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ORIGINAL ARTICLE

Prognostic significance of growth differentiation factor-15 across age in chronic heart failure

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Abstract

Aims Growth differentiation factor-15 (GDF15), a cytokine in the transforming growth factor family, is up-regulated in stress and inflammatory conditions and is elevated in patients with heart failure (HF). However, the age-specific attributes and prognostic significance of GDF15 across age remain unknown in chronic HF (CHF).

Methods and results Serum levels of GDF15 were examined in 942 hypertensive patients (median 68 years) with CHF from the SUPPORT trial across the four age groups [under 50 (n = 73), 51–59 (n = 158), 60–69 (n = 296), and 70–79 years (n = 415)] and in the continuous spectrum. Clinical correlates of GDF15 were explored using the classic stepwise and LASSO (least absolute shrinkage and selection operator) regression approaches. Interaction terms with age were tested in the LASSO regression approach. The associations with the composite outcome of HF hospitalization or all-cause death were investigated across ages. Median GDF15 levels (pg/mL) increased along with aging, from 691 in under 50 years to 855 in 51–59 years, 1114 in 60–69 years, and 1516 in 70–79 years (trend $P < 0.001$). Age, sex, systolic blood pressure, history of diabetes, ischaemic heart disease, left ventricular (LV) end-systolic dimension, LV ejection fraction, estimated glomerular filtration rate, haemoglobin, N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin, C-reactive protein, and the use of angiotensin-converting enzyme inhibitors, diuretics, and statins were mutually selected as clinical covariates of GDF15. The LASSO regression analysis identified significant interactions between age and the history of diabetes and NT-proBNP, with particularly robust associations in patients aged between 60 and 70 years. During the mean follow-up of 8.6 years, 474 composite endpoints of HF hospitalization or death occurred. GDF15 was associated with a higher risk of HF hospitalization or all-cause death [adjusted hazard ratio 1.84 (95% confidence interval 1.45–2.33)], with a particularly heightened risk in patients aged around 70 years ($P_{\text{interaction}}$ = 0.0008). The model with GDF15 on top of other established risk factors yielded marginally higher C-statistics compared with the model without GDF15 (0.803 and 0.796, P = 0.045). The additive value of GDF15 on top of other established risk factors appeared similar across ages. A universal cut-off value of 1400 pg/mL performed well in discriminating between those with and without HF hospitalization or death.

Conclusions Some clinical correlates of GDF15 have an interaction with age. GDF15 is an important determinant of cardiovascular endpoints, particularly in patients aged around 70 years. The additive value of GDF15 appeared consistent across ages, suggesting the use of a universal cut-off value.

Keywords Growth differentiation factor-15; Heart failure; Cardiovascular events; Aging biomarker

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Introduction

Growth differentiation factor-15 (GDF15) is a member of the transforming growth factor beta superfamily known to be up-regulated in response to oxidative stress, tissue injury, and subsequent inflammation.[1] Previous studies suggested robust associations between GDF15 and a variety of diseases, including heart failure (HF), cancer, cognitive decline, pulmonary diseases, diabetes, and renal disease.[2–6] Its remarkable cardioprotective properties[7] and prognostic significance in patients with HF has promoted extensive investiagtions on clinical application as a biomarker.[8]

GDF15 has also been characterized as a biomarker of aging.[9,10] Its levels increase with aging in healthy individuals.[11,12] Because age serves as a non-modifiable confounding factor in all cardiovascular diseases, it is difficult to discern whether the overexpression of GDF15 and its prognostic significance are more reflective of chronological aging or disease state in patients with chronic HF (CHF). Although most previous studies accounted for patient age in their statistical modelling, it is uncertain if the prognostic significance of GDF15 persists to a similar extent across a wide age spectrum. Given that HF encompasses a myriad of biological pathways signified by various risk factors and biomarkers across a wide range of ages, the present study was designed to explore the clinical correlates and prognostic significance of GDF15 across the age spectrum of patients from the SUPPORT (supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan) trial.[13,14]

Methods

Patient population

The rationale, designs, and results of the SUPPORT trial have been previously described.[13,14] In brief, the SUPPORT trial was a prospective, randomized, open-label blinded endpoint study performed in 17 participating institutions in the Tohoku District of Japan. The trial examined the incremental benefit of olmesartan in hypertensive patients with stable HF treated with angiotensin-converting enzyme (ACE) inhibitors and/or beta-blockers. From October 2006 to March 2010, the trial enrolled a total of 1147 patients aged between 20 and 80 years. Patients 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 of HF without the use of any angiotensin receptor antagonists in a 1:1 ratio, and they were followed for incidence of cardiovascular endpoints. Baseline characteristics were obtained at the time of enrolment. The trial adheres to the ethical principles described in the Declaration of Helsinki, and all participants provided written informed consent.

In the present post hoc study of the SUPPORT trial, a total of 1044 patients with baseline GDF15 levels at enrolment were studied. Patients were categorized into four age groups: under 50, 50–59, 60–69, and 70–79 years. Demographic and clinical data collected by an anamnestic interview, physical examination, standardized transthoracic echocardiography, and laboratory examinations performed at the time of enrolment were used for analysis.

Biomarker measurements

N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity troponin T, and GDF15 were retrospectively measured using the blood samples collected and stored at the time of enrolment. Samples collected at enrolment were stored below −20°C at all times. Biomarkers were measured with an electrochemiluminescence sandwich immunoassay using a Cobas analyser (Roche Diagnostics, Indianapolis, IN, USA). The measuring range of GDF15 was between 400 and 20 000 pg/mL. The internal precision assessed with coefficients of variation for repeatability and intermediate precision provided by the vendor were between 1.1–1.4% and 1.8–2.3%, respectively.

Study endpoints

The primary endpoint of the present study was the composite of HF hospitalization or all-cause death. The secondary endpoint was the composite of all-cause death, HF hospitalization, non-fatal myocardial infarction, or non-fatal stroke, namely, the major adverse cardiac events (MACE). The outcome events were adjudicated by the Endpoint Evaluation Committee, which consisted of two cardiologists and neurologists.

Statistical analysis

Baseline characteristics of patients are presented as means ± standard deviations for normally distributed variables and medians with 25th and 75th percentiles for non-normally distributed variables. For categorical variables, the number of patients with percentages is reported. The elevated GDF15 level was defined as ≥1200 pg/mL based on the previous literature,[15,16] and its proportion in each age group is presented. Comparisons of covariates across the age groups were examined using the Kruskal–Wallis test. The χ^2 test was used for categorical variables.

Two statistical approaches were employed to identify the clinical correlates of GDF15. As a standard approach, a multivariable linear regression with a bidirectional, AIC (Akaike in-

formation criteria)-based stepwise variable selection approach was used to determine the clinical correlates of GDF15 in overall and each age group (the *stepAIC* function from the *MASS* package in R). Candidates for clinical correlates included age, sex, body mass index (BMI), New York Heart Association (NYHA) class, heart rate, systolic blood pressure, diastolic blood pressure, history of diabetes, dyslipidaemia, ischaemic heart disease, cardiomyopathy, atrial fibrillation, left ventricular (LV) diastolic and systolic dimensions, LV ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), haemoglobin, haemoglobin A1c, the use of ACE inhibitors, beta-blockers, diuretics, and statins, NT-proBNP, troponin, and high-sensitivity C-reactive protein (hsCRP) (all data at enrolment). Using the same covariates, an advanced variable selection approach using LASSO (least absolute shrinkage and selection operator) regression was used to identify the clinical correlates of GDF15 across the continuous age spectrum as a supplemental analysis. The LASSO regression is a prediction modelling approach suited for identifying a parsimonious set of predictor variables using a regularization technique. Candidates for clinical correlates were first examined for their independent associations with GDF15 and further tested for interactions with continuous age.

Multivariable Cox proportional hazard models adjusted for commonly selected covariates from both the stepwise and LASSO regression approaches were used to determine the risk of study endpoints in overall patients. The interaction term between age and GDF15 was tested in the adjusted model. The associations between GDF15 and study endpoints are demonstrated using cubic spline regression. Statistical indices of C-statistics [area under the curve–receiver operating characteristic curve (AUC–ROC)], likelihood ratio, and R^2 are presented across the prediction models of the study endpoints. Demographic variables included age, sex, BMI, NYHA class, systolic blood pressure, diastolic blood pressure, history of diabetes, ischaemic heart disease, end-systolic LV diameter, LVEF, eGFR, haemoglobin, and the use of ACE inhibitors, beta-blockers, diuretics, and statins. The biomarker adjustments were made with log-transformed concentrations of NT-proBNP, troponin, and CRP. The C-statistics (AUC–ROC) comparisons were performed with DeLong's test, and the log likelihood was tested with the likelihood ratio test. The estimated differences in the probabilities of study endpoints between models with and without GDF15 on top of demographics and other biomarkers are demonstrated across the continuous age spectrum. The optimal cut-off values of GDF15 for discriminating between those with and without study endpoints during the follow-up period were estimated based on maximally selected rank statistics in the overall patients. The risks of study endpoints were examined by the determined cut-off level in a Cox regression model adjusted for demographics and other biomarkers. All statistical analyses were performed using R (4.3.2), and the functions and packages used are explained in the supporting information. A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of the patients are presented in *Table 1*. The median age was 68 years, and 26% were female. Younger patients aged <50 years had the highest BMI and a high prevalence of dyslipidaemia. In these younger patients, fewer patients had a history of ischaemic heart disease, while the prevalence of cardiomyopathy was the highest across the age groups. In patients aged above 60 years, nearly half of the patients had a history of diabetes. The history of ischaemic heart disease exceeded 50% in age groups beyond 60 years. Although their renal function and haemoglobin levels were lower than those of patients aged below 60 years, they remained relatively preserved. The use of ACE inhibitors and beta-blockers was the lowest in patients aged over 70 years. No statistically significant differences were found for patients with NYHA class III across the age groups. HF phenotypes defined by LVEF were not different across the age groups, with 64% of those having HF with preserved ejection fraction (LVEF $\geq$ 50%) in overall patients. Serum levels of NT-proBNP, troponin, and GDF15, but not those of hsCRP, increased along with aging (*Figure 1*). The proportion of patients with higher GDF15 levels [above the established upper limit of normal (1200 pg/mL)] was 51% in overall patients and was the highest in patients in their 70s across the age groups (72%, $P < 0.001$). The correlations between the biomarkers and age were the strongest for GDF15 (Rho = 0.50) compared with NT-proBNP, troponin, and hsCRP (Supporting Information, *Table S1*; Rho = 0.25, 0.28, and 0.05, respectively).

Clinical correlates of growth differentiation factor-15 across the age groups

The AIC-based stepwise approach identified age, sex, systolic blood pressure, history of diabetes, dyslipidaemia, ischaemic heart disease, LV end-diastolic and end-systolic diameters, LVEF, eGFR, haemoglobin, NT-proBNP, troponin, CRP, and the use of ACE inhibitors, diuretics, and statins as clinical covariates of GDF15 in overall patients (*Table 2*). The LASSO regression analysis also selected most of these covariates as clinical correlates of GDF15 that are independent of age (Supporting Information, *Table S2*, left column). Sex, systolic blood pressure, history of diabetes, ischaemic heart disease, LV end-systolic dimension, LVEF, eGFR, haemoglobin, NT-

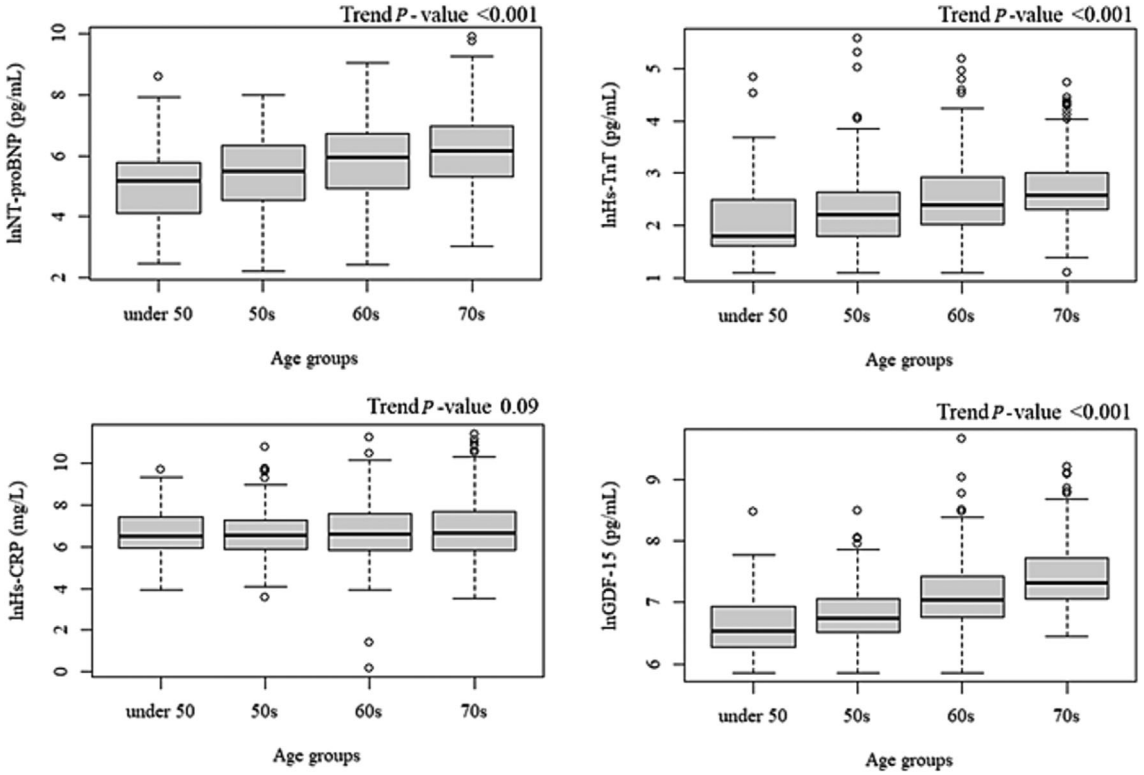
Table 1 Baseline characteristics in overall and age groups

Baseline characteristics	Overall	Age groups				*P*-value
		Under 50 years	50–59 years	60–69 years	70–79 years	
N	942	73 (7.7%)	158 (16.8%)	296 (31.4%)	415 (44.1%)	-
Demographics						
Age (years), median [Q1, Q3]	68.0 [60, 74]	44 [39, 47]	56 [54, 58]	65.5 [63, 80]	75 [72, 77]	NA
Female, *n* (%)	243 (25.8)	13 (17.8)	31 (19.6)	78 (26.4)	121 (29.2)	0.007
BMI (kg/m^2), median [Q1, Q3]	24.2 [22.1, 26.7]	26.2 [23.9, 29.4]	24.6 [21.6, 27.1]	24.2 [22.3, 26.2]	23.8 [21.7, 26.1]	<0.001
NYHA class III, *n* (%)	66 (7.0)	4 (5.5)	8 (5.1)	16 (5.4)	38 (9.2)	0.152
Heart rate (b.p.m.), median [Q1, Q3]	70 [62, 79]	71 [62, 80]	69 [60, 77]	69 [62, 80]	70 [61, 79]	0.631
Systolic BP (mmHg), median [Q1, Q3]	129 [116, 140]	129 [117, 140]	127 [112, 139]	130 [116, 140]	128 [116, 142]	0.511
Diastolic BP (mmHg), median [Q1, Q3]	73 [67, 81]	77 [70, 88]	75 [70, 83]	74 [68.0, 83.0]	70 [65, 79]	<0.001
Medical history, *n* (%)						
Diabetes	449 (47.7)	28 (38.4)	73 (46.2)	147 (49.7)	201 (48.4)	0.356
Dyslipidaemia	490 (52.0)	33 (45.2)	82 (51.9)	172 (58.1)	203 (48.9)	0.061
Ischaemic heart disease	464 (49.3)	18 (24.7)	52 (32.9)	160 (54.1)	234 (56.4)	<0.001
Cardiomyopathy	240 (25.5)	31 (42.5)	62 (39.2)	71 (24.0)	76 (18.3)	<0.001
Atrial fibrillation	391 (41.5)	9 (12.3)	67 (42.4)	126 (42.6)	189 (45.5)	<0.001
LV function						
HF phenotype						0.108
HFrEF (EF ≤ 40%)	161 (17.2)	16 (21.9)	25 (15.9)	54 (18.4)	66 (16.0)	
HFmrEF (EF > 40% and EF < 50%)	174 (18.6)	13 (17.8)	42 (26.8)	49 (16.7)	70 (16.9)	
HFpEF (EF ≥ 50%)	602 (64.2)	44 (60.3)	90 (57.3)	191 (65.0)	277 (67.1)	
LVDd (mm), median [Q1, Q3]	52.0 [47.0, 58.8]	55.7 [48.0, 61.0]	54.0 [48.0, 59.0]	53.0 [47.0, 59.0]	51.0 [46.0, 58.0]	0.007
LVDs (mm), median [Q1, Q3]	36.3 [30.0, 44.0]	37.9 [31.0, 48.3]	39.0 [31.6, 45.0]	36.5 [30.0, 44.0]	35.3 [29.3, 43.0]	0.063
LVEF (%), median [Q1, Q3]	56.0 [45.0, 66.0]	55.0 [43.0, 66.0]	51.5 [44.0, 63.1]	56.0 [45.0, 65.3]	57.0 [46.6, 66.8]	0.276
Laboratory values						
eGFR (mL/min/1.73 m^2), median [Q1, Q3]	64.1 [52.4, 75.4]	76.1 [64.7, 90.4]	76.8 [61.8, 88.9]	65.7 [53.9, 75.4]	57.3 [47.0, 71.5]	<0.001
Haemoglobin (g/L), median [Q1, Q3]	13.8 [12.8, 15.0]	14.8 [13.7, 15.7]	14.7 [13.7, 15.6]	14.1 [13.0, 15.2]	13.3 [12.3, 14.4]	<0.001
HbA1c (%), median [Q1, Q3]	5.7 [5.3, 6.2]	5.5 [5.2, 6.1]	5.6 [5.3, 6.5]	5.6 [5.3, 6.2]	5.7 [5.4, 6.2]	0.435
NT-proBNP (pg/mL), median [Q1, Q3]	361 [142, 848]	178 [60, 327]	244 [94, 553]	379 [136, 840]	480 [202, 1048]	<0.001
Troponin (pg/mL), median [Q1, Q3]	0.012 [0.007, 0.018]	0.006 [0.005, 0.012]	0.009 [0.006, 0.014]	0.011 [0.008, 0.018]	0.013 [0.010, 0.020]	<0.001
hsCRP (mg/L), median [Q1, Q3]	757 [348, 1840]	673 [378, 1660]	696 [363, 1403]	731 [339, 2003]	794 [345, 2215]	0.435
GDF15 (pg/mL), median [Q1, Q3]	1219 [876, 1794]	691 [531, 1026]	855 [675, 1158]	1114 [865, 1671]	1516 [1163, 2275]	<0.001
Elevated GDF15 (≥1200 pg/mL) (%), *n* (%)	479 (51.1)	10 (13.7)	36 (22.9)	138 (46.8)	295 (71.6)	<0.001
Medications at baseline, *n* (%)						
ARB (olmesartan)*	466 (50%)	34 (46.6)	66 (41.8)	159 (53.7)	269 (49.9)	0.104
ACE-I	765 (81.2)	65 (89.1)	136 (86.1)	240 (81.1)	324 (78.1)	0.045
Beta-blocker	671 (71.2)	65 (89.0)	112 (70.9)	224 (75.7)	270 (65.1)	<0.001
Diuretic	515 (54.7)	39 (53.4)	91 (57.6)	159 (53.7)	226 (54.5)	0.871
Statin	470 (49.9)	31 (42.5)	79 (50.0)	168 (56.8)	192 (46.3)	0.025

For continuous variables, the mean (standard deviation) and median [interquartile range] are presented for normally and non-normally distributed variables, respectively. Comparison across the age groups were examined using the Kruskal-Wllist tests. *Olmesartan was the study medication in the SUPPORT trial.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GDF15, growth differentiation factor-15; HbA1c, haemoglobin 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-sensitivity C-reactive protein; LV, left ventricular; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; NA, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

Figure 1 Levels of biomarkers across the age groups. GDF15, growth differentiation factor-15; hsCRP, high-sensitivity C-reactive protein; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide.



proBNP, troponin, CRP, and the use of ACE inhibitors, diuretics, and statins were mutually selected in both approaches. In the stepwise approach, eGFR, haemoglobin, and troponin remained significant correlates across all age groups, while other covariates correlated differently with GDF15 across the age groups (*Table 2*). For example, in patients aged <50 years, increased BMI and a higher prevalence of diabetes were strong additional correlates of GDF15. In middle-aged patients aged 50–59 and 60–69, history of comorbidities such as diabetes, ischaemic heart disease, and dyslipidaemia positively correlated with GDF15. Reduced LV end-systolic dimension and LVEF were associated with increased GDF15 in these groups of patients. In patients aged 70–79 years, the use of diuretics and/or statins appeared as key determinants of GDF15 in addition to robust associations with eGFR and haemoglobin. The LASSO regression analysis, including the interaction terms with continuous age, identified two covariates as correlates of GDF15 with interaction by age: the history of diabetes and NT-proBNP (Supporting Information, *Table S2*, right column). On the continuous age spectrum, the associations between GDF15 and the history of diabetes and NT-proBNP were particularly robust in patients aged between 60 and 70 years (*Figure 2*).

Associations with study endpoints across the age groups

During the mean follow-up of 8.6 years (25th–75th percentiles 5.9–11.5 years), a total of 474 primary endpoints (the composite of HF hospitalization and all-cause death) and 517 secondary endpoints (MACE; all-cause death, HF hospitalization, non-fatal myocardial infarction, or non-fatal stroke) occurred. In overall patients, the highest GDF15 tertile (median 2236 pg/mL, 25th–27th percentiles 1797–2800 pg/mL) had a significantly increased risk of the primary and secondary endpoints compared with the lowest tertile of GDF15 {hazard ratio [HR] 3.79 [95% confidence interval (CI) 2.98–4.80], $P < 0.001$, and HR 3.32 [95% CI 2.65–4.16], $P < 0.001$, respectively}. GDF15 on the continuous spectrum was also associated with both study endpoints in the fully adjusted model with demographic and clinical correlates identified earlier [*Table 3*; HR 1.84 (95% CI 1.45–2.33) and HR 1.59 (95% CI 1.26–2.01), respectively]. There was a significant interaction by age on associations between GDF15 and study endpoints ($P_{interaction}$ = 0.0008 and 0.0003, respectively). On the continuous age spectrum, the association between GDF15 and outcomes was significant in patients aged 55–60 years or older. The associations between GDF15 and the

Table 2 Clinical correlates of GDF15 across age groups (based on stepwise approach)

	Overall		Age groups							
			Under 50 years		50–59 years		60–69 years		70–79 years	
Covariates	β [SE]	*P*-value	β [SE]	*P*-value	β [SE]	*P*-value	β [SE]	*P*-value	β [SE]	*P*-value
Age	**7.8 [3.4]**	**0.025**	-	-	20.4 [15.0]	0.175	-	-	-	-
Sex (female)	−148.2 [77.1]	0.055	−263.1 [149.1]	0.083	−173.7 [118.0]	0.143	-	-	-	-
BMI	-	-	**28.5 [11.4]**	**0.015**	-	-	**−48.8 [15.2]**	**0.001**	−20.1 [14.4]	0.164
NYHA class III	-	-	-	-	**538.6 [178.5]**	**0.003**	-	-	-	-
Heart rate	-	-	-	-	3.6 [2.7]	0.182	-	-	-	-
Systolic BP	**−4.4 [1.8]**	**0.011**	−7.9 [4.1]	0.057	-	-	**−11.4 [4.2]**	**0.008**	-	-
Diastolic BP	-	-	−7.6 [5.8]	0.197	**−9.8 [3.3]**	**0.004**	**15.7 [6.4]**	**0.014**	-	-
Diabetes	**218.3 [61.2]**	**<0.001**	**342.6 [120.3]**	**0.006**	151.0 [88.7]	0.091	**399.2 [109.0]**	**<0.001**	**204.7 [98.7]**	**0.039**
Dyslipidaemia	**530.8 [208.2]**	**0.011**	-	-	-	-	**1379.3 [473.0]**	**0.004**	-	-
Ischaemic heart disease	**186.3 [70.4]**	**0.008**	-	-	**186.6 [93.4]**	**0.048**	-	-	-	-
Cardiomyopathy	-	-	-	-	-	-	-	-	**−267.0 [125.9]**	**0.035**
Atrial fibrillation	-	-	-	-	**189.5 [89.8]**	**0.037**	-	-	**−262.4 [108.8]**	**0.016**
LVDd (mm)	**66.0 [12.7]**	**<0.001**	**−50.6 [24.7]**	**0.045**	35.1 [19.4]	0.073	**155.1 [20.3]**	**<0.001**	**−15.4 [6.1]**	**0.012**
LVDs (mm)	**−112.7 [16.4]**	**<0.001**	70.2 [37.0]	0.063	**−55.2 [25.6]**	**0.033**	**−220.1 [25.4]**	**<0.001**	-	-
LVEF (%)	**−41.3 [6.4]**	**<0.001**	25.8 [15.9]	0.111	**−20.9 [10.0]**	**0.040**	**−78.0 [10.2]**	**<0.001**	-	-
eGFR (mL/min/1.73 m^2)	**−13.2 [1.8]**	**<0.001**	**−14.1 [2.8]**	**<0.001**	**−4.7 [2.2]**	**0.030**	**−9.1 [3.1]**	**0.003**	**−22.7 [3.3]**	**<0.001**
Hb (g/L)	**−126.4 [19.6]**	**<0.001**	**−198.6 [40.7]**	**<0.001**	**−61.8 [29.7]**	**0.004**	**−97.2 [32.3]**	**0.002**	**−99.5 [31.4]**	**0.002**
HbA1c (%)	-	-	-	-	47.3 [34.0]	0.166	-	-	-	-
lnNT-proBNP (pg/mL)	**74.6 [30.9]**	**0.016**	**-**	**-**	**-**	**-**	80.9 [54.2]	0.137	89.8 [54.0]	0.097
lnTroponin (ng/mL)	**329.3 [53.5]**	**<0.001**	**197.1 [73.7]**	**0.009**	**215.6 [55.8]**	**<0.001**	**504.5 [94.5]**	**<0.001**	**272.4 [98.1]**	**0.006**
lnhsCRP (mg/L)	**79.2 [22.8]**	**<0.001**	**-**	**--**	60.0 [34.5]	0.084	-	-	**111.7 [35.1]**	**0.002**
ACE-I	**−128.5 [76.5]**	**0.094**	-	-	-	-	-	-	-	-
Beta-blocker	-	-	-	-	**193.9 [89.0]**	**0.031**	-	-	-	-
Diuretic	**258.7 [68.5]**	**<0.001**	−214.1 [124.9]	0.092	-	-	**271.4 [124.4]**	**0.030**	**366.3 [105.7]**	**<0.001**
Statin	**−669.2 [207.9]**	**0.0001**	-	-	-	-	**−1403.0 [469.2]**	**0.003**	**−256.7 [99.4]**	**0.010**

This table presents the β [SE] and *P*-values of the final linear regression model with a stepwise approach in overall and each age group. - indicates variables that were not included in the final model. Bold indicates statistically significant findings.

ACE-I, angiotensin-converting enzyme inhibitor; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HbA1c, haemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

[a]Olmesartan was the study medication in the SUPPORT trial.

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Figure 2 Coefficient estimates for the (A) history of diabetes mellitus (DM) and (B) N-terminal pro-brain natriuretic peptide (NT-proBNP) across the age spectrum. GDF15, growth differentiation factor-15.

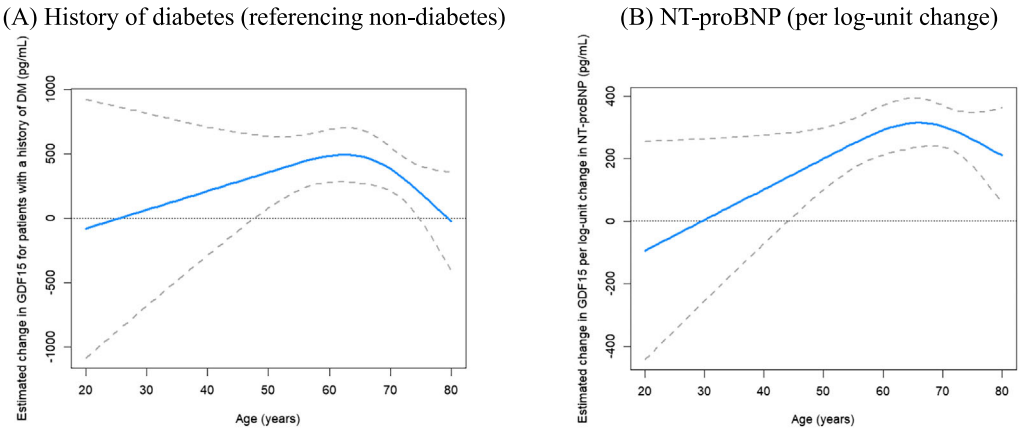

Table 3 The risk of study endpoints by growth differentiation factor-15 and interaction with age

Study endpoints	Number of events (per 100 person-years)	Unadjusted model HR (95% CI)	Adjusted model HR (95% CI)	$P_{interaction}$ (interaction by age)
Composite of HF hospitalization or all-cause death	474 (6.60)	2.80 (2.40–3.29)	1.84 (1.45–2.33)	0.0008
MACE	517 (7.53)	2.48 (2.14–2.88)	1.59 (1.26–2.01)	0.0003

HRs are indicated per log-unit change in growth differentiation factor-15. The adjusted model includes age, sex, systolic blood pressure, history of diabetes, ischaemic heart disease, left ventricular end-systolic dimension, left ventricular ejection fraction, estimated glomerular filtration rate, haemoglobin, N-terminal pro-brain natriuretic peptide, troponin, C-reactive protein, and the use of angiotensin-converting enzyme inhibitors, diuretics, and statins.
CI, confidence interval; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiac events.

composite of HF hospitalization or all-cause death appeared the most prominent in patients aged around 70 years (*Figure 3*). The extent of associations persisted for patients aged after 70 years for MACE.

The C-statistics (AUC–ROC), likelihood ratio, and R^2 were studied across the prediction models for identifying patients with study endpoints (*Table 4*). The *P*-values of the pair-wise comparison of AUC–ROC across all models are available in Supporting Information, *Table S3*. The model with GDF15 added to the fully adjusted model by demographics and other biomarkers (NT-proBNP, troponin, and CRP) showed a marginal improvement of the model performance for HF hospitalization or all-cause death, but not for MACE (AUC–ROC 0.803 vs. 0.796, $P = 0.045$, and 0.785 vs. 0.781, $P = 0.182$, respectively). Improvement of the model performance was marginal between the models with and without interaction terms (between GDF15 and age) for both study endpoints (AUC–ROC 0.808 vs. 0.803, $P = 0.200$, and 0.789 vs. 0.785, $P = 0.250$, respectively). Estimated differences in the probability of the study endpoints between models with and without GDF15 on top of demographic and other biomarker adjustments appeared similar across a wide range of age spectrums (Supporting Information, *Figure S1*).

Optimal cut-off value of growth differentiation factor-15

In overall patients, the optimal cut-off value for discriminating patients with and without both study endpoints was 1397 pg/mL. The cut-off value of 1400 pg/mL precisely discriminated between patients with and without study endpoints (*Figure 4*). In the fully adjusted model with demographics and biomarkers, patients with GDF15 $\geq$ 1400 pg/mL had significantly higher risks of both endpoints compared with those <1400 pg/mL [adjusted HR 2.01 (95% CI 1.59–2.54), $P < 0.001$, and HR 1.79 (95% CI 1.43–2.24), $P < 0.001$, respectively]. There were no interactions between GDF15 $\geq$ 1400 pg/mL and age for both study endpoints ($P_{interaction} = 0.384$ and 0.383, respectively).

Discussion

The participants of the SUPPORT trial reflected the typical HF population in Japan in terms of both demographics and clinical characteristics.[14] In this trial, the majority of participants

Figure 3 (A, B) The risk of study endpoints by growth differentiation factor-15 across the age spectrum. HF, heart failure; HR, hazard ratio; MACE, major adverse cardiac events.

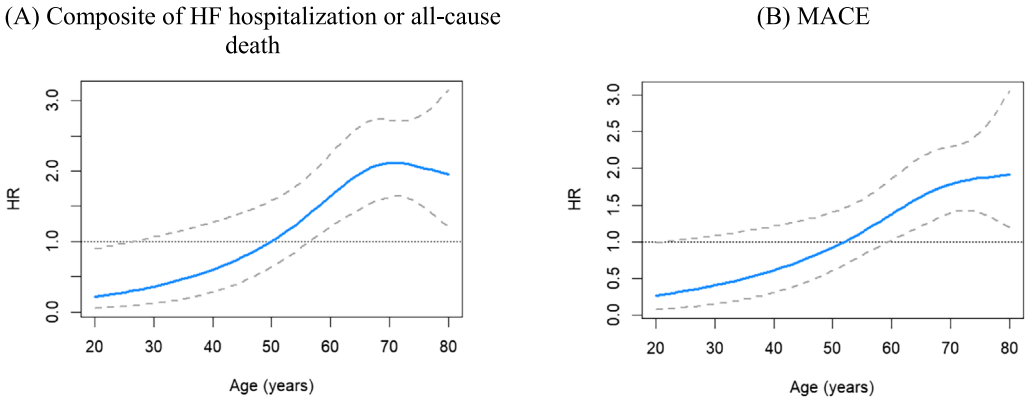

Table 4 Model performance indices across models with different predictors

	AUC–ROC	Log likelihood	R^2
HFH or all-cause death			
(1) Model with demographics	0.747	−535.72	0.246
(2) Model with demographics + biomarkers	0.796*	−495.49†	0.338
(3) Model with demographics + GDF15	0.771*	−518.14†	0.287
(4) Model with demographics + biomarker + GDF15	0.803*	−489.97†	0.350
(5) Model with demographics + biomarker + GDF15 + GDF15 * age	0.808*	−484.13†	0.363
MACE			
(1) Model with demographics	0.728	−546.06	0.211
(2) Model with demographics + biomarkers	0.781*	−509.71†	0.298
(3) Model with demographics + GDF15	0.749*	−534.52†	0.239
(4) Model with demographics + biomarker + GDF15	0.785*	−507.06†	0.304
(5) Model with demographics + biomarker + GDF15 + GDF15 * age	0.789*	−500.65†	0.319

Demographics include age, sex, body mass index, New York Heart Association class, systolic blood pressure, diastolic blood pressure, history of diabetes, ischaemic heart disease, left ventricular end-systolic diameter, left ventricular ejection fraction, estimated glomerular filtration rate, haemoglobin, and the use of angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, and statins. Biomarkers include N-terminal pro-brain natriuretic peptide, troponin, and C-reactive protein. GDF15 * age indicates the interaction term between GDF15 and age.

AUC–ROC, area under the curve–receiver operating characteristic curve; GDF15, growth differentiation factor-15; HFH, heart failure hospitalization; MACE, major adverse cardiac events.

*$P < 0.01$ for AUC–ROC comparison against Model 1 (DeLong's test).

†$P < 0.01$ for likelihood ratio test against Model 1.

(93%) were in NYHA class II, and their extensive follow-up data have enabled us to better understand their prognostic factors. In this explorative post hoc study in patients with stable CHF, GDF15 was robustly and positively associated with age. Both the classic stepwise regression and the more advanced approach using LASSO regression demonstrated variations in clinical correlates of GDF15, in which the extent of the associations between GDF15 and some clinical correlates is dependent on age. The extent of associations between GDF15 and cardiovascular endpoints may also differ across age, with the most robust associations in patients aged around 70 years. To the best of our knowledge, this is the first study demonstrating the long-term prognostic significance of GDF15 with a special reference to age in CHF.

GDF15 has been well recognized as a biomarker of aging that is associated with various diseases, including HF.[17] Therefore, understanding the clinical correlates of elevated GDF15 across a wide age spectrum with different backgrounds and comorbidities is critical for understanding the biological mechanisms involved in elevated GDF15 in CHF. In the present study, consistent with the previous literature, in overall patients with CHF, many clinical covariates such as blood pressure, comorbidity history, LV dimensions and systolic function, renal function, anaemia, and biomarkers including NT-proBNP and troponin were associated with GDF15 independent of age.[18–20] The associations with LV dimensions, systolic function, and other biomarkers are consistent with previous studies demonstrating the essential roles of GDF15 in cardiomyopathy and metabolic diseases via cardiac fibrosis and inflammation.[21–24] Seminal studies also suggest the vital role of elevated GDF15 in the progression of cardiac remodelling.[25,26] The present study also revealed pos-

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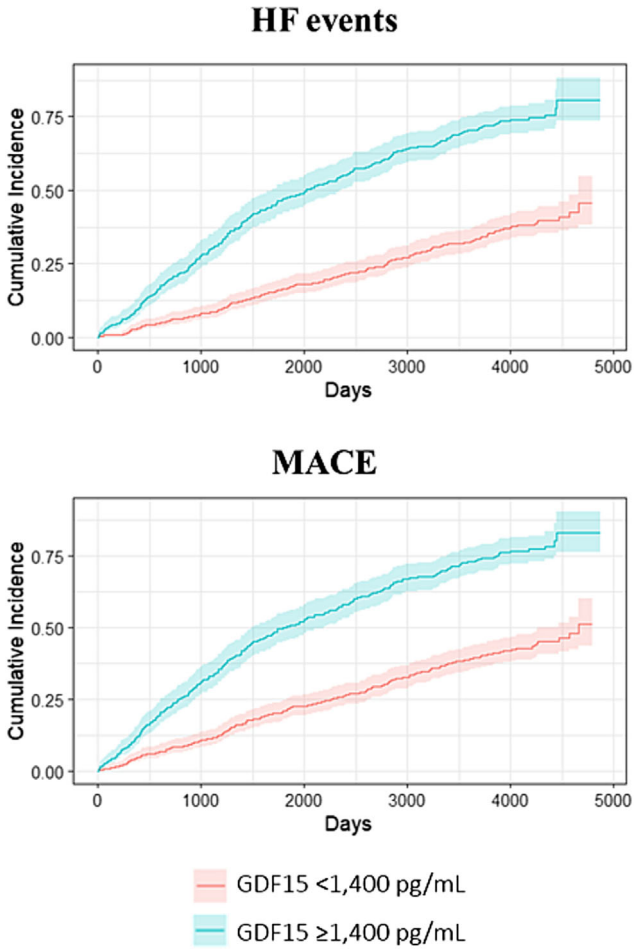
Figure 4 Cumulative incidence of the study endpoints in patients with and without growth differentiation factor-15 (GDF15) above 1400 pg/mL. HF, heart failure; MACE, major adverse cardiac events.



sible variations in the strength of associations across patient ages. In particular, the history of diabetes and NT-proBNP presented robust associations in patients aged between 60 and 70 years. The biological rationale for the difference in the extent of associations between GDF15 and the history of metabolic disease and/or biomarkers of cardiac-specific features across the age spectrum remains inconclusive; however, the present study corroborates the multifaceted involvement of GDF15 in CHF.

The clinical correlates of GDF15 in younger patients appear particularly distinct from other age groups. In addition to the common clinical correlates of impaired renal function, lower haemoglobin, and elevated troponin levels, the classic stepwise variable selection approach identified an increased BMI and prevalent diabetes as key determinants of elevated GDF15 in patients aged under 50 years. This strongly reminds us that GDF15 is not only an aging biomarker but also serves as a metabolic mediator via suppression of food intake and inflammation.[27] Furthermore, the association with BMI is extremely intriguing, as it appears to have a non-linear relationship across the age distribution (the directionality of the association is not consistent across the age groups). The variations in the extent of associations between GDF15 and clinical correlates indicate the need for further studies from a multitude of aspects (i.e. sex, comorbidities, underlying aetiology of HF, and treatment strategies) to determine the multifaceted yet essential roles of GDF15 in HF.

The present results further support the prognostic utility of GDF15 in addition to other established risk factors in CHF, with the most prominent impact in patients aged 60–70 years. The absence of a profound difference in the additive value of GDF15 across the age spectrum suggests the use of a universal cut-off value, regardless of age, which would be particularly useful in the clinical setting. Nevertheless, careful consideration should be given to its potential use as a diagnostic marker, as we demonstrate substantial age-dependent differences in GDF15 concentration in patients with CHF. Notably, the median level of GDF15 in patients over 70 years was more than twice as high as that of those under 50 years in the present study. Importantly, these differences in GDF15 levels were observed regardless of HF severity (i.e. NYHA class) or LVEF across the age groups. These findings exhibit a high burden in utilizing a universal GDF15 level as a diagnostic tool for HF across a wide age spectrum. Thus, more attention should be paid to the age-specific cut-off values of GDF15 before it is utilized for diagnostic purposes.

The present study embraces several strengths and future perspectives. Establishing the prognostic significance of GDF15 in non-elderly patients with modest frailty is important while a clinical trial of ponsegromab, a monoclonal antibody of GDF15, is underway targeting patients with HF and evidence of cachexia (ClinicalTrials.gov Identifier: NCT05492500). In the present study, we were able to demonstrate the prognostic significance of GDF15 in CHF, in addition to that in ischaemic heart disease.[28] The prognostic cut-off level of GDF15 (1400 pg/mL) found in the present study was lower than the level (1800 pg/mL) reported in a recent meta-analysis of eight trials with patients with ischaemic heart disease.[29] Furthermore, the present study also provides novel evidence on the long-term prognostic significance of GDF15 in CHF, which should be useful in future practice.

Several limitations should be mentioned for the present study. First, the general interpretation of the findings is largely limited by the ethnicity and age of the studied patients, wherein the SUPPORT trial patients were Japanese patients aged between 20 and 80 years. Although the mean age of overall patients (66 ± 10 years) aligns with previous studies performed and used in the individual meta-analysis,[29] the majority of the patients were aged between 60 and 79 years. Second, it is important to note that patients in the SUPPORT trial were not on any angiotensin receptor blockers at baseline. Potential statistical power loss due to substantial differ-

ences in the number of patients across the age groups may have resulted in the discrepancy of the suggested clinical correlates between the stepwise and LASSO approaches. Further studies are needed to validate our findings and corroborate the interaction by age on associations between GDF15 and clinical correlates such as diabetes and NT-proBNP. Third, in comparison with previous research,[30,31] GDF15 levels were relatively lower for patients with HF across all age groups in the present study. This may reflect the unique patient characteristics of this cohort, consisting of patients with stable conditions with intensive treatment with either or both ACE inhibitors and beta-blockers. Fourth, although the suggested cut-off value (i.e. 1400 pg/mL) is comparable to the values suggested in the previous literature, the lack of external validation in the present study limits the generalizability of the finding. Above all, the use of data-driven analytical approaches (either the LASSO regression or the cubic spline models) is at risk of overfitting and therefore requires careful interpretation of the findings and validation with external sources. Finally, because the GDF15 measurement was retrospectively performed with stored blood samples from the time of enrolment to the trial, the measurement levels may have been influenced by the sample stability over time, despite appropriate measures taken to minimize such an impact (i.e. proper storage).

Conclusions

GDF15 was associated with a variety of clinical correlates with possible effect modification by age. GDF15 is a powerful determinant of cardiovascular endpoints in addition to other established risk factors, particularly in patients aged around 70 years. The additive prognostic value of GDF15 appeared consistent across the age spectrum, suggesting the use of a universal cut-off level.

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Conflict of interest

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

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Correlations between biomarkers and age.
Table S2. Clinical correlates of GDF15 across the age spectrum identified by the LASSO regression.
Table S3. *P*-values of comparing AUC–ROC across the models.
Figure S1. Estimated difference in the probability of study endpoints across the age spectrum. Each dot represents the frequency of the estimated difference in the probabilities of study endpoints at given age. The black curves indicate the 10th and 90th percentile predicted difference across age. The additive value of GDF15 for estimating the probability of study endpoints appears consistent across the age spectrum.

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