-off value for the predictors, Youden's index (sensitivity + specificity - 1) was used. Univariate and multivariate Cox proportional hazard model were constructed to predict the independent prognostic factors for the clinical endpoint. The odds ratio (OR) and 95% confidence interval (CI) were reported for each predictor variable. The Kaplan–Meier method was used to compare the survival rates, and survival curves were plotted. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

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3. Results

3.1. Baseline Clinical Characteristics

A total of 337 patients with HFpEF, New York Heart Association class II (n = 133) / III (n = 204) and low NT-proBNP at discharge were enrolled in the study and divided into two cohorts depending on a presence of 3-year cumulative end point (n=104) or an absent of it (n=233). The follow-up time was 3 years. The clinical characteristics of patients outlined in Table 1.

Table 1. Basic characteristics of the patients involved in this study.

Variables	Entire Group Patients with Low-NT-proBNP (*n* = 337)	Patients with clinical end point (*n* = 104)	Patients without clinical end point (*n* = 233)	*p* Value
Age (years)	61 (51–73)	65 (54–75)	56 (49–65)	0.040
Male/female (*n* (%))	172 (51.0)/165 (49.0)	57 (54.8)/47 (45.2)	115 (49.4)/118 (50.6)	0.728
BMI (kg/m²)	26.76 ± 6.10	27.10 ± 5.70	25.80 ± 5.10	0.640
Waist circumference (cm)	97.10 ± 3.90	98.10 ± 4.10	96.40 ± 4.20	0.520
WHR (units)	0.89 ± 0.12	0.90 ± 0.10	0.87 ± 0.09	0.430
Dyslipidemia (*n* (%))	203 (60.2)	67 (64.2)	136 (58.4)	0.064
Hypertension (*n* (%))	285 (84.6)	88 (84.6)	197 (84.5)	0.832
Stable CAD (*n* (%))	113 (33.5)	37 (35.6)	76 (32.6)	0.472
Dilated CMP, (*n* (%))	18 (5.3)	11 (10.6)	7 (3.0)	0.010
Atrial fibrillation (*n* (%))	61 (18.1)	22 (21.2)	39 (16.7)	0.020
Smoking (*n* (%))	132 (39.2)	41 (39.4)	91 (39.0)	0.850
Abdominal obesity (*n* (%))	95 (28.2)	30 (28.8)	65 (27.9)	0.720
Diabetes mellitus, (*n* (%))	106 (31.5)	43 (41.3)	63 (27.0)	0.012
LVH (*n* (%))	246 (73.0)	78 (75.0)	168 (72.1)	0.074
CKD stages 1–3 (*n* (%))	72 (21.3)	29 (27.9)	43 (18.5)	0.044
New York Heart Association class II / III	133 (39.5) / 204 (60.5)	40 (38.5) / 64 (61.6)	93 (39.9) / 140 (60.1)	0.662
Systolic BP (mm Hg)	138 ± 9	137± 10	138 ± 9	0.810
Diastolic BP (mm Hg)	83 ± 7	86 ± 8	82 ± 6	0.720
LVEDV (mL)	152 (146–163)	156 (141–171)	153 (144–166)	0.760
LVESV (mL)	70 (62–79)	73 (65–89)	69 (60–76)	0.062
LVEF (%)	54 (51–58)	53 (51–55)	54 (51–58)	0.158
LVMMI (g/m²)	140 ± 12	143 ± 13	138 ± 10	0.161
LAVI (mL/m²)	39 (35–45)	42 (37–48)	37 (35–40)	0.044
E/e` (units)	15 ± 5	17 ± 4	13 ± 5	0.686
GLS (%)	−15.2 (−13.1; −17.7)	−15.7 (−13.2; −18.1)	−14.5 (−12.5; −16.2)	0.224
eGFR (mL/min/1.73 m²)	81 ± 19	75 ± 14	89 ± 16	0.216
Fasting glucose (mmol/L)	4.92 ± 1.1	5.11 ± 1.2	4.84 ± 1.0	0.860
Creatinine (μmol/L)	106.5 ± 22.7	113.4 ± 19.5	99.3 ± 21.4	0.620
SUA (mcmol/L)	332 ± 116	345 ± 85	316 ± 105	0.162
Total cholesterol (mmol/L)	5.87 ± 1.30	5.92 ± 1.24	5.76 ± 1.18	0.226
HDL-C (mmol/L)	0.98 ± 0.23	0.96 ± 0.19	0.99 ± 0.20	0.186
LDL-C (mmol/L)	3.87± 0.24	3.90 ± 0.22	3.85± 0.21	0.650
Triglycerides (mmol/L)	2.26 ± 0.19	2.30 ± 0.17	2.24 ± 0.15	0.440
hs-CRP (mg/L)	5.26 (2.54–8.10)	6.02 (3.10–9.17)	4.46 (2.29–6.76)	0.050
TNF-alpha (pg/mL)	3.11 (2.10–4.22)	3.44 (1.99–4.85)	2.82 (1.80–3.93)	0.070
NT-proBNP (pmol/mL)	198 (115–286)	217 (137–295)	180 (113–253)	0.142

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Adropin (ng/mL)	3.62 (2.10–5.11)	3.89 (2.45–5.28)	3.38 (1.98–4.81)	0.244
Irisin (ng/mL)	8.25 (6.30–10.56)	7.01 (5.80–8.49)	9.45 (6.71–11.80)	0.001
Visfatin (ng/mL)	1.32 (0.87 – 1.79)	1.21 (0.80 – 1.65)	1.50 (0.89 – 2.08)	0.050
Fetuin-A (μg/mL)	67.5 (51.1 – 85.9)	58.6 (43.4 – 74.2)	75.8 (58.2 – 92.5)	0.064
hs-TnT, ng/mL	0.05 (0.012–0.114)	0.05 (0.011–0.123)	0.04 (0.008–0.109)	0.688
ACEIs (*n* (%))	252 (74.7)	72 (69.2)	180 (77.3)	0.576
Angiotensin-II receptor blockers (*n* (%))	38 (11.3)	20 (19.2)	18 (7.70)	0.042
ARNI, (*n* (%))	47 (13.9)	12 (11.5)	35 (15.0)	0.352
Beta-blockers (*n* (%))	317 (94.0)	97 (93.3)	220 (94.4)	0.788
Ivabradine (*n* (%))	34 (10.1)	10 (9.6)	24 (10.3)	0.810
Calcium channel blockers (*n* (%))	83 (24.6)	23 (22.1)	60 (25.8)	0.760
Loop and thiazide-like diuretics (*n* (%))	196 (58.2)	64 (61.5)	132 (56.7)	0.064
Antiplatelet agents (*n* (%))	283 (84.0)	81 (77.9)	202 (86.7)	0.052
Anticoagulants (*n* (%))	61 (18.1)	22 (21.2)	39 (16.7)	0.020
Metformin (*n* (%))	95 (28.2)	37 (35.6)	58 (24.9)	0.010
DPP4 inhibitors (*n* (%))	11 (3.3)	4 (3.8)	7 (3.0)	0.860
GLP-1 receptor agonists (*n* (%))	13 (3.9)	3 (2.9)	10 (4.3)	0.226
SGLT2 inhibitors (*n* (%))	332 (98.5)	101 (97.1)	231 (99.1)	0.884
Statins (*n* (%))	301 (89.3)	92 (88.4)	209 (89.7)	0.870

Notes: Variables are given as Ms ± SDs or Ms (25–75% IQRs). The Chi-square test was used to compare categorical variables. The Mann–Whitney U test, and Chi-square test were used to compare continuous variables between cohorts. LVH was detected when LVMI ≥ 95 g/m^2 in women or ≥115 g/m^2 in men. Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARNI, *a*ngiotensin receptor-neprilysin inhibitors; BMI, body mass index; CAD, coronary artery disease; CMP, cardiomyopathy; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; E/e', early diastolic blood filling to longitudinal strain ratio; GLS, global longitudinal strain; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVMMI, left ventricle myocardial mass index; NT-proBNP, N-terminal natriuretic pro-peptide; SGLT2, sodium–glucose cotransporter-2; SUA, serum uric acid; TNF-alpha, tumor necrosis factor-alpha; WHR, waist-to-hip ratio.

Patients in entire group had a mean age of 61 years and showed the following profile of comorbidity conditions: dyslipidemia (60.2%), hypertension (84.6%), stable coronary artery disease (33.5%), atrial fibrillation (18.1%), smoking (39.2%), abdominal obesity (28.2%), diabetes mellitus (31.5%), left ventricular hypertrophy (73.0%), and chronic kidney disease 1-3 stages (21.3%). Therefore, all patients were hemodynamically stable, had a mean LVEF of 54%, an average of LAVI of 39 mL/m^2, a mean of GLS of -15.2%. The therapy of the patients were personally optimized and included antagonists of renin-angiotensin-aldosterone system (ACE inhibitors, or angiotensin-II receptor blockers or angiotensin receptor-neprilysin inhibitors), beta-blockers, mineralocorticoid receptor antagonists and sodium–glucose cotransporter-2 inhibitor and other concomitant medications. There were no significant differences between the two cohorts with respect to sex, body mass index, anthropometric parameters, presence of dyslipidemia, hypertension, stable coronary artery disease, smoking, abdominal obesity, left ventricular hypertrophy, systolic and diastolic blood pressure, left ventricular dimensions, LVEF, LVMMI, E/e`, GLS, eGFR, lipid profile, glucose levels, TNF-alpha, NT-proBNP, adropin, visfatin, fetuin-A, hs-TrT. Patients in the cumulative clinical endpoint cohort were older, more likely to have atrial fibrillation, diabetes mellitus, CKD stages 1-3, dilated cardiomyopathy and higher LAVI and lower irisin levels than those in the free endpoint cohort. The patients in the cumulative clinical endpoint cohort tended to treat frequently with

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angiotensin-II receptor blockers, anticoagulants, metformin when compared with those who had no clinical endpoint.

3.2. Receiver Operating Characteristic Curve Analysis for Predictive Factors of Cumulative Clinical Endpoint

ROC curve analysis was performed to determine the optimal cutoff for possible predictors of clinical outcome in (Table 2). Age ≥64 years exhibited area under curve (AUC) for cumulative endpoint of 0.726 (95% confidence interval [CI] = 0.712 – 0.740, P = 0.001) with a sensitivity of 76.2% and a specificity of 74.5%. Optimal predictive cutoff point for LAVI was 39 mL/m² (AUC = 0.771, 95% CI = 0.723 – 0.835) with a sensitivity of 78.5% and a specificity of 82.0%. The AUC for hs-CRP was 0.755 (95% CI = 0.695 – 0.819) and predictive cutoff point was 6.10 mg/L (sensitivity = 77.3%; specificity = 80.8%). Optimal cutoff points for irisin and visfatin were 7.2 ng/mL (AUC = 0.868, 95% CI = 0.799 – 0.948, sensitivity = 83.4%; specificity = 86.3) and 1.1 ng/mL (AUC = 0.757, 95% CI = 0.733 – 0.787; sensitivity = 80.5%; specificity = 81.9), respectively.

Table 2. Receiver Operating Characteristic (ROC) Curve Analysis for Predictive Factors of 3-year cumulative clinical outcome.

Variables	AUC	95% CI	P value	Cutoff	Se, %	Sp,%
Age	0.726	0.712 – 0.740	0.001	64 years	76.2	74.5
LAVI	0.771	0.723 – 0.835	0.001	39 mL/m²	78.5	82.0
hs-CRP	0.755	0.695 – 0.819	0.001	6.10 mg/L	77.3	80.8
Irisin	0.868	0.799 – 0.948	0.0001	7.2 ng/mL	83.4	86.3
Visfatin	0.757	0.733 – 0.787	0.001	1.1 ng/mL	80.5	81.9

Abbreviations: AUC, area under curve; CI, confidence interval; Se, sensitivity; Sp, specificity.

3.3. Predictive Factors for 3-Year Cumulative Clinical Endpoint: Unadjusted and Adjusted for Multivariate Cox Proportional Hazard Models

Cox proportional hazards model was constructed for assessment of independent predictors of 3-year cumulative clinical endpoint (Table 3). Significant variables (P<0.05) comparing cohorts with and without cumulative endpoints were entered into univariate Cox regression analysis, and those retaining statistical significance (P<0.05) were entered into multivariate Cox proportional hazards model.

Table 3. Cox regression analysis for predictive factors of cumulative clinical endpoint.

Predictive factors	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
Age≥64 years	1.327 (1.064–1.673)	0.026	-	
AF (presence vs absent)	2.035 (1.313–3.184)	0.012	-	
Dilated CMP (presence vs absent)	1.614 (1.151–2.120)	0.047	-	
DM (presence vs absent)	1.226 (1.115–1.338)	0.048	-	
CKD stages 1–3 (presence vs absent)	1.116 (1.002–1.237)	0.050	-	
LAVI ≥39 mL/m²	1.408 (1.122–1.806)	0.048	1.206 (0.966–1.437)	0.523
hs-CRP ≥6.10 mg/L	1.183 (1.106–1.450)	0.042	1.042 (1.006–1.092)	0.121
Irisin ≤7.2 ng/mL	1.415 (1.211–1.644)	0.042	1.386 (1.254–1.5904)	0.044
Visfatin ≤1.1 ng/mL	1.190 (1.102–1.276)	0.049	1.121 (1.003–1.220)	0.068

Notes: Model 1: unadjusted rough model; Model 2: model adjusted for age ≥ 64 years and a presence of concomitant conditions (atrial fibrillation, diabetes mellitus, CKD stages 1–3 and dilated cardiomyopathy).

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Abbreviations: AF, atrial fibrillation; CMP, cardiomyopathy; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.

After adjusting for age ≥ 64 years, a presence of atrial fibrillation, diabetes mellitus, CKD stages 1–3 and dilated cardiomyopathy (Model 2), the multivariable Cox regression analysis revealed that the levels of irisin ≤7.2 ng/mL was an independent predictor of cumulative clinical endpoint.

3.4. Kaplan–Meier Curves Survival Analysis

The Kaplan–Meier curves revealed different probability rates of 3-year cumulative clinical endpoint between patients with HFpEF and serum irisin levels of ≤7.2 ng/mL and >7.2 ng/mL (Figure 2). To note, the patients with the levels of irisin >7.2 ng/mL had a sufficient benefit in survival than those with serum irisin levels of ≤7.2 ng/mL.

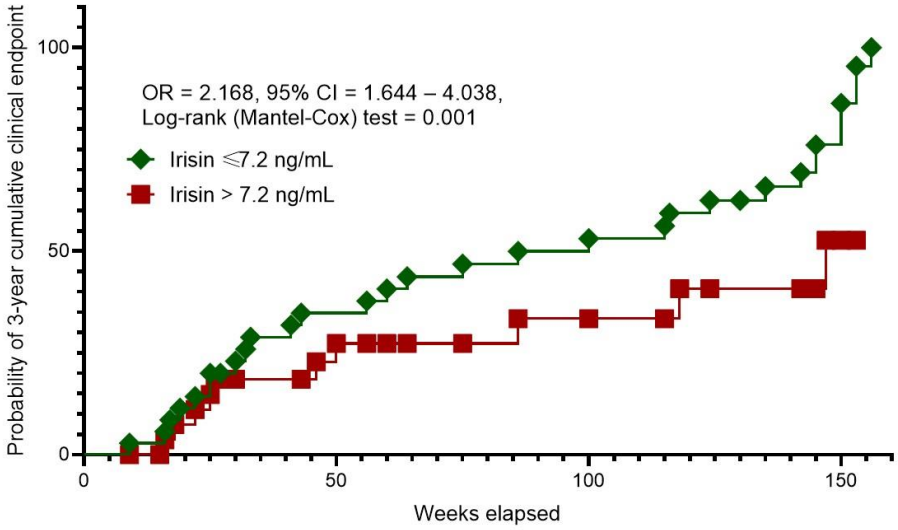

Figure 2. Kaplan–Meier curves for 3-year cumulative clinical endpoint. Abbreviations: OR, odds ratio; CI, confidence interval.

4. Discussion

In the study we identified age ≥ 64 years, the presence of atrial fibrillation, diabetes mellitus, CKD stages 1–3 and dilated cardiomyopathy, LAVI ≥39 mL/m², serum levels of hs-CRP ≥6.10 mg/L, irisin ≤7.2 ng/mL and visfatin ≤1.1 ng/mL as predictors of poor clinical outcome in HFpEF patients treated with guideline-based optimal therapy with target level of NT-proBNP less than 300 pmol/mL. After adjusting for concomitant comorbidities and age serum levels of irisin ≤7.2 ng/mL remained to be an independent predictive factor for 3-year cumulative clinical endpoint. Moreover, the individuals with circulating irisin >7.2 ng/mL exerted a significant superiority in survival rate when compared with those with lower irisin levels (≤7.2 ng/mL). These findings offer new perspectives in the stratification of patients with HFpEF who have achieved target NT-proBNP levels as a result of conventional management and / or concomitant comorbidities such as obesity.

Previous studies and systematic reviews highlighted the plausible prognostic role of BNP and NT-proBNP in predicting adverse clinical outcome including all-cause mortality, cardiovascular events, and hospitalization in HFpEF patients, [13, 30, 31]. However, predictive role of NPs in HFpEF seem to be controversial, because low levels of NT-proBNP often leave the risk of HF progression underestimated [32]. Meanwhile, patients hospitalized with HFpEF often have low NT-proBNP levels, which was associated with age < 65 years, ischemic etiology, obesity, higher LVEF, eGFR > 80 ml/kg/1.73m², and lower NYHA class, whereas chronic kidney disease and diabetes mellitus were associated with elevated levels of NT-proBNP [9, 33, 34]. Along with it, clinical status was similarly impaired in HF patients with lower and higher NT-proBNP levels [35]. Azzo JD et al. (2024) [36] reported that higher levels of NT-proBNP rather associated with inflammation and fibrosis than low

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concentrations of the biomarker. On the other hand, the elevation of NT-proBNP in serial measurements reflected dynamic change in risk for HF events and death, whereas stable levels of NT-proBNP were related to lower risk of incident HF and mortality [37]. Thus, the risk of patients with low NP levels remains often out of the zone of interest or is only used as a reference level when comparing to higher values of NT-proBNP. The use of cardiac troponins as an alternative biomarker for risk stratification in a patient with low NT-proBNP levels also remains inadequate because a positive troponin test improves the predictive and diagnostic value of natriuretic peptides only when their concentrations are high [38]. In this context, the search for new biomarkers with independent predictive value for adverse clinical events in HFpEF and low NT-proBNP remains very relevant.

We hypothesized that the comorbidity signature may not only contribute to adverse cardiac remodeling, but also be associated with a distinct cytokine profile reflecting metabolic homeostasis of distant organs such as skeletal muscle, adipose tissue, and liver. Although these organs synthesizes and secretes a wide range of metabolically active molecules involved in the development and progression of HF, their discriminative properties for HF, particularly in people with HFpEF, have not been established. In this study, we established that apart from older age and such known concomitant comorbidities as atrial fibrillation, diabetes mellitus, CKD stages 1–3 and dilated cardiomyopathy, altered levels of hs-CRP, visfatin and irisin, which belong to adipokines / myokines were predictors for cumulative clinical endpoint for 3 years in patients with HFpEF and low levels of NT-proBNP. In fact, irisin ≤7.2 ng/mL alone was found to be an independent predictor of adverse clinical outcomes for patients with HFpEF after adjusting for age and concomitant comorbidities.

Previous studies have shown that irisin can be synthesized and secreted not only by skeletal muscle but also by myocardium to maintain energy homeostasis [39]. Alteration of irisin levels in HF is considered a possible mechanism of skeletal muscle metabolic remodelling, cardiac hypertrophy and persistence of a clinical sign such as fatigue [40]. Moreover, in chronic HFpEF patients rather than HFmrEF and HFrEF low levels of irisin exerted predictive potency for adverse outcomes [15, 41, 42]. Since irisin has shown inverse correlation with inflammatory biomarkers such as CRP and TNF-alpha, and LDL in previous studies, it was hypothesized that one of the possible molecular mechanisms for the negative impact of altered levels of irisin on prognosis is excessive inflammatory response, oxidative stress / damage and mitochondrial dysfunction due to activation of apoptosis / pyroptosis and autophagy via irisin precursor fibronectin type III domain-containing protein 5 and AKT/GSK3β/FYN/Nrf2 axis in an mTOR-independent manner [43, 44]. In this context, altered irisin regulation links adverse cardiac remodeling and skeletal muscle dysfunction with metabolic comorbidities such as diabetes mellitus, obesity and metabolic syndrome [45, 46]. However, the predictive value of irisin for distant events in patients with HFpEF requires further explanation. An indirect effect of irisin deficiency on the number of cardiovascular events through the progression of microvascular inflammation and impaired myocardial perfusion cannot be excluded. This suggestion seems to be a purpose for further investigations.

5. Study Limitations

The study has several limitations. The first limitation affects the lack of data regarding a trajectory of biological markers during the observational period in connection with the rate of adverse clinical outcomes. Yet, we did not investigate quality of life of the patients and its association with the changes of irisin levels. Finally, we did not compare the discriminative value of irisin with previously validate risk score. However, we do not believe that these limitations will have an impact on the interpretation of the results.

6. Conclusions

We found that age ≥ 64 years, the presence of atrial fibrillation, diabetes mellitus, CKD stages 1–3 and dilated cardiomyopathy, LAVI ≥39 mL/m^2, serum levels of hs-CRP ≥6.10 mg/L, irisin ≤7.2 ng/mL and visfatin ≤1.1 ng/mL as predictors of poor clinical outcome in HFpEF. Serum levels of irisin ≤7.2 ng/mL could emerge as valuable biomarker for predicting long-term prognosis among HFpEF patients with low or near normal levels of NT-proBNP.

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Informed Consent Statement: Written informed consent has been obtained from all patients in this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy restrictions.

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