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Role and prognostic value of growth differentiation factor 15 in patient of heart failure with preserved ejection fraction: insights from the PURSUIT-HFpEF registry

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ABSTRACT

Background Growth differentiation factor 15 (GDF15) is a cytokine responding to oxidative stress and inflammation, and it regulates appetite and energy balance. The association between GDF15 and clinical factors and its prognostic value in elderly multimorbid patients with heart failure with preserved ejection fraction (HFpEF) have not been well unknown.

Methods This exploratory analysis is part of the Prospective mUlticenteR obServational stUdy of patIenTs with Heart Failure with preserved Ejection Fraction study (N=1231), an ongoing, prospective, multicentre observational study of acute decompensated HFpEF (UMIN000021831). A predefined subcohort of 212 patients underwent multi-biomarker testing. Of these, we analysed 181 patients with available GDF15 data. The primary endpoint was a composite of all-cause death and hospitalisation for HF.

Results In this analysis population, the median age was 81 (75–85) years, with 48% male patients. GDF15 significantly correlated with cardiac burden, anaemia, renal dysfunction and inflammation. Notably, poor nutritional status was significantly associated with GDF15. GDF15 was linked to poor prognosis in this elderly multimorbid cohort with HFpEF (adjusted HR for log-transformed GDF15: 13.67, 95% CI: 2.78 to 67.22, p=0.001). Furthermore, GDF15 added significant incremental value to the MAGGIC risk score (net reclassification improvement=0.4955 (95% CI: 0.1367 to 0.8543), p=0.007; integrated discrimination improvement=0.0278 (95% CI: 0.0013 to 0.0543), p=0.040).

Conclusions GDF15 was associated with anaemia, inflammation, renal dysfunction, cardiac burden and malnutrition. It demonstrated prognostic value in elderly multimorbid HFpEF patients, suggesting its potential role as a complementary marker for the prognostic risk assessment of HFpEF patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Growth differentiation factor 15 (GDF15) increases in response to multifactorial stresses such as obesity, anaemia, renal dysfunction, inflammation and cardiac burden, and acts as a feedback mechanism against these stresses by suppressing appetite, exerting anti-inflammatory effect and protecting cardiomyocytes from apoptosis. High GDF15 levels have been reported to have a correlation with poor prognosis in young obese heart failure with preserved ejection fraction (HFpEF).

WHAT THIS STUDY ADDS

⇒ In elderly multimorbid HFpEF patients, GDF15 was associated with anaemia, inflammation, renal dysfunction, cardiac burden and malnutrition, and showed incremental prognostic utility over traditional risk assessment tools.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ GDF15 could serve as a complementary marker to traditional heart failure risk assessment score like MAGGIC score. In this study, a strong association between GDF15 and malnutrition was demonstrated, which should be kept in mind when considering GDF15 as a therapeutic target.

Trial registration number UMIN-CTR ID: UMIN000021831.

INTRODUCTION

Growth differentiation factor 15 (GDF15) is an oxidative stress and inflammation response cytokine of the glial cell line derived neurotrophic factor family belonging to the

transforming growth factor beta superfamily. GDF15 is systemically activated in a variety of stress conditions like pregnancy, cancer, diabetes and cardiac disease.[1–4]

GDF15 acts primarily through a brainstem receptor, where it regulates appetite and energy balance.[5 6] GDF15, because of its bioactivity, is thought to play both protective and detrimental roles depending on patients' characteristics. In obese and patients with diabetes, GDF15 is thought to play protective roles, causing them to refrain from high caloric intake and regulating body weight through blood glucose homeostasis, whereas, in elderly multimorbid patients, GDF15 can be one of the molecules playing detrimental roles in weight loss by reduction of appetite and decreasing physical activity.[3 7] High serum GDF15 levels have been correlated with the progression of frailty and cachexia, which characterise the last stage in human life.[8 9]

There are some reports about the prognostic value of GDF15 for patients with heart failure with preserved ejection fraction (HFpEF).[10 11] However, these data were from the cohort who were relatively young, had preserved renal function, and were well nourished. In those patients, the detrimental roles of GDF15 may be less pronounced. The prognostic value of GDF15 in elderly multimorbid patients, in whom the detrimental roles of GDF15 can theoretically be more pronounced, is hypothetically different from known reports. Therefore, we aimed (1) to examine the association between GDF15 and clinical factors, and (2) to examine the prognostic value of GDF15 for relatively elderly multimorbid HFpEF patients.

METHODS

Study subjects

This study represents a post hoc analysis of the database from the ongoing Prospective mUlticenteR obServational stUdy of patIenTs with Heart Failure with preserved Ejection Fraction (PURSUIT-HFpEF) study, which is a multi-referral centre, prospective and observational study (UMIN-CTR ID: UMIN000021831). Consecutively enrolled patients with acute decompensated HF and preserved ejection fraction (≥50%) were registered. Diagnosis of acute decompensated HF was based on the clinical symptoms and signs using the Framingham Heart Study criteria, as well as a serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of ≥400 pg/mL or brain natriuretic peptide level of ≥100 pg/mL. Comprehensive patient characteristics, echocardiography, laboratory tests and medication lists were collected at admission, discharge and during annual follow-up time points.

In the ongoing PURSUIT-HFpEF registry, a predetermined subgroup underwent multi-biomarker assessments. This subgroup consisted of patients who consented to additional blood sampling. Out of the overall cohort of 1231 patients, a total of 212 patients had biomarker data in the data set analysed in this study, which was finalised in April 2022. The study was conducted in compliance with the ethical principles stated in the Declaration of Helsinki, and the study protocol was approved by the ethics committees of all participating hospitals. All patients provided written informed consent before participating in the study.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data collection

We collected data including detailed medical history, comorbidities, clinical frailty scale, New York Heart Association class, laboratory data and transthoracic echocardiographic data. Laboratory data included complete blood count and serum chemistry. In echocardiography, we measured left atrial volume index, and left ventricular ejection fraction by the modified Simpson's method. Left ventricular mass index was calculated by dividing left ventricular mass by body surface area. E/e' was the mean of septal E/e' and lateral E/e'. Tricuspid annular plane systolic excursion and inferior vena cava diameter were measured using the standard method.[12] Tricuspid pressure gradient was measured using the simplified Bernoulli equation.

Measurement of GDF15

All study subjects were admitted to the hospital due to acute decompensated HF. Blood sampling for the biomarker test was conducted after completion of acute phase treatment. The blood samples were centrifuged within 30 min at 4°C and stored at −20°C until assay. GDF15 was assessed using the Quantikine Human GDF-15 immunoassay. This assay is a 3.5 hours solid phase ELISA designed to measure GDF-15. The minimum detectable dose of human GDF-15 ranged from 0 to 4.4 pg/mL.

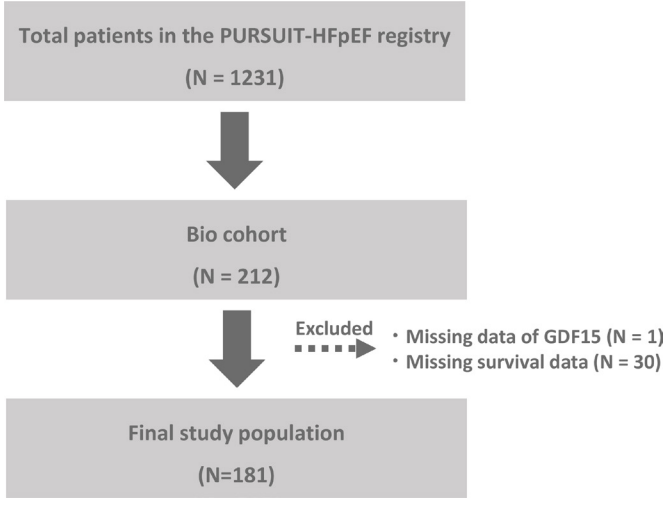

Figure 1 Patient flowchart. GDF15, growth differentiation factor 15; PURSUIT-HFpEF, Prospective mUlticenteR obServational stUdy of patIenTs with Heart Failure with preserved Ejection Fraction.

Table 1 Patient background

Characteristic	GDF15 tertile ≤2360 pg/mL (N=61)	2360 to 3880 pg/mL (N=60)	≥3880 pg/mL (N=60)	P value	Data missing (%)
GDF15	1690 (1290–2090)	3135 (2675–3378)	5170 (4448–6885)	<0.01	0
Age (years)	78.0 (73.0–83.0)	82.5 (77.8–86.0)	81.0 (73.8–86.0)	0.06	0
Male sex	25 (41.0)	21 (35.0)	40 (66.7)	<0.01	0
Body mass index (kg/m^2)	21.5 (19.2–24.3)	21.3 (19.4–24.7)	21.7 (19.6–24.2)	0.87	0
NYHA≥II	32 (52.5)	42 (70.0)	42 (70.0)	0.07	0
Clinical frailty scale ≥5	8 (13.1)	15 (25.0)	9 (15.0)	0.18	0
Smoking history	21 (34.4)	17 (28.8)	37 (61.7)	<0.01	0.6
Systolic blood pressure	124.0 (108.0–133.0)	127.0 (112.5–135.2)	128.5 (117.5–140.0)	0.07	0
Heart rate	70.0 (61.0–76.0)	69.5 (60.0–78.0)	70.0 (61.8–76.0)	0.93	0
Medical history					
Atrial fibrillation	25 (41.0)	26 (43.3)	19 (31.7)	0.38	0
Coronary artery disease	8 (13.1)	10 (16.9)	17 (28.8)	0.08	1.1
Hypertension	17 (27.9)	24 (40.0)	26 (44.1)	0.16	0.6
Diabetes mellitus	51 (83.6)	55 (91.7)	56 (93.3)	0.17	0
Dyslipidaemia	26 (43.3)	27 (45.0)	34 (56.7)	0.28	0.6
COPD	5 (8.3)	7 (11.9)	6 (10.0)	0.81	1.1
Dialysis	0 (0.0)	0 (0.0)	6 (10.0)	<0.01	0
Medication at discharge					
ACE-Is/ARBs	40 (65.6)	28 (46.7)	22 (36.7)	0.01	0
β blockers	45 (73.8)	41 (68.3)	42 (70.0)	0.80	0
Diuretics	46 (75.4)	56 (93.3)	53 (88.3)	0.01	0
MRAs	25 (41.0)	25 (41.7)	20 (33.3)	0.58	0
SGLT2 inhibitors	4 (6.6)	9 (15.0)	5 (8.3)	0.26	0
Biguanides	3 (4.9)	1 (1.7)	3 (5.0)	0.56	0
Laboratory data					
Albumin (g/dL)	3.4 (3.2–3.7)	3.4 (3.1–3.7)	3.3 (3.0–3.5)	0.03	0.6
Haemoglobin (g/L)	126 (108–136)	115 (98–134)	104 (94–119)	<0.01	0
Sodium (mEq/L)	140.0 (139.0–142.0)	140.0 (138.0–141.2)	138.0 (136.8–141.0)	0.02	0
eGFR (mL/min/1.73 m^2)	56.2 (45.0–69.2)	40.5 (31.2–56.0)	25.5 (14.7–40.3)	<0.01	0
Cholinesterase (U/L)	242.0 (197.0–285.0)	212.5 (194.5–250.5)	179.5 (153.8–221.2)	<0.01	13.3
C-reactive protein (mg/dL)	0.3 (0.1–1.2)	0.5 (0.2–1.0)	1.1 (0.3–2.1)	<0.01	1.1
Haemoglobin A1c	6.0 (5.6–6.5)	6.2 (5.8–6.8)	5.9 (5.4–6.4)	0.08	17.7
LDL cholesterol	99.0 (76.5–112.5)	101.0 (82.2–124.2)	78.5 (71.5–102.0)	0.01	9.9
NT-proBNP (pg/mL)	672 (273–1345)	1090 (569–2470)	2431 (1280–6018)	<0.01	14.9
Echocardiography at discharge					
LVDd (mm)	45.8 (41.8–51.1)	45.1 (40.2–49.6)	49.0 (43.8–53.8)	0.01	1.1
LVEF (%)	61.0 (57.0–64.7)	61.0 (54.3–68.1)	60.0 (53.5–64.8)	0.30	3.9
LAVI (mL/m^2)	50.0 (37.5–65.5)	51.0 (35.5–62.5)	45.0 (37.0–66.0)	>0.99	6.1
LVMI (g/m^2)	113.1 (91.2–143.7)	111.6 (97.8–143.9)	125.7 (109.7–147.6)	0.11	1.7
TAPSE (mm)	17.4 (15.6–20.4)	17.6(14.8–20.4)	17.1 (14.6–20.6)	0.89	2.8
Mean E/e'	11.6 (8.8–15.7)	12.8 (10.9–17.6)	13.7 (10.7–17.2)	0.03	2.8
TRPG (mm Hg)	25.0 (20.0–29.3)	26.3 (21.2–34.0)	25.7 (20.1–32.7)	0.36	9.4
Nutritional status					
CONUT score	3.0 (1.8–5.0)	3.0 (2.0–5.0)	4.0 (3.0–6.0)	0.01	16

Continued

Table 1 Continued

Characteristic	GDF15 tertile ≤2360 pg/mL (N=61)	2360 to 3880 pg/mL (N=60)	≥3880 pg/mL (N=60)	P value	Data missing (%)
GNRI	91.1 (83.9–102.3)	91.7 (85.7–96.4)	91.0 (83.5–95.6)	0.52	0.6
PNI	42.0 (38.5–45.5)	40.8 (37.5–43.9)	38.2 (34.8–42.2)	0.01	2.2

Data are shown as median (IQR) or number (percentage).
ACE-Is, ACE inhibitors; ARBs, angiotensin II receptor blockers; CONUT, controlling nutritional status; COPD, chronic obstructive pulmonary disease; e', early diastolic velocity of the mitral valve annulus; E, early diastolic velocity on transmitral doppler; eGFR, estimated glomerular filtration rate; GDF15, growth differentiation factor 15; GNRI, Geriatric Nutritional Risk Index; LAVI, left atrial volume index; LDL, low-density lipoprotein; LVDd, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PNI, Prognostic Nutritional Index; SGLT2 inhibitors, sodium glucose cotransporter-2 inhibitors; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

Clinical endpoints

The primary endpoint of this study was a composite of all-cause death and hospitalisation for HF. After discharge, enrolled patients were followed-up at an outpatient clinic in each hospital. Clinical follow-up data was obtained either by direct contact with patients or giving a telephone or a mail with their families.

Statistical analysis

Data are presented with listwise deletion. Categorical variables are expressed as counts (percentages) and compared with the χ^2 test or Fisher's exact test. Continuous variables are expressed as mean (SD) or median (IQR) and compared using the Student's t-test or the Mann-Whitney U test as appropriate. The normality of distribution of continuous data was examined with the Shapiro-Wilk test.

Multiple linear regression analysis was used to identify correlates of GDF15. Covariates in the multivariable linear regression model were age, sex, body mass index, smoking history, diabetes mellitus, atrial fibrillation, haemoglobin, estimated glomerular filtration rate, C-reactive protein, NT-proBNP and left ventricular mass index. These covariates were selected based on the previous findings.[2 10 13]

In addition, to assess the association between GDF15 and nutritional status, multiple linear regression analysis for the Geriatric Nutritional Risk Index and the Prognostic Nutritional Index and ordinal logistic regression analysis for the controlling nutritional status score were conducted. In the ordinal logistic regression model, the proportional odds assumption was tested using the Brant test and found to be satisfied. In all models, GDF15 was a variable of interest, and covariates were age, clinical frailty scale, body mass index, haemoglobin and estimated glomerular filtration rate. These covariates were selected based on the previous reports.[14]

Cox proportional hazards regression models were used to analyse the prognostic impact of the GDF15 level by calculating the multivariable-adjusted HR and 95% CI. The initial model included the following potential covariates: age, sex, body mass index, clinical frailty scale, New York Heart Association class, history of diabetes, atrial fibrillation, history of coronary artery disease, systolic blood pressure, haemoglobin, sodium, estimated glomerular filtration rate, albumin, C-reactive protein, NT-proBNP, left ventricular mass index, tricuspid annular plane systolic excursion, tricuspid pressure gradient and GDF15. These covariates were reported to have prognostic significance in HF patients.[15 16]

We used a stepwise selection method to determine the most parsimonious model. This approach combined forward selection and backward elimination procedures to iteratively add and remove covariates based on the Akaike information criterion (AIC). Specifically,

Table 2 Correlation between GDF15 and clinical factors

	β-coefficient (95% CI)	P value
Age (years)	0.0039 (0.0010 to 0.0067)	0.008
Male sex	0.0984 (0.0431 to 0.1537)	0.001
Body mass index	−0.0038 (−0.0100 to 0.0024)	0.229
Smoking history	0.0539 (−0.0029 to 0.1108)	0.065
Diabetes mellitus	0.0582 (0.0063 to 0.1100)	0.029
Atrial fibrillation	−0.0067 (−0.0583 to 0.0449)	0.799
Haemoglobin (g/L)	−0.0018 (−0.0031 to 0.0004)	0.010
eGFR (mL/min/1.73 m^2)	−0.0057 (−0.0071 to 0.0043)	<0.001
Log-transformed C-reactive protein (mg/dL)	0.0496 (0.0082 to 0.0909)	0.020
Log-transformed NT-proBNP (pg/mL)	0.0742 (0.0184 to 0.1300)	0.010
LVMI	−0.0004 (−0.0011 to 0.0002)	0.167

We used the multivariable linear regression model including 181 cases to assess the correlation between log-transformed GDF15 and clinical factors.
eGFR, estimated glomerular filtration rate; GDF15, growth differentiation factor 15; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide.

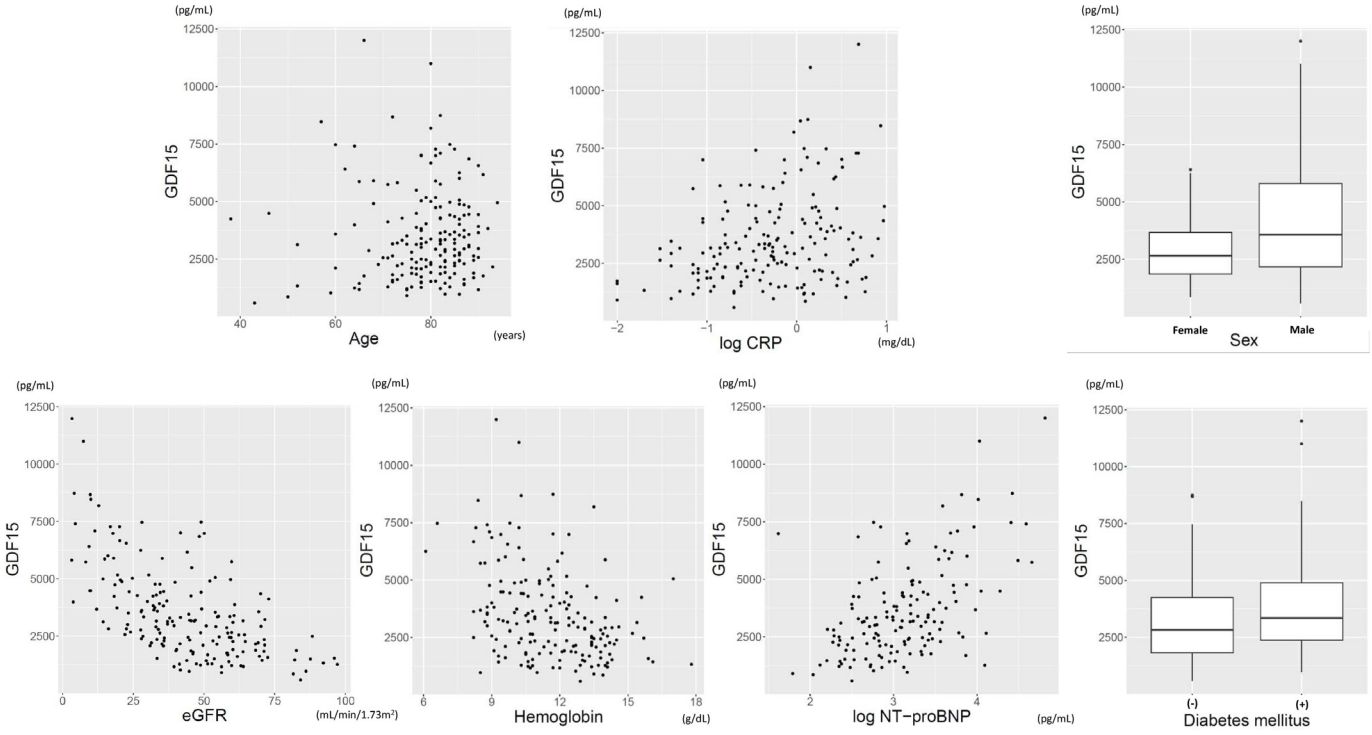

Figure 2 Correlation of GDF15 with clinical factors. Correlation of growth differentiation factor 15 with numeric clinical factors is shown in a scatter plot. Correlation of growth differentiation factor 15 with categorical clinical factors is shown in a box-and-whisker plot. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GDF15, growth differentiation factor 15.

the stepwise procedure started with no covariates and sequentially added covariates that significantly improved the model fit, as determined by a reduction in AIC. After each addition, all included covariates were re-evaluated, and any covariates that no longer contributed significantly to the model were removed. This process was repeated until no further covariates met the criteria for inclusion or exclusion. The final model included the following covariates: body mass index, clinical frailty scale, New York Heart Association class and GDF15. The HR for GDF15 is presented per one unit increase in the base-10 log-transformed GDF15. This increment corresponds to a 900% increase in the absolute GDF15 value. All variables had missing data <20%. The missing data were imputed by random forest imputation using 'missForest' package prior to these multivariable analyses.

The primary endpoint was assessed according to the stratification by tertile of GDF15 value in a time-to-first-event fashion with the Kaplan-Meier method and compared with the log-rank test.

The incremental discriminative utility of GDF15 for 1-year primary endpoint over the MAGGIC risk score, one of the most famous risk scores for HF patients was assessed by comparing the areas under the curve (AUC) of receiver operating characteristics curves of MAGGIC model and GDF15 model, using the DeLong test.

Table 3 Correlation between nutrition scores and GDF15

	GNRI		PNI		CONUT score	
	β-coefficient (95% CI)	P value	β-coefficient (95% CI)	P value	OR (95% CI)	P value
Log-transformed GDF15 (pg/mL)	−5.73 (−10.36 to 1.10)	0.016	−5.02 (−9.14 to 0.89)	0.018	7.18 (1.68 to 31.76)	0.008
Age (years)	−0.05 (−0.14 to 0.05)	0.323	−0.05 (−0.13 to 0.04)	0.257	1.02 (0.99 to 1.05)	0.163
Clinical frailty scale ≥5	−1.87 (−4.20 to 0.47)	0.119	−2.20 (−4.28 to 0.13)	0.039	2.56 (1.24 to 5.38)	0.012
Body mass index	1.88 (1.68 to 2.08)	<0.001	0.14 (−0.04 to 0.32)	0.124	0.97 (0.91 to 1.03)	0.313
Haemoglobin per 10 (g/L)	1.02 (0.57 to 1.47)	<0.001	−0.03 (−0.08 to 0.02)	0.177	0.72 (0.62 to 0.83)	<0.001
eGFR (mL/min/1.73 m^2)	−0.06 (−0.12 to 0.01)	0.032	0.69 (0.29 to 1.09)	0.001	1.02 (1.00 to 1.03)	0.091

We used the multivariable linear regression model to assess the correlation of GNRI and PNI with clinical factors and the ordinal logistic regression model to assess the correlation of CONUT score with clinical factors.
CONUT, controlling nutritional status; eGFR, estimated glomerular filtration rate; GDF15, growth differentiation factor 15; GNRI, Geriatric Nutritional Risk Index; PNI, Prognostic Nutritional Index.

Table 4 Prognostic impact of GDF15

Multivariable Cox proportional hazard model	HR (95% CI)	P value
Log-transformed GDF15 (pg/mL)	6.95 (2.44 to 19.80)	<0.001
Body mass index	0.91 (0.84 to 0.97)	0.004
Clinical frailty scale ≥5	2.04 (1.17 to 3.54)	0.011
New York Heart Association class ≥2	1.88 (1.00 to 3.55)	0.051

We used the multivariable Cox regression analysis including 181 cases to assess the adjusted impact of GDF15 on the primary endpoint (a composite of all-cause death and rehospitalisation for heart failure).
GDF15, growth differentiation factor 15.

MAGGIC model included the MAGGIC risk score and GDF15 model included MAGGIC model plus GDF15.[17] One of the items for the MAGGIC risk score calculation, history of HF for more than 18 months, was substituted for a history of HF hospitalisation in this study. The net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) were calculated when GDF15 was added to MAGGIC model.

All statistical analyses were performed using R software (V.4.3.1; R Foundation for Statistical Computing, Vienna, Austria). A p value of <0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

Patient flowchart is shown in figure 1. This study analysed a subcohort of 212 patients who underwent biomarker testing, out of the overall cohort of 1231 patients. Of these, 181 patients with clinical follow-up data available were analysed to assess the prognostic value of GDF15 (figure 1). Online supplemental figure 1 illustrates the histograms showing the distribution of GDF15.

In this study population (n=181), the median age was 81 (75–85) years, male patients accounted for 48%, the median body mass index at discharge was 21.5 (19.3–24.3) kg/m^2. Clinical characteristics of patients included and those excluded are summarised in online supplemental table 1. The study population was stratified by GDF15 level tertiles as follows: low GDF15 level ≤2360 pg/mL (N=61); 2360 pg/mL <middle GDF15 level <3880 pg/mL (N=60); and high GDF15 level ≥3880 pg/mL (N=60). Patients' baseline characteristics are shown in table 1. Compared with patients with low GDF15 level, those with high GDF15 level had a significantly higher percentage of men, smoking history, higher C-reactive protein level, higher serum NT-proBNP level, lower haemoglobin level, lower estimated glomerular filtration rate level and lower albumin level.

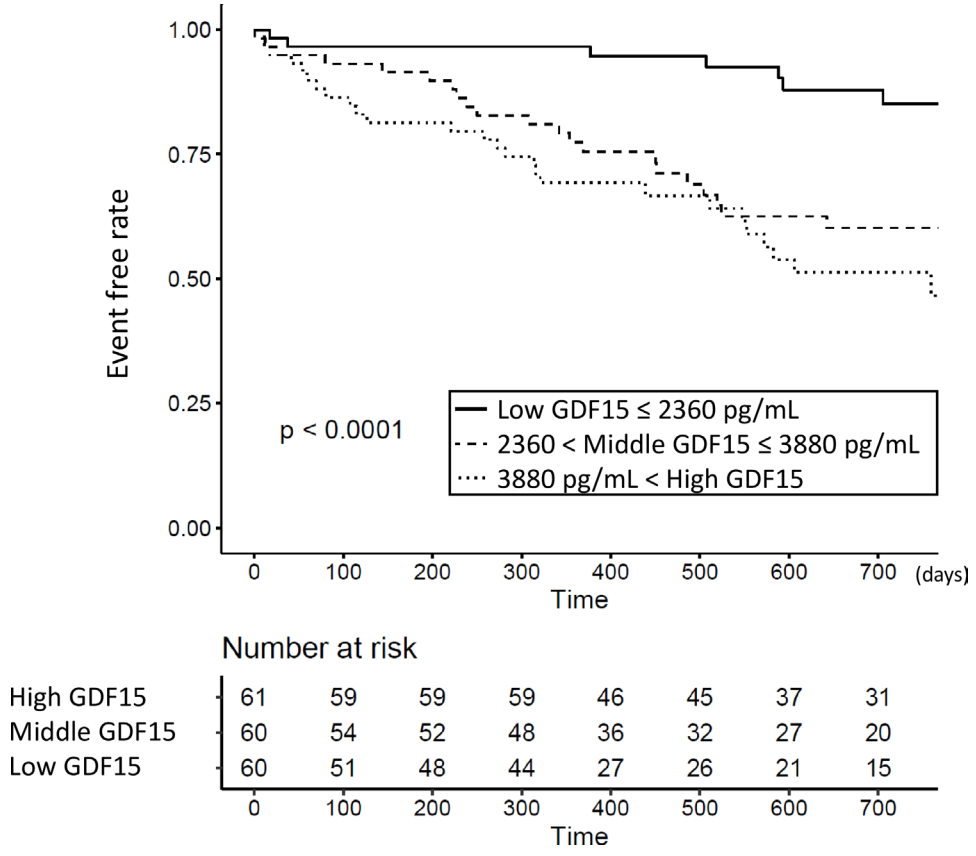

Figure 3 Kaplan-Meier curves demonstrating the composite endpoint stratified by GDF15 tertile. The Kaplan-Meier analysis for comparing the composite of all-cause death and hospitalisation for heart failure in three groups divided by GDF15 tertile. GDF15, growth differentiation factor 15.

Correlates of GDF15 with clinical factors

Correlates of GDF15 are shown in table 2. Age, male, diabetes mellitus, log-transformed C-reactive protein and log-transformed NT-proBNP were positively and haemoglobin, estimated glomerular filtration rate were negatively correlated with GDF15 level. Scatter plots and box-and-whisker plot with GDF15 are presented for factors that were found to be significantly correlated (figure 2).

Association between nutritional status and GDF15

GDF15 was independently associated with all nutritional scores, the Geriatric Nutritional Risk Index, the Prognostic Nutritional Index and the controlling nutritional status score, after adjustment with covariates (table 3).

Association of GDF15 with outcome

A mean follow-up duration was 1.6±1.0 years. The primary endpoint, a composite of all-cause death and hospitalisation for HF, occurred in 63 patients (all-cause death, 38 patients; and hospitalisation for HF, 41 patients).

GDF15 remained to be an independent predictor of the primary endpoint even after multivariable adjustment (adjusted HR for log-transformed GDF15; 13.67, 95% CI: 2.78 to 67.22, p=0.001) (table 4).

The Kaplan-Meier analysis revealed that GDF15 divided into tertile successfully stratified the patient prognosis (figure 3).

To assess the incremental discriminative power of GDF15, we compared c-statistics of MAGGIC model and GDF15 model and found numerically higher AUC in GDF15 model (MAGGIC model; AUC=0.661 (95% CI: 0.563 to 0.759), GDF15 model; AUC=0.707 (95% CI: 0.621 to 0.793), DeLong test p=0.299) (figure 4). The NRI and the IDI for the addition of GDF15 to the MAGGIC model were significant (NRI=0.4955 (95% CI: 0.1367 to 0.8543), p=0.007; IDI=0.0278 (95% CI: 0.0013 to 0.0543), p=0.040).

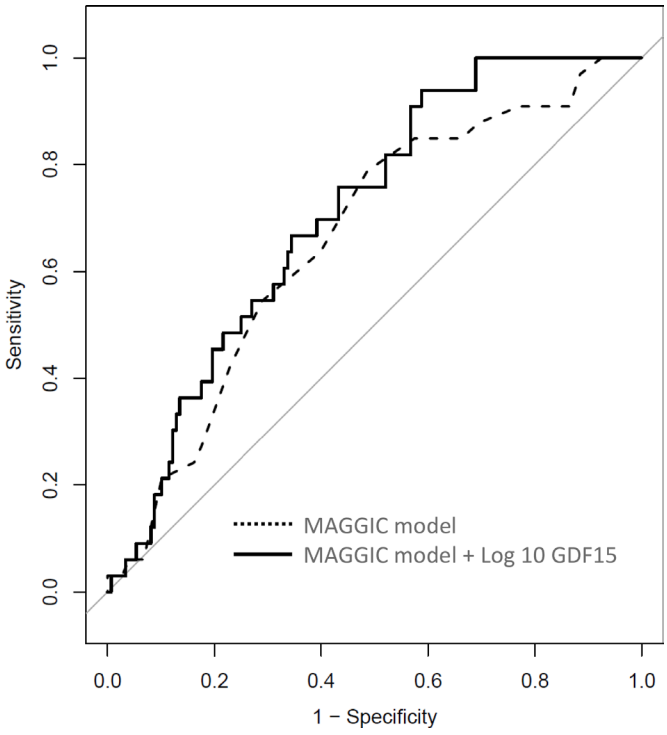

Figure 4 Comparison of ROC curves for primary endpoint within 1 year. The AUCs of MAGGIC model and GDF15 model were compared. MAGGIC model included the MAGGIC risk score, and GDF15 model included MAGGIC model plus GDF15. The AUC of GDF15 model was higher than MAGGIC model (MAGGIC model; AUC=0.661 (95% CI: 0.563 to 0.759), GDF15 model; AUC=0.707 (95% CI: 0.621 to 0.793), DeLong test p=0.299). NRI and IDI were calculated for the addition of GDF15 to the MAGGIC model (NRI=0.4955, 95% CI: 0.1367 to 0.8543, p=0.007, IDI=0.0278, 95% CI: 0.0013 to 0.0543, p=0.040). AUC, area under the curve; GDF15, growth differentiation factor 15; IDI, integrated discrimination improvement; NRI, net reclassification improvement; ROC, receiver operating characteristics.

DISCUSSION

Main findings of the present study can be summarised as follows: (1) GDF15 was correlated with cardiac burden, anaemia, renal dysfunction, inflammation and malnutrition; (2) GDF15 was associated with the poor prognosis in relatively elderly multimorbid cohort with HFpEF; and (3) significant incremental value of GDF15 added to the established risk assessment system (MAGGIC risk score) was identified.

Correlation factors and prognostic value of GDF15

Our study demonstrates that GDF15 levels are independently associated with adverse outcomes in relatively elderly multimorbid HFpEF cohort. The prognostic utility of GDF15 in HFpEF patients was first reported in Singapore Heart Failure Outcomes and Phenotypes study.[10] This study, including 186 HFpEF patients, revealed that GDF15 had the significant prognostic value even after multivariable adjustment. Following this initial report, similar findings were also reported from several studies.[11 18] These findings suggest important insights into the practical use of GDF15 in our HF care. However, there remains a large evidence gap in this topic. GDF15 levels have been known to have an association with various clinical status such as age, renal function, inflammation and metabolism. Although they are the same HFpEF cohort, they are younger, better-nourished and have better renal function than our cohort.

Possibly due to such differences in patients background, median GDF15 levels seemed to show noticeable differences between our study and other studies (3130 pg/mL in our study vs about 2600–2900 pg/mL in other studies). In our study, we have observed significant correlations between GDF15 levels and several clinical indicators such as age, sex, diabetes mellitus, anaemia, C-reactive protein, renal function and NT-proBNP, which is consistent with previous studies.[10 11] Notably, our cohort, which is characterised by elderly and multiple comorbidities, uniquely showed significant negative correlations between GDF15 and nutritional status represented by the controlling nutritional status score and the Geriatric Nutritional Risk

Index. In HF patients, it is well recognised that inflammation and malnutrition are interrelated.[19] GDF15, which is associated with inflammation, has been suggested to promote appetite loss, potentially leading to malnutrition. These points presumably suggest that the prognostic role of GDF15 may be universally significant in both cohorts, although the cause of GDF15 increase can be distinct.

The incremental prognostic value of GDF15 in combination with the MAGGIC risk score was found in our study as presented by the NRI and the IDI. It suggested that GDF15 could serve as a complementary marker to traditional HF risk assessment score. The MAGGIC risk score was developed from a broader HF population. However, it does not incorporate the pathophysiological dimensions such as systemic stress and inflammation, which may drive the progression of frailty and cachexia. GDF15 may capture such pathophysiological dimensions, potentially offering an incremental prognostic advantage beyond the MAGGIC risk score in our multimorbid elderly HFpEF cohort. The development of a more comprehensive, HFpEF-specific risk prediction model incorporating GDF15 would be one of the future scientific topics.

Pathophysiological roles of GDF15 in HFpEF

HFpEF presents a variety of pathological states, not only cardiac load but also systemic stress such as inflammation, anaemia, arteriosclerosis, renal failure and metabolic disorders, consequently elevating the GDF15 levels. GDF15 has been known to regulate appetite, tissue homeostasis, inflammation and to protect cardiomyocytes from apoptosis.[6 20 21] GDF15 is basically similar to BNP, as its levels increase in response to multifactorial stresses and act in a feedback mechanism to these stresses. Recent therapeutic interventions in HF patients have established the efficacy of sacubitril/valsartan for brain natriuretic peptide. Similarly, GDF15 may also emerge as a target for therapeutic intervention.

However, the physiological activity of GDF15 warrants careful consideration. In type II diabetics and obese patients, it can suppress their appetite and contribute to the metabolic homeostasis, whereas in elderly and patients with cancer, it can suppress their appetite and therefore promote cachexia and frailty.[3 7 9] There is a duality of protective and detrimental roles depending on patients' characteristics. In HFpEF with diverse pathologies, it is plausible that GDF15 could act beneficially in some populations and detrimentally in other populations. Current report has shown that the blood levels of GDF15 are increased by sodium glucose cotransporter-2 inhibitors (SGLT2-Is) which have cardioprotective effects and improve the prognosis of HFpEF.[22 23] However, the beneficial effects of SGLT2-Is on prognosis vary among different populations. The benefit of SGLT2-Is in an Asian cohort of the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial was reported.[22] The population was relatively young (mean age 71.4 years), met the diagnostic criteria for obesity in Asia (mean body mass index 25 kg/m^2), had preserved renal function (mean estimated glomerular filtration rate 61 mL/min/1.73 m^2). In this population, the protective roles of GDF15, appetite control and metabolic homeostasis, may be pronounced rather than the detrimental roles of GDF15, appetite suppression and promoting cachexia and frailty. On the other hand, a recent report indicated that the effectiveness of SGLT2-Is diminished in HFpEF patients with more advanced frailty.[24] In highly vulnerable HFpEF patients represented by those with severe frailty, elevating GDF15 levels due to SGLT2-Is may play detrimental roles and reduce the overall benefit of SGLT2-Is.

As discussed, GDF15 can have both detrimental and protective roles depending on the patients' condition, and this duality suggests a variable impact on prognosis. Therefore, caution may be warranted when considering GDF15 as a target for therapeutic intervention.

Study limitation

Several limitations must be acknowledged in this study. First, only a small proportion of patients (14.7%) were included in this study. As presented in online supplemental table 1, there were some differences in clinical characteristics between the patients included and excluded, which might have resulted in a potential selection bias. Second, GDF15 is a bioactive biomarker, but its causal role, whether as cause or effect, in relation to prognostic factors is largely unknown. Third, we have demonstrated the potential prognostic utility of GDF15 by integrating it into the MAGGIC risk score. Nonetheless, the development of a more comprehensive, HFpEF-specific risk prediction model incorporating GDF15 would be highly desirable. Unfortunately, the limited sample size of our current study population precludes the construction of such a specialised predictive model. Finally, the generalisability of the findings to other regions and ethnicities is limited due to differing races, social healthcare systems and dietary habits in Japan compared with other countries. Further large-scale global studies and basic research to explore the mechanistic pathways of GDF15 in HFpEF are needed to address these limitations.

CONCLUSIONS

GDF15 was associated with anaemia, inflammation, renal dysfunction, cardiac burden and malnutrition. It demonstrated prognostic value in elderly multimorbid HFpEF patients, suggesting its potential role as a complementary marker for the prognostic risk assessment of HFpEF patients.

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REFERENCES

1 Wollert KC, Kempf T, Wallentin L. Growth Differentiation Factor 15 as a Biomarker in Cardiovascular Disease. *Clin Chem* 2017;63:140–51.
2 Luan HH, Wang A, Hilliard BK, *et al*. GDF15 Is an Inflammation-Induced Central Mediator of Tissue Tolerance. *Cell* 2019;178:1231–44.
3 Ling T, Zhang J, Ding F, *et al*. Role of growth differentiation factor 15 in cancer cachexia (Review). *Oncol Lett* 2023;26:462.
4 Adela R, Banerjee SK. GDF-15 as a Target and Biomarker for Diabetes and Cardiovascular Diseases: A Translational Prospective. *J Diabetes Res* 2015;2015:490842.
5 Tsai VW-W, Manandhar R, Jørgensen SB, *et al*. The anorectic actions of the TGFβ cytokine MIC-1/GDF15 require an intact brainstem area postrema and nucleus of the solitary tract. *PLoS ONE* 2014;9:e100370.
6 Ago T, Sadoshima J. GDF15, a cardioprotective TGF-beta superfamily protein. *Circ Res* 2006;98:294–7.
7 Zhang SY, Danaei Z, Bruce K, *et al*. Acute Activation of GFRAL in the Area Postrema Contributes to Glucose Regulation Independent of Weight. *Diabetes* 2024;73:426–33.
8 Raffin J, Rolland Y, Parini A, *et al*. Association between physical activity, growth differentiation factor 15 and bodyweight in older adults: A longitudinal mediation analysis. *J Cachexia Sarcopenia Muscle* 2023;14:771–80.
9 Oba K, Ishikawa J, Tamura Y, *et al*. Serum Growth Differentiation Factor 15 Levels Predict the Incidence of Frailty among Patients with Cardiometabolic Diseases. *Gerontology* 2024;70:517–25.
10 Chan MMY, Santhanakrishnan R, Chong JPC, *et al*. Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction. *Eur J Heart Fail* 2016;18:81–8.
11 Otaki Y, Shimizu M, Watanabe T, *et al*. Growth Differentiation Factor 15 and Clinical Outcomes in Japanese Patients With Heart Failure. *Circ J* 2023;87:1120–9.
12 Lang RM, Badano LP, Mor-Avi V, *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
13 Benes J, Kotrc M, Wohlfahrt P, *et al*. The Role of GDF-15 in Heart Failure Patients With Chronic Kidney Disease. *Can J Cardiol* 2019;35:462–70.
14 Doğan Akagündüz D, Şahin H, Akagündüz B. Malnutrition and Related Factors in Older Patients With Gastrointestinal Cancer Receiving Chemotherapy. *Cureus* 2024;16:e58252.
15 Sotomi Y, Iwakura K, Hikoso S, *et al*. Prognostic significance of the HFA-PEFF score in patients with heart failure with preserved ejection fraction. *ESC Heart Fail* 2021;8:2154–64.
16 Sunaga A, Hikoso S, Yamada T, *et al*. Prognostic impact of Clinical Frailty Scale in patients with heart failure with preserved ejection fraction. *ESC Heart Fail* 2021;8:3316–26.
17 Pocock SJ, Ariti CA, McMurray JJV, *et al*. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;34:1404–13.
18 Lyu L, Xu J, Xv C, *et al*. Prognostic value of growth differentiation factor-15 in heart failure among whole ejection fraction phenotypes. *ESC Heart Fail* 2024;11:2295–304.
19 Nakagomi A, Kohashi K, Morisawa T, *et al*. Nutritional Status is Associated with Inflammation and Predicts a Poor Outcome in Patients with Chronic Heart Failure. *J Atheroscler Thromb* 2016;23:713–27.
20 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;98:351–60.
21 Hsu J-Y, Crawley S, Chen M, *et al*. Non-homeostatic body weight regulation through a brainstem-restricted receptor for GDF15. *Nature New Biol* 2017;550:255–9.
22 Wang X, Lam CSP, Vaduganathan M, *et al*. Effects of Dapagliflozin in Patients in Asia: A Post Hoc Subgroup Analysis From the DELIVER Trial. *JACC Asia* 2024;4:108–18.
23 Omar M, Jensen J, Kistorp C, *et al*. The effect of empagliflozin on growth differentiation factor 15 in patients with heart failure: a randomized controlled trial (Empire HF Biomarker). *Cardiovasc Diabetol* 2022;21:34.
24 Coats AJS, Butler J, Tsutsui H, *et al*. Efficacy of empagliflozin in heart failure with preserved ejection fraction according to frailty status in EMPEROR-Preserved. *J Cachexia Sarcopenia Muscle* 2024;15:412–24.