Growth differentiation factor-15 and routine laboratory parameters are associated with one-year mortality in patients with end-stage heart failure undergoing heart transplantation evaluation

Wioletta Szczurek-Wasilewicz[1], Oliwia Warmusz[2], Michał Skrzypek[3], Andrzej Karmański[4], Michał Jurkiewicz[2], Piotr Wyrobiec[2], Mariusz Gąsior[5], Bożena Szyguła-Jurkiewicz[5]

[1]2nd Ward of Cardiology and Angiology, Silesian Centre for Heart Diseases, Zabrze, Poland
[2]Student's Scientific Society, 3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[3]Department of Biostatistics, Faculty of Public Health in Bytom, Medical University of Silesia in Katowice, Katowice, Poland
[4]Department of Descriptive and Topographic Anatomy, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[5]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

Correspondence to:
Wioletta Szczurek-Wasilewicz, MD, PhD,
Silesian Centre for Heart Diseases,
Skłodowskiej-Curie 9,
41–800 Zabrze, Poland,
phone: +48 694 138 970,
e-mail:
wiolettaszczurek@interia.pl

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ABSTRACT

Background: Growth differentiation factor-15 (GDF-15) is a hormone that regulates inflammatory responses, tissue repair, and cardiac remodeling, the three key processes underlying the development and progression of heart failure (HF). Furthermore, GDF-15 integrates information from cardiac and extracardiac disease pathways that are linked to multiorgan dysfunction in advanced stages of HF.

Aims: This study aimed to determine which factors are associated with one-year mortality in patients with end-stage HF, with particular emphasis on GDF-15.

Methods: We prospectively analyzed 315 consecutive hospitalized patients with end-stage HF who underwent heart transplantation evaluation between 2018 and 2022. The endpoint was all-cause mortality during one-year follow-up. We measured routine laboratory parameters and the serum GDF-15 concentration using a sandwich enzyme-linked immunosorbent assay (ELISA) (SunRedBio Technology Co, Ltd, Shanghai, China).

Results: The median age of the patients was 57 (50–62) years. During follow-up, 97 patients died. Higher serum concentrations of GDF-15 (hazard ratio [HR], 1.119; 95% CI, 1.095–1.144; P <0.001), high-sensitivity C-reactive protein (HR, 1.140; 95% CI, 1.037–1.253; P = 0.006), fibrinogen (HR, 1.003; 95% CI, 1.001–1.005; P = 0.003), bilirubin (HR, 1.055; 95% CI, 1.027–1.084; P <0.001), N-terminal pro-B-type natriuretic peptide (HR, 1.342; 95% CI, 1.206–1.493; P <0.001), and gamma-glutamyl transpeptidase (HR, 1.007; 95% CI, 1.002–1.012; P = 0.003) were independently associated with one-year mortality.

Conclusions: Higher GDF-15, high-sensitivity C-reactive protein, fibrinogen, bilirubin, gamma-glutamyl transpeptidase, and N-terminal pro-B-type natriuretic peptide concentrations were independently associated with worse survival in patients with end-stage HF.

Key words: biomarkers, end-stage heart failure, growth differentiation factor-15, risk stratification

INTRODUCTION

Patients with end-stage heart failure (HF) constitute an etiologically and functionally heterogeneous group, which makes it difficult to optimize their management and assess their outcomes [1, 2]. Physicians routinely use biomarkers reflecting pathophysiological pathways involved in HF development and progression for diagnosis, risk stratification, and management of HF patients [3, 4]. Candidate biomarkers for risk stratification are still being investigated because their type and prognostic value have changed over time as a result of medical progress, as reflected

WHAT'S NEW?

In this single-center study, we found that noninvasive and simple indicators are associated with worse prognosis in patients with end-stage heart failure. Our study demonstrated that an elevated growth differentiation factor-15 serum level, along with the routinely used laboratory parameters — fibrinogen, bilirubin, gamma-glutamyl transpeptidase, N-terminal pro-B-type natriuretic peptide, and high-sensitivity C-reactive protein are strongly associated with one-year mortality in patients with end-stage heart failure.

by modifications in the guidelines for HF management. The most useful stratification tools in daily clinical practice are those that explore the main disease pathways, such as activation of neurohormonal systems, inflammation, oxidative stress, dysfunctional calcium handling, impaired energy utilization, mitochondrial dysfunction, cardiac fibrosis, and matrix remodeling, and impaired endothelial function [5, 6]. They should also be accurately and precisely measurable, their results should be easily interpretable and quickly available, their biological variation and reference limits should be defined, and possible sources of error should be well known [5–7].

A promising new HF biomarker is growth differentiation factor-15 (GDF-15), which has not yet been adopted in the guidelines or routine clinical care for HF patients [6, 7]. GDF--15 is emerging as a biomarker that integrates information from cardiac and extracardiac disease pathways and is linked to the incidence, progression, and prognosis of HF. Given that end-stage HF affects multiple organ systems, GDF-15 may provide adequate prognostic information in this population [3, 6, 7].

As a member of the transforming growth factor-beta superfamily, GDF-15 is a newly studied heart-derived endocrine hormone that regulates inflammatory response, tissue repair, and cardiac remodeling [3, 6, 7]. The effects of GDF-15 on the heart seem to be linked to its spectrum of autocrine/paracrine properties, including anti-inflammatory, antifibrotic, antihypertrophic, antioxidant, and antiapoptotic effects [5–7]. GDF-15 is expressed and secreted by numerous cell types, including smooth and endothelial muscle cells and cardiomyocytes, in response to cellular stress, inflammation, and mitochondrial dysfunction, i.e. processes closely related to HF [6]. GDF-15 is also involved in coordinating endothelial function by regulating vasoconstriction and relaxation and the release of nitric oxide [7]. Given the associations of biomarkers with the complex pathogenesis of HF, we aimed to determine the potential risk factors associated with the one-year mortality rate in patients with end-stage HF, with particular emphasis on GDF-15.

METHODS

We prospectively analyzed 404 consecutive patients with end-stage HF who were hospitalized in the cardiology department and underwent heart transplantation evaluation between 2018 and 2022. The flowchart of the study design with the inclusion and exclusion criteria is presented in Figure 1.

At the time of enrollment, a panel of laboratory tests, an ergospirometric exercise test, echocardiography, and right heart catheterization were performed on all patients. Blood samples of peripheral venous blood were drawn after 12 hours of fasting at the time of enrollment. The hematologic parameters were measured with automated blood cell counters (Sysmex XS1000i and XE2100, Sysmex Corporation, Kobe, Japan), which had intra-assay and interassay coefficients of variation of 5% and 4.5%, respectively. The biochemical parameters of the blood samples were determined with a COBAS Integra 800 analyzer (Roche Instrument Center AG, Rotkreuz, Switzerland). Fibrinogen levels were measured using a modified Clauss method (Dade Behring) in a Sysmex CA-6000 automated coagulation analyzer. The plasma high-sensitivity C-reactive protein (hs-CRP) concentration was determined with a COBAS Integra 70 analyzer (Roche Diagnostics, Ltd., Mannheim, Germany). The detection limit of hs-CRP was 0.0175 mg/dl. Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured by a commercially available kit from Roche Diagnostics (Mannheim, Germany) on an Elecsys 2010 analyzer with an analytical sensitivity of <5 pg/ml. In addition, 10 ml of peripheral blood was collected to measure the serum GDF-15 concentration. Human GDF-15 was measured by sandwich enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (Human GDF-15 ELISA, SunRedBio Technology Co., Ltd., Shanghai, China). This ELISA was performed using a BioTek Elx50 reader (BioTek Instruments Inc., Tecan Group, Switzerland). The concentration of GDF-15 was expressed as pg/ml.

Information on survival data during long-term follow-up was obtained from the official registry of the National Health Fund or during protocol visits at our institution. The endpoint was defined as all-cause mortality within 12 months of the index hospitalization. The Medical University of Silesia's local Institutional Review Board approved the study protocol, and all patients provided informed consent (specific ethics codes — KNW/0022/KB1/53/18, PCN/0022/KB1/69/I/19, PCN/0022/KB/159/20, PCN/CBN/0052/KB1/20/II/21/22). The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

Statistical analysis was performed with SAS software version 9.4. Continuous variables were expressed as the

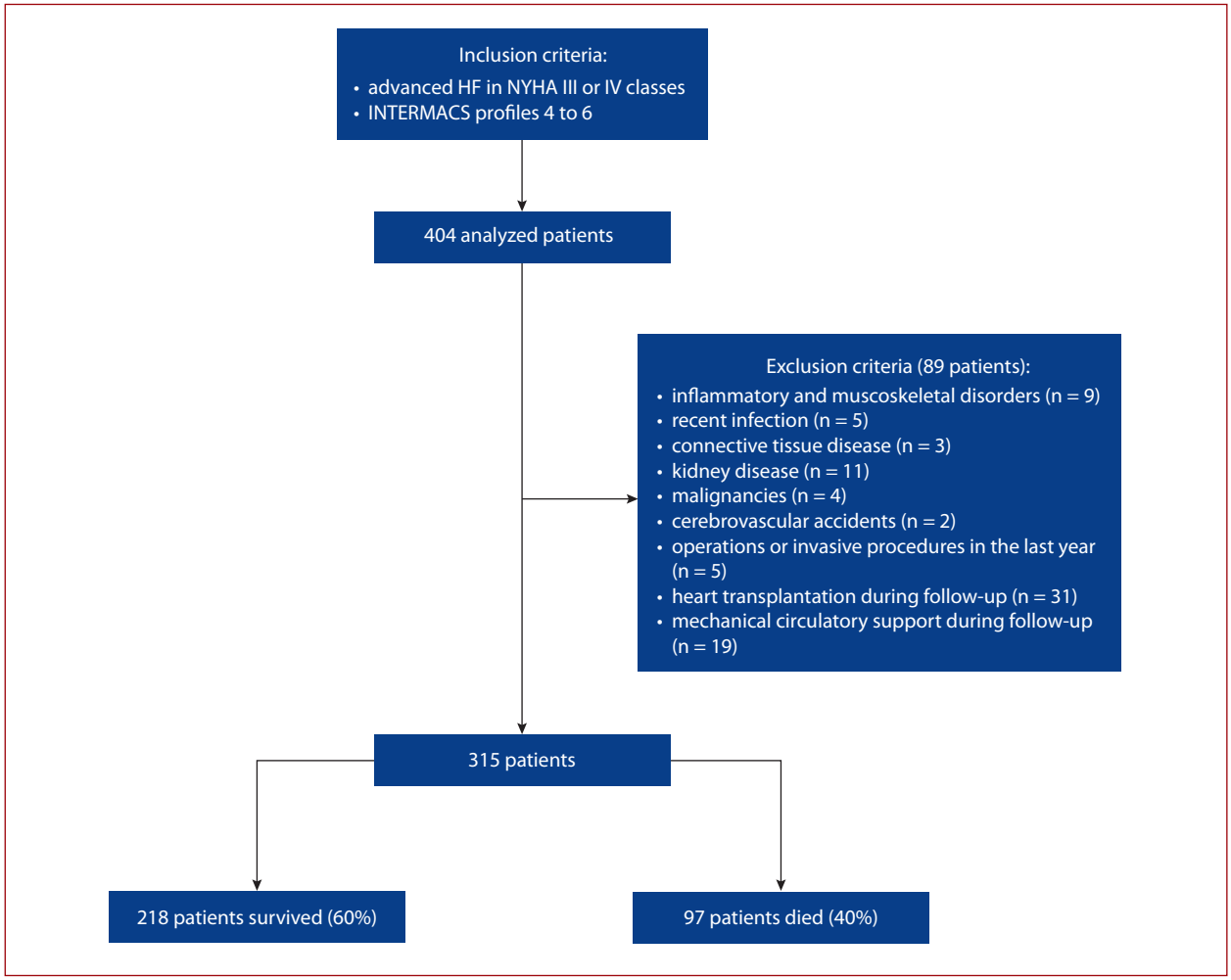

Figure 1. Flow chart of the study design for the inclusion and exclusion criteria

Abbreviations: HF, heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association

mean (standard deviation) or, if not normally distributed, median (first–third quartiles). Differences in continuous variables were compared using Student's t-test for normally distributed variables and the Mann–Whitney U test for nonnormally distributed variables. Categorical variables were expressed as numbers and percentages and were compared by the χ^2 test. Cox's univariable proportional hazard analysis was used to select potential independent predictive factors of death for inclusion in the multivariable analysis. The examined covariates included age, male sex, ischemic etiology of HF, history of arterial hypertension and dyslipidemia, body mass index, maximal oxygen uptake, cardiac index, and echocardiography parameters (left atrium, left ventricular end-diastolic diameter, right ventricular, and left ventricular ejection fraction), as well as laboratory parameters (bilirubin, albumin, glomerular filtration rate, gamma-glutamyl transpeptidase [GGTP], alkaline phosphatase [ALP], hs-CRP, fibrinogen, NT-proBNP, and uric acid). The relationships between explanatory variables were calculated by the Spearman rank correlation coefficient, and multicollinearity was evaluated using tolerance and variance inflation factors. Since several covariates were highly correlated (e.g., the correlation was 0.74 for GDF-15 with dyslipidemia, 0.51 for ALP with GGTP, and 0.41 for NT-proBNP with ALP), those covariates that provided a better fit for the model were selected for further analysis. Univariable predictors of death with a *P*-value of 0.05 or less, which did not correlate significantly, were entered into the multivariable Cox proportional hazards model. Schoenfeld residuals were used to check the proportional hazards assumption. The proportional hazards assumption was not met, so weighted Cox regression analysis was conducted using the SAS macro language [8, 9]. The results were presented as hazard ratios with 95% confidence intervals. A *P*-value of <0.05 was considered significant.

RESULTS

The final study group consisted of 315 patients with end-stage HF who underwent heart transplantation evaluation classified into New York Heart Association (NYHA) functional classes III and IV (79.7% and 20.3%, respectively) and profiles 4 to 6 according to the Interagency Registry

Table 1. Baseline characteristics of the study population

	All included patients n = 315	Survival n = 218	Nonsurvival n = 97	*P*-value
Age, years	57.0 (50.0–62.0)	56.0 (50.0–61.0)	59.0 (54.0–62.0)	0.05
Male, n (%)	288 (91.4)	195 (89.4)	93 (95.9)	0.08
Ischemic etiology of HF (%), n (%)	186 (59.0)	112 (51.4)	74 (76.3)	<0.001
BMI, kg/m^2	26.7 (24.1–30.0)	26.9 (24.4–30.5)	26.4 (23.4–28.8)	0.02
Hypertension, n (%)	188 (59.7)	123 (56.4)	65 (67.0)	0.08
Type 2 diabetes, n (%)	127 (40.3)	83 (38.1)	44 (45.4)	0.22
Dyslipidemia, n (%)	215 (68.3)	120 (55)	95 (97.9)	<0.001
Persistent AF, n (%)	154 (49.0)	111 (50.9)	43 (44.3)	0.28
GDF-15, pg/ml	601.6 (445.4–1346.3)	505.1 (380.3–634.8)	1617.9 (1381.1–1934.7)	<0.001
WBC, × 10^9/l	7.4 (6.1–8.7)	7.2 (6.1–8.5)	7.7 (6.1–8.9)	0.11
Hemoglobin, mmol/l	8.9 (0.9)	8.8 (0.8)	8.9 (1.1)	0.7
GFR, ml/min/1.73 m^2	65.5 (54.2–74.2)	67.1 (61.3–75.9)	56.7 (45.3–69.1)	<0.001
Total bilirubin, µmol/l	16.3 (12.3–20.4)	15.6 (12.3–19.4)	19.1 (12.3–23.0)	0.002
Albumin, g/l	43.0 (40.0–46.0)	44.0 (41.0–47.0)	42.0 (38.0–44.0)	<0.001
Uric acid, µmol/l	426.0 (360.0–496.0)	413.0 (351.0– 470.0)	456.0 (389.0–520.0)	0.004
Urea, µmol/l	7.8 (5.9–11.2)	7.8 (5.9–10.1)	7.4 (6.3–16.3)	0.03
Fibrinogen, mg/dl	377.0 (310.0–453.0)	345.0 (302.0–414.00)	450.0 (381.0–536.0)	<0.001
AST, U/l	26.0 (20.0–31.0)	26.0 (20.0–32.0)	27.0 (20.0–31.0)	0.74
ALT, U/l	23.0 (17.0–33.0)	23.0 (18.0–33.0)	23.0 (15.0–35.0)	0.87
ALP, U/l	77.0 (62.0–100.0)	73.0 (60.0–97.0)	90.0 (65.0–105.0)	0.008
GGTP, U/l	76.0 (35.0–134.0)	73.0 (33.0–130.0)	82.0 (49.0–147.0)	0.02
Cholesterol, mmol/l	4.0 (0.9)	4.04 (0.9)	3.95 (1.1)	0.46
hsCRP, mg/l	4.3 (2.3–5.5)	3.8 (2.1–5.1)	5.5 (4.1–7.7)	<0.001
Sodium, mmol/l	139.0 (137.0–140.0)	139.5 (138.0–141.0)	137.0 (135.0–139.0)	<0.001
NT-proBNP, pg/ml	3480.0 (2370.0–5863.0)	2685.0 (2300.0–4500.0)	5600.0 (3798.0–7089.0)	<0.001
VO_2max, ml/kg/min	11.3 (10.2–12.2)	11.8 (10.8–12.3)	10.4 (9.1–11.5)	<0.001
mPAP, mm Hg	25.0 (19.0–32.0)	25.0 (19.0–30.0)	26.0 (19.0–36.0)	0.17
CI, l/min/m^2	1.9 (1.8–2.0)	2.0 (1.8–2.1)	1.9 (1.7–2.0)	<0.001
TPG, mm Hg	9.0 (7.0–12.0)	9.0 (7.0–12.0)	9.0 (7.0–12.0)	0.45
PVR, Wood units	1.8 (1.5–2.2)	1.8 (1.4–2.2)	2.0 (1.5–2.4)	0.06
Echocardiographic parameters				
LA, mm	50.0 (47.0–57.0)	50.0 (46.0–56.0)	54.0 (49.0–57.0)	0.02
RVEDd, mm	39.00 (35.0–40.0)	38.0 (34.0–40.0)	40.0 (37.0–43.0)	<0.001
LVEDd, mm	71.0 (65.0–80.0)	71.0 (65.0–80.0)	75.0 (66.0–80.0)	0.21
LVEF, %	18.0 (15.0–20.0)	18.0 (15.0–20.0)	15.0 (15.0–18.0)	<0.001
Cardiac medication on admission, n (%)				
β-blockers	312 (99)	215 (98.6)	97 (100)	0.55
ACEI/ARB	313 (99.4)	216 (99.1)	97 (100)	0.34
Loop diuretics	315 (100)	218 (100)	97 (100)	1.00
MRA	315 (100)	218 (100)	97 (100)	1.00
Flozins	70 (22.2)	56 (25.7)	14 (14.4)	0.03
ICD/CRT-D	315 (100)	218 (100)	97 (100)	1.00

The data are presented as medians (25th–75th percentiles), mean (SD) or numbers (percentages) of patients

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ARB, angiotensin receptor blocker; BMI, body mass index; CI, cardiac index; CRT-D, cardiac resynchronization therapy-defibrillator; GGTP, gamma-glutamyl transpeptidase; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; LA, left atrium; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; RVEDd, right ventricular end-diastolic dimension; TPG, transpulmonary gradient; VO_2max, maximal oxygen uptake; WBC, white blood cells

for Mechanically Assisted Circulatory Support classification. During the one-year follow-up, the mortality rate was 31% (n = 97). The demographic and clinical characteristics of the patients in the whole population and in the survival and nonsurvival groups are presented in Table 1. The multivariable Cox proportional hazards analysis demonstrated that an elevated GDF-15 concentration, along with the routinely used laboratory parameters fibrinogen, bilirubin, GGTP, N-terminal pro-B-type natriuretic peptide, and high-sensitivity C-reactive protein, was strongly associated with one-year mortality in patients with end-stage HF. The univariable and multivariable Cox proportional hazards analyses for the prediction of one-year mortality are shown in Table 2.

DISCUSSION

Our single-center prospective study showed that higher GDF-15, hs-CRP, fibrinogen, GGTP, bilirubin, and NT-proBNP

Table 2. Univariable and multivariable analysis of predictors associated with one-year mortality (weighted Cox regression)

	Univariable analysis		Multivariable analysis	
Parameter	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Bilirubin$^{(+)}$	1.058 (1.030–1.087)	<0.001	1.055 (1.029–1.081)	<0.001
Albumin$^{(-)}$	1.129 (1.074–1.186)	<0.001		
GDF-15[a]	1.132 (1.113–1.152)	<0.001	1.142 (1.109–1.177)	<0.001
GFR$^{(-)}$	1.052 (1.035–1.070)	<0.001		
CRP$^{(+)}$	1.321 (1.243–1.404)	<0.001	1.186 (1.092–1.289)	<0.001
Fibrinogen$^{(+)}$	1.006 (1.004–1.008)	<0.001	1.004 (1.002–1.006)	<0.001
NT-proBNP[b]	1.366 (1.269–1.204)	<0.001	1.342 (1.206–1.493)	<0.001
BMI$^{(-)}$	1.073 (1.021–1.126)	0.005		
GGTP$^{(+)}$	1.004 (1.000–1.007)	0.04	1.007 (1.002–1.012)	0.003
Uric acid$^{(+)}$	1.003 (1.001–1.008)	0.02		
VO_2max$^{(-)}$	1.242 (1.143–1.287)	<0.001		
RV$^{(+)}$	1.065 (1.031–1.100]	<0.001		
LA$^{(+)}$	1.023 (1.008–1.048)	0.054		
LVEDD$^{(+)}$	1.016 (0.996–1.037)	0.12		
EF$^{(-)}$	1.124 (1.062–1.189)	<0.001		
Cardiac index$^{(-)}$	6.711 (2.564–17.544)	<0.001		
Age$^{(+)}$	1.020 (0.955–1.045)	0.11		
Male sex	2.441 (0.897_6.640)	0.08		
Ischemic etiology of HF	2.470 (1.547–3.945)	<0.001		
Hypertension	1.397 (0.915–2.133)	0.12		

Abbreviations: CI, confidence interval; HR, hazard ratio; other — see Table 1

$^{(-)}$ per one unit decrease; $^{(+)}$ per one unit increase

[a]Per 100-unit increase. [b]Per 1000-unit increase

were associated with one-year outcomes in patients with end-stage HF. From a pathophysiological point of view, the most interesting finding of our study was the strong association between higher GDF-15 levels and worse prognosis. Our results highlight the continuing importance of elevated GDF-15 levels in the risk stratification of patients with end-stage HF treated according to the current HF guidelines.

GDF-15 is a pleiotropic protein indicating several pathological processes associated with HF, but its mechanism of action is still unclear [6, 7, 10]. GDF-15 expression is controlled by various transcriptional pathways and is present nonpathologically only in placental and prostate tissue while in other tissues, its expression is very low. Its expression increases strongly in response to stress stimuli that activate several signaling pathways. Cardiac myocytes produce and secrete GDF-15 in response to injury, such as inflammation, ischemia, pressure, and volume overload, possibly through proinflammatory cytokines and oxidative stress-dependent signaling pathways [6, 7, 10–12]. Additionally, GDF-15 plays an important role in the development of endothelial dysfunction, a key feature in the onset and progression of HF [11]. GDF-15 directly modulates vascular contraction and relaxation responses in the endothelium by reducing nitric oxide release [11]. GDF-15 is not specific to cardiac myocytes. Other cellular sources of GDF-15 include macrophages, vascular smooth muscle cells, endothelial cells, and adipocytes in organs such as the kidney and liver [6, 7, 10, 11]. Thus, GDF-15, a noncardiospecific marker, may indicate both myocardial stress and related systemic abnormalities. This allows GDF--15 to integrate information from cardiac and extracardiac disease pathways that are linked to multiorgan dysfunction in the advanced stages of the disease. Elevated GDF-15 may reflect additional inflammatory and oxidative stress in HF beyond hemodynamic wall stress [13].

GDF-15 might have a limited role in the diagnosis of HF, but it may provide incremental prognostic information on HF morbidity and mortality [11]. Clinical studies have shown that initial and repeat measurements of GDF-15 can predict worse outcomes in different populations of HF patients [7, 10, 11, 14]. However, most of these studies followed earlier guidelines for HF management before modern medical therapy and devices came into use. Anand et al. [10], in a *post hoc* analysis of patients from the Val--Heft Trial (Valsartan in Heart Failure Trial), reported that baseline circulating GDF-15 was associated with adverse outcomes independent of established clinical, echocardiographic, and biochemical markers. We must emphasize that patients from Val-Hefts were randomized 20 years ago, and the study population differed significantly from ours, especially in terms of pharmacological treatment for HF. Only 33% of patients were treated with beta-blockers, 2% with spironolactone, and none with flozins.

In a meta-analysis by Luo et al. [14], the relationship between GDF-15 and all-cause mortality was studied in more than 6000 stable HF patients randomized between 2007 and 2017 [15]. The authors found that GDF-15 was strongly associated with all-cause mortality among chronic ischemic HF patients, while no such association was found

among chronic nonischemic HF patients [15]. Another meta-analysis of 8 studies with over 4000 stable NYHA II–III HF patients randomized before 2017 also indicated an association between elevated GDF-15 and a greater risk of mortality in this population [15]. These results should be interpreted with caution due to the substantial heterogeneity and publication bias among the studies included in the meta-analyses. Some studies reported that both initial and repeat measurements of GDF-15 have greater prognostic utility than NT-proBNP, which is considered the gold-standard biomarker in HF [10, 16].

Other factors associated with the one-year mortality rate in the analyzed group of patients were markers of systemic inflammation, such as hs-CRP and fibrinogen. Hs-CRP is considered the most important single marker of low-grade inflammatory processes in HF. It is synthesized by hepatocytes in response to cytokines, and it is part of the immune response [16]. Fibrinogen, a nonspecific acute-phase reactant, is also a component of the inflammatory cascade increasingly implicated in the pathogenesis of HF [17]. There is strong evidence that inflammation contributes to the pathogenesis, progression, and complications of HF through various pathways [18]. Proinflammatory cytokines, which are components of the immune response that mediate inflammation and arise from the gastrointestinal tract, spleen, and adipose tissue, induce low-grade inflammation that promotes ventricular systolic and diastolic dysfunction and contributes to endothelial dysfunction, cardiomyocyte apoptosis, cardiac fibrosis, and cardiac remodeling [19].

There is growing evidence that one of the important causes of inflammation in HF patients is translocation of bacterial endotoxin through edematous bowel walls. The activation of angiotensin II and mineralocorticoid receptors may cause vascular inflammation by promoting the production of reactive oxygen species and adhesion molecules and the polarization of macrophages toward a proinflammatory phenotype [19, 20]. The hs-CRP level is associated with cardiac decompensation, myocardial tissue and other organ damage, low cardiac output, and venous congestion, as well as the presence of muscle wasting, anemia, renal dysfunction, and other common comorbidities in HF [21]. There is also evidence to suggest that CRP itself is toxic to the myocardium, suggesting a mechanism by which inflammation may continue to damage the heart [17, 22].

In turn, fibrinogen is a major coagulation protein in the blood and is an important determinant of thrombogenicity, blood viscosity, and platelet aggregation [23]. Fibrinogen regulates the function of intercellular adhesion molecules that enhance monocyte and leukocyte adhesion to endothelial cells [23, 24]. It also stimulates mononuclear cells to express pro-inflammatory cytokines, which induce nitric oxide-mediated negative inotropic effects and cardiac myocyte apoptosis in experimental animal models [18, 23, 24]. Upon binding to endothelial cells, fibrinogen also causes the release of vasoactive mediators, promotes smooth muscle cell proliferation, and modulates endothelial cell permeability and migration [25]. Fibrinogen augments platelet reactivity, aggregation, and degranulation and promotes microthrombus formation [25–27]. The results of platelet hyperreactivity, hypercoagulability from enhanced thrombogenicity, and impaired fibrinolysis predispose a patient to microvascular thrombosis. The association between fibrinogen and myocardial function suggests that the postulated pathogenetic mechanisms of procoagulation and inflammation may contribute to subclinical impairment of myocardial function independently of altered ventricular filling dynamics. It has also been suggested that fibrinogen contributes directly to the onset of arrhythmias, which often lead to sudden cardiac death [27]. The involvement of fibrinogen in arrhythmogenesis has been attributed to pathways associated with the inflammatory cascade and hemodynamic alterations [27].

Our study also demonstrated that two liver function parameters, GGTP and bilirubin, were strongly associated with worse prognosis in patients with end-stage HF. End-stage HF is characterized by a prevalent cholestatic profile pattern characterized by increased bilirubin, GGTP, and ALP, whereas transaminase levels (hepatitis profile) usually remain within the normal range [28]. These abnormalities reflect the pathophysiology of liver function abnormalities in end-stage HF, which is associated with reduced cardiac output and the transmission of elevated central venous pressure to the hepatic venous system, leading to passive hepatic congestion [29, 30]. Another theory suggests that cardiac cirrhosis is not a simple reaction to chronic pressure and stasis but is associated with high-grade vascular occlusion due to intrahepatic thrombosis [29–32]. In individuals with cholestasis secondary to HF, GGTP is increased because of increased synthesis of the enzyme protein, and this increase is usually accompanied by an elevated bilirubin level [33]. Furthermore, GGTP, which is less specific for hepatobiliary injury than bilirubin, may not only reflect disease severity and hemodynamic perturbations but also be associated with systemic inflammation and oxidative stress [28]. In turn, an increase in total bilirubin in HF is also caused by impaired uptake of indirect bilirubin from blood, conjugation in hepatocytes, and secretion of direct bilirubin into bile. Moreover, hemolysis secondary to lung congestion may indirectly contribute to an increase in bilirubin levels [34].

In concordance with other studies, our findings demonstrated that elevated NT-proBNP concentrations were associated with worse prognosis in patients with end-stage HF [35–38]. NT-proBNP is a useful biomarker that supports diagnosing or ruling out HF as well as identifying patients with worsening HF [35–37]. Natriuretic peptides play an important role in HF by counteracting the effects of excessive stimulation of the sympathetic nervous system, renin-angiotensin-aldosterone system, and arginine-vasopressin system [39]. Moreover, natriuretic peptides influence cardiac remodeling through antihypertrophic and antifibrotic effects, including the inhibition of cardiac fibroblast proliferation, macrophage infiltration, and the

secretion of proinflammatory factors. In the early stages of HF, natriuretic peptides play a protective role in maintaining homeostasis. However, as cardiac function deteriorates, the effectiveness of natriuretic peptides decreases due to decreased availability, increased removal, enzymatic degradation by neprilysin, or an increase in the proportion of inactive proBNP secreted from the heart [36, 39].

Limitations

Several limitations must be noted. This single-center study was limited to patients with HF of NYHA classes III and IV. The inclusion and exclusion criteria applied may have limited the generalizability of our findings. Furthermore, blood samples were obtained only at the time of enrollment, but serial assessment of parameters during follow-up is required to accurately assess the prognostic value of the analyzed markers. A further limitation of the study is the lack of an independent validation cohort that would support our results. Although the cohort was relatively large for a single-center study, it can be considered small compared with the epidemiological scale of HF.

In conclusion, this study evaluated noninvasive and simple indicators associated with poor prognosis in patients with end-stage HF. Although limited to a single center, our study demonstrated that an elevated GDF-15 concentration, along with routinely used laboratory parameters such as fibrinogen, bilirubin, GGTP, NT-proBNP, and hs-CRP, is strongly associated with one-year mortality in patients with end-stage HF.

Article information

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REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022; 24(1): 4–131, doi: 10.1002/ejhf.2333, indexed in Pubmed: 35083827.
2. Wojtaszczyk A, Gąsior M, Szyguła-Jurkiewicz B, et al. Prevalence of heart rhythm disorders in patients with end-stage heart failure referred to qualification for heart transplantation. Kardiol Pol. 2022; 80(3): 339–341, doi: 10.33963/KP.a2022.0010, indexed in Pubmed: 35023568.
3. Gürgöze MT, van Vark LC, Baart SJ, et al. Multimarker analysis of serially measured GDF-15, NT-proBNP, ST2, GAL-3, cTnI, creatinine, and prognosis in acute heart failure. Circ Heart Fail. 2023; 16(1): e009526, doi: 10.1161/CIRCHEARTFAILURE.122.009526, indexed in Pubmed: 36408685.
4. Paul S, Harshaw-Ellis K. Evolving use of biomarkers in the management of heart failure. Cardiol Rev. 2019; 27(3): 153–159, doi: 10.1097/CRD.0000000000000224, indexed in Pubmed: 30192238.
5. Berezin AE, Berezin AA. Biomarkers in heart failure: From research to clinical practice. Ann Lab Med. 2023; 43(3): 225–236, doi: 10.3343/alm.2023.43.3.225, indexed in Pubmed: 36544334.
6. Rochette L, Dogon G, Zeller M, et al. GDF15 and cardiac cells: Current concepts and new insights. Int J Mol Sci. 2021; 22(16): 8889, doi: 10.3390/ijms22168889, indexed in Pubmed: 34445593.
7. Mazagova M, Buikema H, Landheer SW, et al. Growth differentiation factor 15 impairs aortic contractile and relaxing function through altered caveolar signaling of the endothelium. Am J Physiol Heart Circ Physiol. 2013; 304(5): H709–H718, doi: 10.1152/ajpheart.00543.2012, indexed in Pubmed: 23262134.
8. Heinze G. WCM: A SAS® macro for weighted parameter estimation for Cox's model. Technical Report 3/2008 (updated 2009.09.24).
9. Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. Stat Med. 2009; 28(19): 2473–2489, doi: 10.1002/sim.3623, indexed in Pubmed: 19472308.
10. Anand IS, Kempf T, Rector TS, et al. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. Circulation. 2010; 122(14): 1387–1395, doi: 10.1161/CIRCULATIONAHA.109.928846, indexed in Pubmed: 20855664.
11. Kempf T, Eden M, Strelau J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res. 2006; 98(3): 351–360, doi: 10.1161/01.RES.0000202805.73038.48, indexed in Pubmed: 16397141.
12. Szczygieł JA, Michałek P, Truszkowska G, et al. Clinical features, etiology, and survival in patients with restrictive cardiomyopathy: A single-center experience. Kardiol Pol. 2023; 81(12): 1227–1236, doi: 10.33963/v.kp.97879, indexed in Pubmed: 37937352.
13. Xu J, Kimball TR, Lorenz JN, et al. GDF15/MIC-1 functions as a protective and antihypertrophic factor released from the myocardium in association with SMAD protein activation. Circ Res. 2006; 98(3): 342–350, doi: 10.1161/01.RES.0000202804.84885.d0, indexed in Pubmed: 16397142.
14. Luo JW, Duan WH, Song L, et al. A meta-analysis of growth differentiation factor-15 and prognosis in chronic heart failure. Front Cardiovasc Med. 2021; 8: 630818, doi: 10.3389/fcvm.2021.630818, indexed in Pubmed: 34805295.
15. Zeng X, Li L, Wen H, et al. Growth-differentiation factor 15 as a predictor of mortality in patients with heart failure: A meta-analysis. J Cardiovasc Med (Hagerstown). 2017; 18(2): 53–59, doi: 10.2459/JCM.0000000000000412, indexed in Pubmed: 27454651.
16. Lok DJ, Klip IT, Lok SI, et al. Incremental prognostic power of novel biomarkers (growth-differentiation factor-15, high-sensitivity C-reactive protein, galectin-3, and high-sensitivity troponin-T) in patients with advanced chronic heart failure. Am J Cardiol. 2013; 112(6): 831–837, doi: 10.1016/j.amjcard.2013.05.013, indexed in Pubmed: 23820571.
17. Pellicori P, Zhang J, Cuthbert J, et al. High-sensitivity C-reactive protein in chronic heart failure: patient characteristics, phenotypes, and mode of death. Cardiovasc Res. 2020; 116(1): 91–100, doi: 10.1093/cvr/cvz198, indexed in Pubmed: 31350553.
18. van de Stolpe A, Jacobs N, Hage W, et al. Fibrinogen binding to ICAM-1 on EA.hy 926 endothelial cells is dependent on an intact cytoskeleton. Thromb Haemost. 2018; 75(01): 182–189, doi: 10.1055/s-0038-1650240.
19. Murphy SP, Kakkar R, McCarthy CP, et al. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 75(11): 1324–1340, doi: 10.1016/j.jacc.2020.01.014, indexed in Pubmed: 32192660.
20. Jungbauer CG, Riedlinger J, Block D, et al. Panel of emerging cardiac biomarkers contributes for prognosis rather than diagnosis in chronic heart failure. Biomark Med. 2014; 8(6): 777–789, doi: 10.2217/bmm.14.31, indexed in Pubmed: 25224934.
21. Brasier AR, Recinos A, Eledrisi MS. Vascular inflammation and the renin-angiotensin system. Arterioscler Thromb Vasc Biol. 2002; 22(8): 1257–1266, doi: 10.1161/01.atv.0000021412.56621.a2, indexed in Pubmed: 12171785.
22. Buonafine M, Bonnard B, Jaisser F. Mineralocorticoid receptor and cardiovascular disease. Am J Hypertens. 2018; 31(11): 1165–1174, doi: 10.1093/ajh/hpy120, indexed in Pubmed: 30192914.
23. Schneider DJ, Taatjes DJ, Howard DB, et al. Increased reactivity of platelets induced by fibrinogen independent of its binding to the IIb-IIIa surface glycoprotein: a potential contributor to cardiovascular risk. J Am Coll

Cardiol. 1999; 33(1): 261–266, doi: 10.1016/s0735-1097(98)00515-4, indexed in Pubmed: 9935039.
24. Hicks RC, Golledge J, Mir-Hasseine R, et al. Vasoactive effects of fibrinogen on saphenous vein. Nature. 1996; 379(6568): 818–820, doi: 10.1038/379818a0, indexed in Pubmed: 8587603.
25. Szaba FM, Smiley ST. Roles for thrombin and fibrin(ogen) in cytokine/chemokine production and macrophage adhesion in vivo. Blood. 2002; 99(3): 1053–1059, doi: 10.1182/blood.v99.3.1053, indexed in Pubmed: 11807012.
26. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res. 2002; 91(11): 988–998, doi: 10.1161/01.res.0000043825.01705.1b, indexed in Pubmed: 12456484.
27. Kunutsor SK, Kurl S, Zaccardi F, et al. Baseline and long-term fibrinogen levels and risk of sudden cardiac death: A new prospective study and meta-analysis. Atherosclerosis. 2016; 245: 171–180, doi: 10.1016/j.atherosclerosis.2015.12.020, indexed in Pubmed: 26724527.
28. Ess M, Mussner-Seeber C, Mariacher S, et al. γ-Glutamyltransferase rather than total bilirubin predicts outcome in chronic heart failure. J Card Fail. 2011; 17(7): 577–584, doi: 10.1016/j.cardfail.2011.02.012, indexed in Pubmed: 21703530.
29. Samsky MD, Patel CB, DeWald TA, et al. Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol. 2013; 61(24): 2397–2405, doi: 10.1016/j.jacc.2013.03.042, indexed in Pubmed: 23603231.
30. Szczurek W, Gąsior M, Skrzypek M, et al. Factors associated with elevated pulmonary vascular resistance in ambulatory patients with end-stage heart failure accepted for heart transplant. Pol Arch Intern Med. 2020; 130(10): 830–836, doi: 10.20452/pamw.15532, indexed in Pubmed: 32715717.
31. Suzuki K, Claggett B, Minamisawa M, et al. Liver function and prognosis, and influence of sacubitril/valsartan in patients with heart failure with reduced ejection fraction. Eur J Heart Fail. 2020; 22(9): 1662–1671, doi: 10.1002/ejhf.1853, indexed in Pubmed: 32407608.
32. Hilscher M, Sanchez W. Congestive hepatopathy. Clin Liver Dis (Hoboken). 2016; 8(3): 68–71, doi: 10.1002/cld.573, indexed in Pubmed: 31041066.
33. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. Am J Cardiol. 2002; 90(12): 1405–1409, doi: 10.1016/s0002-9149(02)02886-2, indexed in Pubmed: 12480058.
34. Shinagawa H, Inomata T, Koitabashi T, et al. Prognostic significance of increased serum bilirubin levels coincident with cardiac decompensation in chronic heart failure. Circ J. 2008; 72(3): 364–369, doi: 10.1253/circj.72.364, indexed in Pubmed: 18296830.
35. Senni M, Lopez-Sendon J, Cohen-Solal A, et al. Vericiguat and NT-proBNP in patients with heart failure with reduced ejection fraction: analyses from the VICTORIA trial. ESC Heart Fail. 2022; 9(6): 3791–3803, doi: 10.1002/ehf2.14050, indexed in Pubmed: 35880474.
36. Tsutsui H, Albert NM, Coats AJS, et al. Natriuretic peptides: role in the diagnosis and management of heart failure: a scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. Eur J Heart Fail. 2023; 25(5): 616–631, doi: 10.1002/ejhf.2848, indexed in Pubmed: 37098791.
37. Brunner-La Rocca HP, Sanders-van Wijk S. Natriuretic peptides in chronic heart failure. Card Fail Rev. 2019; 5(1): 44–49, doi: 10.15420/cfr.2018.26.1, indexed in Pubmed: 30847245.
38. Kang SH, Park JJ, Choi DJ, et al. Prognostic value of NT-proBNP in heart failure with preserved versus reduced EF. Heart. 2015; 101(23): 1881–1888, doi: 10.1136/heartjnl-2015-307782, indexed in Pubmed: 26319121.
39. Bayes-Genis A, Morant-Talamante N, Lupón J. Neprilysin and natriuretic peptide regulation in heart failure. Curr Heart Fail Rep. 2016; 13(4): 151–157, doi: 10.1007/s11897-016-0292-x, indexed in Pubmed: 27260315.