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Growth differentiation factor-15 and metabolic features in chronic heart failure: Insights from the SUPPORT Trial -GDF15 across the BMI spectrum☆

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ABSTRACT

Background: GDF15 plays pivotal metabolic roles in nutritional stress and serves as a physiological regulator of energy balance. However, the patterns of GDF15 levels in underweight or obese patients with chronic heart failure (CHF) are not well-understood.

Methods: We assessed serum GDF15 levels at baseline and 3 years and the temporal changes in 940 Japanese patients (642 paired samples), as a sub-analysis of the SUPPORT trial (age 65.9 ± 10.1 years). The GDF15 levels were analyzed across BMI groups (underweight [<18.5 kg/m^2; n = 50], healthy weight [18.5–22.9; n = 27 5], overweight [23–24.9; n = 234], and obese [≥25; n = 381]), following WHO recommendations for the Asian-Pacific population. Landmark analysis at 3 years assessed the association between GDF15 levels and HF hospitalization or all-cause death.

Results: Compared to the healthy weight group, the underweight group included more females (54.0%) with advanced HF (NYHA class III; 20.0%) and exhibited increased GDF15 level (1764 pg/mL [IQR 1067-2633]). Obese patients, younger (64.2 years) and diabetic (53%), had a similar GDF15 level to the healthy weight group. A higher baseline GDF15 level was associated with worse outcomes across the BMI spectrum. GDF15 increased by 208 [21–596] pg/mL over 3 years, with the most substantial increase observed in the underweight group (by +28.9% [6.2–81.0]). Persistently high GDF15 levels (≥1800 pg/mL) was independently associated with worse outcomes after 3 years (adjusted HR 1.8 [95%CI 1.1–2.9]).

Conclusions: In underweight patients with CHF, GDF15 level was elevated at baseline and experienced the most significant increase over 3 years. Its consistent elevation suggested a worse outcome.

1. Introduction

Growth differentiation factor-15 (GDF15) is a pleiotropic protein involved in diverse biological pathways, linked to various diseases from malignancies to metabolic disorders, [1,2] and downstream cardiovascular conditions, such as heart failure (HF) [3]. GDF15 is involved in a multitude of pathophysiological pathways, such as oxidative stress, inflammation, and cellular aging, which is significantly elevated in

Abbreviations: ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; eGFR, Estimated glomerular filtration rate; GDF15, Growth differentiation factor 15; GDMT, Guideline-directed medical therapy; GNRI, Geriatric nutritional risk index; LVEF, Left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; SUPPORT trial, Supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using Olmesartan.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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patients with HF, particularly those with advanced stages [4] [5]. Additionally, a seminal study indicates two essential metabolic roles for GDF15; 1) functioning as a marker of dietary/nutritional status, and 2) acting as a physiological regulator of energy balance [6]. While nutritional and dietary interventions play an essential role in HF management, the long-term behavior of GDF15 remains unexplored in patients with HF exhibiting signs of cachexia (i.e., underweight) or obesity.

Even in patients with stable conditions, HF can continue to deteriorate without prominent signs or symptoms of worsening [7]. Underlying pathophysiological mechanisms, such as nutrition and metabolism play essential roles in this progressive nature of the disease [8], thus it is essential to monitor and manage these non-cardiac factors appropriately. In this context, the identification of a non-cardiac specific biomarker reflective of the key factors including aging, nutrition, and metabolism could significantly aid in the long-term management of HF. Over the past decade, elevated serum levels of GDF15 have been observed in patients with cachexia or obesity, serving as a stress marker indicative of dietary and nutritional status. [9,10] However, the role of GDF15 in HF, particularly in patients with varying body sizes and nutritional risks, remains less understood. There is also a limited evidence on the long-term relationship between GDF15 levels and body size in HF patients.

The SUPPORT trial (Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients with Stable Heart Failure Using Olmesartan) was a prospective, randomized, open-label, blinded endpoint study conducted in Japan. [11,12] It aimed to assess the additional benefit of olmesartan, in addition to standard therapy, in hypertensive patients with HF for mortality and morbidity. Given the well-characterized clinical characteristics and long-term follow-up data from the SUPPORT trial, we aimed to provide insight into the dynamics of GDF15 and its relationship with key metabolic and nutritional factors in chronic HF. In this study, we retrospectively analyzed serum GDF15 levels based on body sizes and investigated their prognostic relevance. Additionally, we examined temporal changes in GDF15 levels over a 3-year period to determine their significance as prognostic indicators for long-term outcomes in HF.

2. Methods

2.1. Patient population

The SUPPORT trial (NCT00417222) was performed in 17 institutions in the Tohoku District of Japan. [11,12] The trial evaluated the efficacy of the incremental benefit of olmesartan for reducing the mortality and morbidity of hypertensive patients with stable chronic HF who were treated with conventional therapies with angiotensin-converting enzyme (ACE) inhibitors and/or β-blockers. A total of 1147 Japanese patients aged between 20 and 80 years were enrolled between October 2006 and March 2010, and were randomized into either a group of 5–10 mg/day of olmesartan (up titrated to 40 mg/day, if tolerable) or a control group with standard treatment without the use of any angiotensin receptor antagonists. In the SUPPORT trial, the diagnosis of HF was made by attending physicians, using the Framingham criteria for HF at the time of study enrollment. HF phenotypes were determined based on left ventricular ejection fraction (LVEF) at baseline as follows; HF with reduced ejection fraction (HFrEF), LVEF $\leq$40%; HF with mildly reduced ejection fraction (HFmrEF), LVEF between 40 and 50%; and HF with preserved ejection fraction (HFpEF), LVEF $\geq$50%. Patients underwent anamnestic interview, standard physical assessment, a 12-lead ECG, blood sample collection, and transthoracic echocardiography at the time of enrolment as their baseline characteristics. Patients were then followed for incidence of cardiovascular endpoints. Similar physical assessments and medical examinations were performed at 3-year follow-up from baseline observations. The SUPPORT trial adheres to the ethical principles of the Declaration of Helsinki, and all participants of the trial have provided written informed consent. [11,12]

Supplemental Table 1 summarizes the study flow. In the present study, a total of 940 patients with GDF15 and BMI measurement at baseline were subjected to cross-sectional analysis. A descriptive analysis of the studied patients was performed across the four BMI groups defined by the baseline BMI levels; 1) underweight (BMI <18.5 kg/m^2), 2) healthy weight (BMI 18.5–22.9 kg/m^2), 3) overweight (BMI 23–24.9 kg/m^2), and 4) obese (BMI $\geq$25 kg/m^2), based on the recommendation from the WHO for the Asian-Pacific population [13]. A geriatric nutritional risk index (GNRI) was used to assess the risk of malnutrition at baseline and 3 years [14]. GNRI is an objective screening tool to assess the nutritional risk in older individuals, that is well validated in the HF population [15]. It was estimated using the following formula; GNRI = (14.89 × serum albumin [g/dl]) + (41.7 × body weight [kg] / ideal body weight [kg]), in which the ideal body weight was estimated using the Lorentz equation defined as height [cm] – 100 – (height [cm] – 150/4) for men and height [cm] – 100 – (height [cm] – 150/2.5) for women [14]. The malnutrition risks were categorized into an absence of risk (GNRI >98), low risk (GNRI 92–98), moderate risk (GNRI 82–98), and high risk (GNRI <82) [14]. Using the baseline data, a controlling nutritional status (CONUT) score and prognostic nutritional index (PNI) were estimated [16]. The CONUT score was based on three factors: serum albumin, total cholesterol and lymphocyte count in which the lower values for each of the factors were given higher points. The severity of malnutrition was based on the aggregate of the points where >8 points had severe, 5–8 points had moderate, 2–4 points had low, and 0–1 point had normal nutritional states. The PNI was calculated as 10 × serum albumin (g/dL) + 0.005 × lymphocyte count (per mm^3), and the severity of malnutrition were defined as severe for PNI <35, moderate for 35 < PNI >38, and low for PNI $\geq$38.

Paired samples of GDF15 measurement at baseline and 3 years were studied for a total of 642 patients. To study the dynamic changes in GDF15 levels over 3 years, GDF15 level at baseline and 3 years were categorized into three groups; 1) very high ($\geq$1800 pg/mL), 2) high (1200–1800 pg/mL), and 3) normal (<1200 pg/mL) according to the established cut-off points for cardiovascular events [17]. Subsequently, based on the three GDF15 groups, five transitional categories of GDF15 groups were defined as follows; 1) persistently very high, 2) persistently high, 3) escalated (either from normal to very high, from normal to high, or from high to very high), 4) maintained normal, and 5) improved (either from very high to high or from very high to normal, or from high to normal).

2.2. Measurement of serum GDF15 concentration

Serum GDF15 concentration were retrospectively measured using the blood samples that were collected and stored below -20 °C in the central laboratory at the Tohoku University Hospital. Electrochemiluminescence sandwich immunoassay was performed using Cobas analyzer (Roche Diagnostics, Indianapolis, USA). The coefficients of variation for repeatability and intermediate precision were between 1.1 and 1.4% and 1.8–2.3%, respectively.

2.3. Study endpoints

The study endpoint was the composite of HF hospitalization or all-cause death from the baseline visit. Outcome events collected in the SUPPORT trial were all adjudicated by the Endpoint Evaluation Committee. [11,12]

2.4. Statistical analysis

The means ± SD or medians with interquartile range [IQR] are presented for normally and non-normally distributed variables, respectively. The number of patients and percentages are presented for categorical variables. Pairwise comparisons of each of the BMI groups against the healthy weight group were performed using Tukey or Steel

tests, adjusted for multiple comparisons. Multivariable Cox proportional hazard regression models were used to identify the risk of the study endpoint across the BMI groups. Adjusted variables include age, sex, NYHA class, intervention group (i.e. olmesartan vs. no olmesartan), history of diabetes, atrial fibrillation, eGFR, log-transformed NT-proBNP level, and LVEF at baseline which were selected on a priori knowledge of clinical importance.

Baseline GDF15 levels are summarized by BMI groups and in the continuous BMI spectrum. Projected GDF15 levels across the continuous BMI spectrum is presented using spline regression with four knots specified at each BMI point at 18.5, 23, 25, and 30 kg/m^2. Cox proportional hazard regression models were used to identify the risk of study endpoint per log-transformed GDF15 level across the BMI groups and also on the continuous BMI spectrum modelled using the cubic spline Cox regression.

The change in GDF15 levels over 3 years is illustrated using Sankey plots. The clinical characteristics across the transitional groups of GDF15 levels and its incident curves of study endpoint are presented. A landmarked, time-to-event analysis was performed using multivariable Cox proportional hazard regression models to determine the association between transitional groups of GDF15 and outcomes after 3 years. The clinical characteristics of patients without GDF15 or BMI data at 3 years, and those who were censored from the landmark analysis are detailed in **Supplemental Table 2**. All statistical analyses were performed using R (4.1.3). A two-tailed *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics and study endpoint across the BMI groups

A total of 940 Japanese patient data were analyzed, where the mean age was 65.9 ± 10.1 years and 26% were female. The median BMI was 24.4 [IQR 22.3–36.9] kg/m^2 and 17.9% of patients had nutrition-related risk based on GNRI. 64% of the overall study patients had LVEF ≥50% (i.e. HFpEF). There were 50 (5.3%) patients with BMI <18.5 kg/m^2 (underweight), 275 (29.3%) patients with BMI between 18.5 and 22.9 kg/m^2 (healthy weight), 234 (24.9%) patients with BMI between 23 and 24.9 kg/m^2 (overweight), and 381 (40.5%) patients with BMI ≥25 kg/m^2 (obese) (Table 1). Compared to patients in the healthy weight group, those in the underweight group were more female (54% vs. 28%) with advanced HF (NYHA class III; 20% vs. 7%). The GNRI was lower in the underweight patients compared to those with healthy weight (mean of 91.4 vs. 101.4 points), and had more patients with moderate to high nutrition-related risk (54% vs. 9%). The CONUT score and PNI also indicated a higher risk of malnutrition in underweight patients. Conversely, patients in the obese group were younger (64.2 ± 10.9 years) and had a higher prevalence of diabetes (53% vs. 42%) and dyslipidemia (56% vs. 51%) compared to those with healthy weight. Median N-terminal pro-brain natriuretic peptide (NT-proBNP) was higher (1056 [448–2086] pg/mL) in underweight patients and was lower (279 [115–651] pg/mL) in obese patients compared to those with healthy weight (460 [182–963] pg/mL). Similar findings were observed in patients with GDF15 measurement at both baseline and 3 years (**Supplemental Table 3**).

Over the mean follow-up of 7.6 years, 474 composite endpoints of HF hospitalization or all-cause death occurred. Patients in the underweight group had the highest event rate (13.7 per 100 person-years), and patients in the obese group had the lowest event rate (5.6 per 100 person-years) (**Supplemental Table 4 & Supplemental Fig. 1**). When referencing patients with healthy weight, the risk of the composite of HF hospitalization or death was higher in the underweight group (adjusted HR 1.58, 95%CI [1.09–2.29]). The hazard ratio of the study endpoint in the overweight and obese groups were not significant in the adjusted models (**Supplemental Table 4**) including intervention group (olmesartan vs. no olmesartan) left ventricular ejection fraction (LVEF), eGFR, and NT-proBNP.

3.2. GDF15 level and BMI at baseline

In overall patients, the median level of serum GDF15 was 1219 [876–1793] pg/mL (Table 1). There was a marginal decreasing trend of GDF15 across the BMI groups in which the GDF15 level was elevated in the underweight group and was similar across the healthy weight, overweight, and obese groups (1764 [1067-2633], 1226 [855–1916], 1228 [890–1743], and 1183 [857–1661] pg/mL, respectively). The adjusted means of lnGDF15 was the highest in the underweight group across the four BMI groups (**Supplementary Fig. 2**).

Across the continuous BMI spectrum, there was a sharp spike of GDF15 level at BMI below 20 kg/m^2 (Fig. 1). In between BMI around 30 and 45 kg/m^2, there was a modest increase in GDF15 level. The distribution of NT-proBNP level had a right-skewed distribution with a single sharp peak at BMI below 20 kg/m^2 and a declining trend beyond BMI of 35 kg/m^2.

3.3. GDF15 level at baseline and study endpoint

In overall patients, per log-unit change in baseline GDF15 was associated with a 2.2-fold higher risk of HF hospitalization or all-cause death (adjusted HR 2.23 [95%CI 1.80–2.76]) (**Supplemental Table 5**). The stratified analysis by BMI groups showed that higher GDF15 level was associated with a greater risk of the study endpoint in all BMI groups except for the overweight group, in which per log-unit increase in GDF15 was associated with 2.9, 2.6, and 2.2-fold higher risk in the underweight, healthy weight, and obese group, respectively. The nadir of the adjusted hazard ratio of the study endpoint per log-unit increase in GDF15 level on the continuous BMI spectrum was at around BMI 25 kg/m^2, while the hazard ratio was higher at both ends of the BMI spectrum (Fig. 2). Similar findings were observed in patients with GDF15 data at baseline and 3 years ($n = 642$) as shown in **Supplemental Table 6** and **Supplemental Fig. 3**).

3.4. Changes in GDF15 levels over 3 years

Among a total of 642 patients with GDF15 measurement at both baseline and 3 years, the median GDF15 level increased from 1181 [870–1685] at baseline to 1412 [1014-2164] pg/mL at 3 years. GDF15 level at 3 years was higher in the underweight group (2338 [1220-3308]) compared to that of the healthy weight group (1383 [977–2072] pg/mL) (**Supplemental Table 7 & Supplemental Fig. 4**). The percent change of GDF15 level over 3 years was not different across the BMI groups at baseline.

Neither the median GDF15 level at 3 years or percent change in GDF15 level over 3 years were not different between the olmesartan and placebo groups (GDF15 level at 3 years; 1427 [970–2189] vs. 1396 [1060-2117] pg/mL; percent change in GDF15 level: 23.1 [2.7–52.7] vs. 17.4 [1.4–40.0] %, $p = 0.069$, respectively).

3.5. Transition of GDF15 levels over 3 years

Over 3 years, there were 125 (19.4%) patients with persistently very high GDF15 levels (≥1800 pg/mL), 79 (12.3%) with persistently high GDF15 levels (1200–1800 pg/mL), 193 (30.0%) with escalated GDF15 levels, 220 (34.3%) with maintained normal GDF15 levels, and 25 (3.4%) with improved GDF15 levels (**Supplemental Fig. 5**). Clinical characteristics of the transitional groups are described in **Supplemental Table 8**. The greatest decline in BMI over 3 years was found in patients with persistently very high GDF15 levels and the greatest increase in BMI was found in patients who experienced improvement in GDF15 levels. A significant reduction in GNRI over 3 years was noted in patients with persistently very high GDF15 levels.

After censoring patients with study endpoint in the first 3 years from

Table 1
Baseline characteristics of the studied patients across the BMI groups.

Baseline characteristics	Overall	BMI groups				Trend *p*-value
		Underweight BMI < 18.5 kg/m^2	Healthy weight BMI 18.5–22.9 kg/m^2	Overweight BMI 23–24.9 kg/m^2	Obese BMI ≥ 25 kg/m^2	
N, n (%)	940	50 (5.3)	275 (29.3)	234 (24.9)	381 (40.5)	NA
Demographics						
Age (years)	65.9 (10.1)	69.9 (9.7)	66.7 (9.0)	67.9 (9.5)	64.2 (10.9)*	< 0.001
Female, n (%)	243 (25.9)	27 (54.0)*	78 (28.4)	50 (21.4)	88 (23.1)	< 0.001
Body weight (kg)	63.4 (12.7)	41.9 (5.7)*	55.0 (7.2)	62.1 (7.1)*	73.2 (10.9)*	< 0.001
Nutritional indices						
GNRI	103.1 (7.0)	91.4 (9.5)*	101.4 (7.1)	104.1 (5.3)*	105.3 (5.5)*	< 0.001
GNRI classification, n (%)						< 0.001§
Absence of risk (GNRI >98)	770 (82.1)	13 (26)	199 (72.4)	212 (91)	346 (91.1)	
Low risk (GNRI 92–98)	109 (11.6)	10 (20)	52 (18.9)	18 (7.7)	29 (7.6)	
Moderate risk (GNRI 82–92)	47 (5.0)	21 (42)	19 (6.9)	2 (0.9)	5 (1.3)	
High risk (GNRI <82)	12 (1.3)	6 (12)	5 (1.8)	1 (0.4)	0	
CONUT score	1.23 (1.27)	2.14 (1.97)*	1.36 (1.31)	1.16 (1.17)	1.06 (1.13)*	< 0.001
CONUT classification, n (%)						< 0.001§
Normal (CONUT score <1)	327 (50.2)	11 (29.7)	79 (43.2)	89 (52.7)	148 (56.5)	
Low (CONUT score 2–4)	306 (47.0)	19 (51.4)	99 (54.1)	79 (46.7)	109 (41.6)	
Moderate (CONUT score 5–8)	17 (2.6)	7 (18.9)	4 (2.2)	1 (0.6)	5 (1.9)	
Severe (CONUT score ≥8)	1 (0.2)	0	1 (0.5)	0	0	
PNI	51.1 (5.5)	47.0 (7.3)*	50.4 (5.5)	51.0 (4.9)	52.3 (5.2)*	< 0.001
PNI classification, n (%)						
Low (PNI >38)	919 (98.2)	43 (86.0)	268 (97.8)	230 (99.1)	378 (99.5)	< 0.001§
Middle (PNI 35–38)	10 (1.1)	3 (6.0)	3 (1.1)	2 (0.9)	2 (0.5)	
High (PNI <35)	7 (0.7)	4 (8.0)	3 (1.1)	0	0	
NYHA Class III, n (%)	66 (7.0)	10 (20.0)*	18 (6.5)	16 (6.8)	22 (5.8)	0.028
Medical history, n (%)						
Diabetes	447 (47.6)	17 (34.0)	115 (41.8)	114 (48.7)	201 (52.8)*	< 0.001
Dyslipidemia	489 (52.0)	22 (44.0)	134 (48.7)	119 (50.9)	214 (56.2)	0.02 5
Ischemic heart disease	462 (49.1)	20 (40.0)	129 (46.9)	123 (52.6)	190 (49.9)	0.22
Cardiomyopathy	238 (25.3)	14 (28.0)	71 (25.8)	58 (24.8)	95 (24.9)	0.66
Atrial fibrillation	391 (41.6)	22 (44.0)	117 (42.5)	99 (42.3)	153 (40.2)	0.47
LV function						
HF phenotype						
HFrEF (EF ≤40%)	160 (17.1)	12 (24.0)	50 (18.3)	46 (19.7)	52 (13.8)	0.038
HFmrEF (EF >40 & <50%)	174 (18.6)	8 (16.0)	48 (17.6)	39 (16.7)	79 (20.9)	0.22
HFpEF (EF ≥50%)	601 (64.3)	30 (60.0)	17 5 (64.1)	149 (63.7)	247 (65.3)	0.53
LVEF (%)	54.9 (14.6)	52.5 (15.6)	54.4 (15.4)	54.1 (14.4)	56.1 (14.0)	0.08
LVDd (mm)	53.1 (8.7)	49.5 (9.2)	52.3 (8.6)	53.4 (8.3)	53.9 (8.8)	< 0.001
LVDs (mm)	37.8 (10.5)	34.9 (11.7)	37.5 (10.6)	38.5 (10.1)	38.1 (10.4)	0.11
LAD (mm)	42.90 (8.18)	39.6 (9.3)	41.9 (8.6)	42.6 (7.0)	44.2 (8.2)*	< 0.001
E/A	0.96 (0.62)	0.89 (0.46)	0.96 (0.62)	1.03 (0.80)	0.94 (0.51)	0.282
Laboratory values						
Albumin (g/dL)	4.2 (0.4)	4.0 (0.6)*	4.2 (0.4)	4.2 (0.4)	4.3 (0.4)*	< 0.001
eGFR (mL/min per 1.73m^2)	65 (19)	65 (20)	65 (21)	65 (18)	65 (18)	0.97
Hemoglobin (g/L)	13.8 (1.7)	12.0 (1.6)*	13.4 (1.7)	13.9 (1.5)*	14.3 (1.7)*	< 0.001
HbA1c (%)	5.9 (1.0)	5.7 (0.7)	5.8 (1.0)	5.9 (0.8)	6.0 (1.0)*	< 0.001
NT-proBNP (pg/mL)	361 [143–847]	1056 [448–2086]*	460 [182–963]	359 [120–810]	279 [115–651]*	<0.001
GDF15 (pg/mL)	1219 [876–1793]	1764 [1067-2633]*	1226 [855–1916]	1228 [890–1743]	1183 [857–1661]	0.038
Medications at baseline, n (%)						
ARB (olmesartan; trial drug)	46 5 (49.5)	27 (54.0)	13 5 (49.1)	121 (51.7)	182 (47.8)	NA
ACEi	763 (81.2)	42 (84.0)	212 (77.1)	190 (81.2)	319 (83.7)	0.11
Beta blocker	670 (71.3)	38 (76.0)	206 (74.9)	163 (69.7)	263 (69.0)	0.08
Diuretic	513 (54.6)	35 (70.0)	148 (53.8)	124 (53.0)	206 (54.1)	0.29
Statin	469 (49.9)	20 (40.0)	127 (46.2)	116 (49.6)	206 (54.1)	0.020

For continuous variables, the mean (SD) and median [IQR] are presented for normally and non-normally distributed variables, respectively.
Abbreviations: ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor antagonist; BMI, body mass index; BP, blood pressure; BSA, body surface area; CONUT, controlling nutrition status; eGFR, estimated glomerular filtration rate; GDF-15, growth differential factor − 15; GNRI, geriatric nutritional risk index; HbA1c, hemoglobin A1c; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hsCRP, high sensitive C-reactive protein; hsTnT, high sensitive troponin T; IQR, inter quartile range; LAD, left atrial

dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVDs, left ventricular end-systolic dimension; NA, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PNI, prognostic nutritional index.

* *p*-values <0.05 when compared with the healthy weight group using Tukey or Steel test.

§ *p*-value indicates the significance of comparison between the prevalence of moderate and high categories vs. normal and low categories.

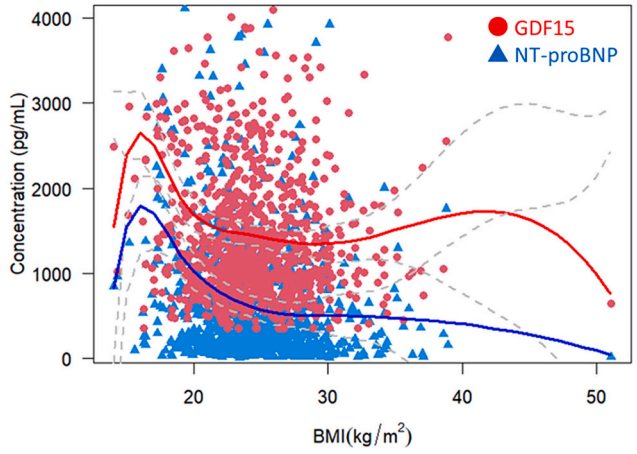

Fig. 1. GDF15 levels at baseline across the continuous BMI spectrum.
NT-proBNP level is also given for reference.

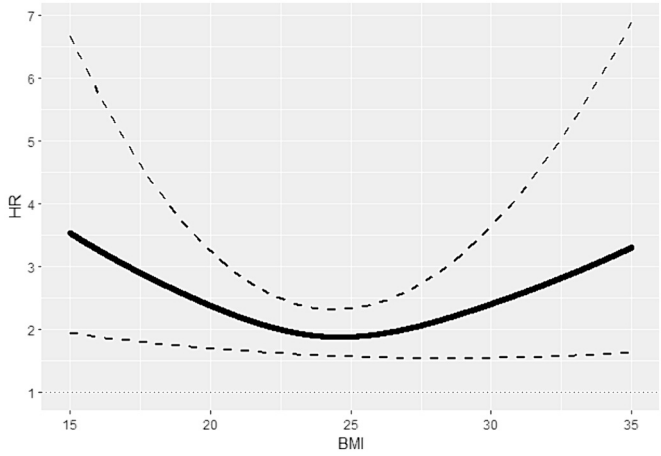

Fig. 2. The risk of HF hospitalization or all-cause death per log-unit increase in GDF15 levels across the BMI spectrum.
Presenting the hazard ratio of the study endpoint per log-unit increase in GDF15 level across the continuous BMI spectrum modelled using cubic spline Cox regression. The model was adjusted for age, sex, NYHA class, history of diabetes, atrial fibrillation, intervention group (olmesartan vs. no olmesartan), LVEF, eGFR, and lnNT-proBNP.

the baseline, 585 patient data were studied for the landmark analysis. The cumulative incidence of the study endpoint after 3 years was particularly higher for patients with persistently very high GDF15 levels, high GDF15 levels, and escalated GDF15 levels over 3 years (**Supplemental Fig. 6**). Persistently very high GDF15 levels or high GDF15 levels over 3 years were associated with a greater risk of study endpoint after 3 years, independent of age, sex, diabetes, atrial fibrillation, intervention group, NYHA class, BMI, LVEF, eGFR, and lnNT-proBNP at 3 years compared to maintained normal GDF15 levels (adjusted HR 1.81 [95%CI 1.13–2.91] and 2.04 [1.25–3.32], respectively) (Table 2).

4. Discussion

GDF15 belongs to a superfamily of transforming growth factor β, known for its overexpression under cellular stress induced by inflammation, oxidative stress, tissue hypoxia, and injury [4]. In patients with HF, GDF15 level, unlike that of natriuretic peptides, is consistently elevated irrespective of HF phenotype and is linked to adverse outcomes [18]. This implies that GDF15 may serve as an indicator of the pathogenesis of HF beyond ventricular function or loading conditions. While HF is recognized as a progressive syndrome with multifactorial origins involving nutritional and metabolic factors, GDF15 is expected to play a pivotal role in reflecting non-cardio-specific entities, possibly useful for a long-term management of HF.

A recent study suggested that GDF15 is agnostic to temporal energy balance, such as short-term overconsumption or fasting, but instead mirrors chronic, long-term nutritional disturbances [6]. In the present study, a significant proportion of patients, particularly those classified as underweight with lower GNRI, exhibited substantial nutritional risk, indicating a persistent nutritional deficit, accompanied by a substantial elevation in GDF15 level.

In the present study, the limited number of patients with BMI >30 kg/m^2 may have reduced the statistical power to precisely describe GDF15 level in extremely obese patients with chronic HF. Yet, the distribution of GDF15 level across the continuous BMI spectrum suggests a distinctive pattern that is different from that of NT-proBNP in chronic HF. The absence of the "obesity-survival paradox" when accounting for possible confounding factors indicates comparable adverse risk in obese patients (relative to healthy weight patients). A universal prognostic significance found across the continuous BMI spectrum further indicates that GDF15 is a valuable biomarker in HF for risk stratification, regardless of BMI.

The overall increase in GDF15 level over time was consistent with the previous report from the secondary analysis of the Val-HeFT trial [19]. Yet, inconsistency remains regarding the impact of guideline-directed medical therapy (GDMT) on trajectories of GDF15 level in HF. In the PARADIGM-HF trial, neither the sacubitril/valsartan nor enalapril group increased GDF15 level at 8 months despite positive results in reducing the risk of adverse outcomes [20]. Conversely, the secondary analysis of the Empire HF trial reported a greater increase in plasma GDF15 level in the empagliflozin arm compared to the placebo arm [21]. Possible explanations of these discrepancies in response to HF therapies may be rooted in diversities in patient characteristics and trial designs (targeted patients and study period), as well as differences in pharmacological actions of each HF therapy. While a reduction in NT-proBNP accompanies the clinical benefit of most of these therapies, this inconsistency also suggests multifaceted pathophysiological involvement of GDF15 beyond cardio-specific entities, possibly providing a more long-term, general and systematic conditions of HF.

Besides being a biomarker, GDF15 is known as a physiological regulator of energy metabolism based on findings of decreased body weight and progressive cachexia in GDF15-administered mice [22]. GDF15 mediates the GDNF-family (GRFAL) receptor in the hindbrain resulting in reduced food intake. [23,24] A significant association between elevated GDF15 level and weight loss in cancer-modelled mice suggests the anorexigenic effect of GDF15 in its advanced stage [22]. In the present study, we showed that patients with long-term exposure to very high GDF15 levels over 3 years had a 2.2% reduction in BMI and 0.6% reduction in GNRI (i.e. increased nutritional risk), which was not observed in other transitional groups of GDF15 levels. Prospective studies are needed to determine the impact of long-term exposure to elevated GDF15 levels on progressive cachexia and cardiac deterioration.

In the present study, we demonstrated that patients with persistently elevated GDF15 levels faced a higher risk of HF hospitalization or all-cause death, irrespective of their age, sex, NYHA class, history of

Table 2
Transitional groups of GDF15 levels and the risk of HF hospitalization or all-cause death after 3 years. (landmark analysis).

			Unadjusted model		Adjusted model 1		Adjusted model 2	
GDF15 levels over 3 years	Number of patients	Number of events (incident rate)	HR [95%CI]	P-value	HR [95%CI]	P-value	HR [95%CI]	P-value
Persistently very high	108	68 (12.9)	3.98 [2.77–5.72]	< 0.001	2.26 [1.42–3.59]	< 0.001	1.81 [1.13–2.91]	0.013
Persistently high	72	37 (8.6 5)	2.65 [1.74–4.04]	< 0.001	2.09 [1.29–3.39]	0.003	2.04 [1.25–3.32]	0.005
Escalated	170	77 (7.44)	2.28 [1.60–3.24]	< 0.001	1.79 [1.20–2.67]	0.004	1.48 [0.98–2.23]	0.064
Improved	19	5 (3.74)	1.13 [0.45–2.84]	0.790	0.57 [0.17–1.85]	0.347	0.66 [0.20–2.16]	0.492
Maintained Normal	216	52 (3.30)	Ref	Ref	Ref	Ref	Ref	Ref

Incident rate presented per 100 person-years.
Adjusted model 1; adjusted for age, sex, NYHA class, diabetes, atrial fibrillation, intervention group (olmesartan vs. no olmesartan) at baseline, BMI, LVEF, and eGFR at 3 years.
Adjusted model 2; adjusted for variables in Adjusted model 1 + lnNT-proBNP at 3 years.

diabetes, BMI, LVEF, or NT-proBNP. The causality of the observed reduction in BMI and increased nutritional risk over time in patients with persistently elevated GDF15 remains inconclusive, but an ongoing clinical trial evaluating the efficacy and safety of a GDF15 antibody in patients with HF and signs of cachexia (GARDEN TIMI-74, NCT05492500) may provide further insights into the clinical utility of GDF15 in advanced HF and also help to understand its impact on body weights and nutritional status.

The present study has several limitations. The number of patients with obesity, particularly those with BMI >30 kg/m^2 was small in this cohort. Furthermore, the number of events was relatively small in the underweight group, which may have led to statistical insufficiency in the time-to-event analysis. Other anthropometric measurements, such as waist-to-height ratio, relative fat mass, and body roundness, indices that are known to robustly reflect intra-abdominal fat, may be more useful for describing the distribution of GDF15 level across the extent of adiposity but they were not available in this study. Collective data on the intentional use of mineralocorticoid receptor antagonist (MRA) for its antinurohormonal response were not available in the present study. Importantly, the present analysis lacked objective evidence for signs of cachexia. Despite our effort to describe the nutritional status using GNRI, we acknowledge that being underweight does not necessarily indicate that such patients are being truly cachectic. Additionally, the present results may be prone to selection and survival biases as patients subjected to the landmark analysis were limited to those with sufficient data at 3 years. Lastly, it is important to stress that the criteria used in the SUPPORT trial for the diagnosis of HF are different from the currently recommended diagnostic flow.

5. Conclusions

In chronic HF, GDF15 levels were higher in patients with lower BMI and greater nutritional risk. Its prognostic significance extended across BMI categories. Over 3 years, GDF15 level increased, particularly to a greater extent in underweight patients. Persistent elevation of GDF15 level predicted a higher risk of HF hospitalization or death. GDF15 level may serve as a useful biomarker, offering more comprehensive insights into HF management.

CRediT authorship contribution statement

Kanako Teramoto: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kotaro Nochioka:** Supervision, Project administration, Funding acquisition, Data curation. **Yasuhiko Sakata:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Eri Toda Kato:** Writing – review & editing. **Kunihiro Nishimura:** Writing – review & editing, Project administration. **Hiroaki Shimokawa:** Writing – review & editing, Project administration, Funding acquisition. **Satoshi Yasuda:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

H.S. has received lecture fees from Bayer Yakuhin, Ltd. (Osaka, Japan) and Daiichi Sankyo Co., Ltd. (Tokyo, Japan). ETK received lecture fees from Bayer Yakuhin, Ltd. outside of the current work. The remaining authors have nothing to disclose.

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Appendix A. Supplementary data

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