ORIGINAL ARTICLE

Serum Meteorin-like is associated with weight loss in the elderly patients with chronic heart failure

Juan Cai[1], Qi-Ming Wang[2], Jia-Wen Li[3,4], Fan Xu[3,4], Yun-Ling Bu[3,4], Man Wang[3,4], Xiang Lu[3,4] & Wei Gao[3,4*] (ID)

[1]Department of Cardiology, Nantong Hospital of Traditional Chinese Medicine, Nantong, China; [2]Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [3]Department of Geriatrics, Sir Run Run Hospital, Nanjing Medical University, Nanjing, China; [4]Key Laboratory for Aging & Disease, Nanjing Medical University, Nanjing, China

Abstract

Background Unintentional weight loss (cachexia) has been associated with poor outcomes in chronic heart failure (CHF). Meteorin-like (Metrnl) is a novel myokine with protective effects on cardiovascular diseases. However, the change of Metrnl concentrations and its role in elderly patients with CHF remains unclear. The aim of this study was to evaluate the association of serum Metrnl with weight loss and outcomes in elderly patients with CHF.

Methods A total of 931 consecutive elderly patients (aged 60 years and older) with CHF and 135 age-matched and sex-matched control subjects were enrolled. Serum Metrnl concentration was measured by enzyme-linked immunosorbent assay. Body weight was measured at baseline and 12 months.

Results Median of serum Metrnl levels was lower in CHF patients when compared with controls [201.31 (184.95–261.16) pg/mL vs. 168.68 (103.15–197.54) pg/mL, $P < 0.001$]. Patients with the lowest levels of Metrnl had higher N-terminal pro brain natriuretic peptide (NT-proBNP) levels but lower left ventricular eject fraction (LVEF) and estimated glomerular filtration rate ($P < 0.001$). Lower serum Metrnl was associated with a higher risk of >5% weight loss from baseline to 12 months [odds ratio = 6.13, 95% confidence interval (CI) = 2.57–14.62 per log decrease; $P < 0.001$]. Serum Metrnl levels were decreased as LVEF decreased ($P < 0.001$) and were positively correlated with LVEF ($r = 0.267$, $P < 0.001$) but negatively correlated with NT-proBNP levels ($r = -0.257$, $P < 0.001$). Cox regression analysis suggested that lower serum Metrnl was associated with higher cardiovascular mortality [hazard ratio (HR) = 6.71, 95% CI = 3.41–13.18 per log decrease; $P < 0.001$], CHF rehospitalization (HR = 3.07, 95% CI = 1.82–5.17 per log decrease; $P < 0.001$), and the combined major adverse cardiac event(s) (MACEs) (HR = 5.38, 95% CI = 3.51–8.25 per log decrease; $P < 0.001$). The Kaplan–Meier survival curves showed that low concentration of Metrnl was a prognostic indicator of MACEs in patients with CHF.

Conclusions Our study suggests that lower serum Metrnl level is correlated with weight loss and the severity of cardiac dysfunction in elderly patients with CHF.

Keywords Chronic heart failure; Elderly; Meteorin-like; Weight loss; Outcome

Introduction

Chronic heart failure (CHF) is a major cause of disability and mortality in the elderly.[1] The higher incidence of comorbidities with ageing further worsens clinical outcomes in CHF, with the elderly patients more often having unintentional weight loss.[2] Cachexia, which is characterized by loss of >5% body weight during the previous 12 months or less, is particularly associated with reduced exercise capacity and worsened outcomes.[3]

Meteorin-like (Metrnl) has been identified as a novel myokine that can be induced in skeletal muscle and adipose tissue by acute bouts exercise and cold exposure, respectively.[4] Increased circulating Metrnl improves insulin sensitivity via stimulating thermogenesis in brown/beige adipocytes and the production of anti-inflammatory cytokines in skeletal muscle.[4–6] Recently, Baht *et al.*[7] demonstrated that Metrnl is secreted from macrophages in response to local muscle injury and promotes muscle regeneration through the inhibition of inflammation and induction of insulin-like growth factor 1. Besides, Metrnl is also abundantly expressed in the heart and plays critical roles in the pathogenesis of cardiovascular diseases.[8] It has been shown that Metrnl attenuates ischaemia/reperfusion injury-induced and doxorubicin-induced cardiomyocyte apoptosis via activation of AMP-activated protein kinase (AMPK)/p21 activated kinase 2 (PAK2) signalling[9] and cyclic AMP/protein kinase A pathway,[10] respectively. A very recent study revealed that mice lacking Metrnl are prone to develop cardiac hypertrophy and Metrnl can act directly in cardiomyocytes to protect against hypertrophic processes in mice.[11] We and others previously reported that decreased serum Metrnl levels are associated with the presence and severity of coronary artery disease in humans.[12,13] However, the relationship between serum Metrnl and CHF in the elderly remains to be further elucidated. Therefore, the aims of the present study were to evaluate the prognostic value of serum Metrnl and its association with weight loss in elderly patients with CHF.

Methods

Study population

A total of 931 consecutive elderly patients (aged 60 years and older) with CHF admitted to the affiliated hospitals of Nanjing Medical University were recruited between September 1, 2016 and October 31, 2019. All patients had a history of CHF for at least 6 months and were in stable condition on medication for at least 1 month before blood sampling. The diagnosis of CHF was on the basis of typical symptoms and signs and evidence of diastolic and/or systolic dysfunction, according to the American College of Cardiology/American Heart Association guidelines.[14] All subjects included in this study had no history of significant concomitant diseases, including hepatic failure, severe renal failure [estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2], congenital heart disease, bleeding disorders, previous thoracic irradiation therapy, neuromuscular disorders, autoimmune diseases, and malignant disease. Body weight was measured at baseline and at 12 months. A total of 135 age-matched and sex-matched control subjects were recruited during the same period from the health examination centre. This study

was performed in accordance with the principles outlined in the Declaration of Helsinki[15] and approved by the Ethics Committee of Nanjing Medical University. Written informed consent was obtained from each participant.

Laboratory measurements

Venous blood sample was collected and separated into serum and cellular fractions within 2 h. The obtained serum was stored at −80°C before further analysis. Total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, and creatine levels were measured enzymatically on a chemistry analyser (Olympus AU5400; Chemical Ltd., Tokyo, Japan). N-terminal pro brain natriuretic peptide (NT-proBNP) was assessed on the Elecsys system using Roche assays (Roche, Basel, Switzerland). eGFR was calculated using the simplified Modification of Diet in Renal Disease formula.

Serum Metrnl measurements

Serum Metrnl levels were measured by using an enzyme-linked immunosorbent assay kit (Catalogue # DY7867-05, R&D, MN, USA) according to the manufacturer's protocol. The intra-assay and inter-assay coefficients of variance were 2.55% and 3.42%, respectively. The analytic sensitivity of the assays was 15.625 pg/mL.

Clinical outcomes

The primary clinical outcome was major adverse cardiac event(s) (MACEs), which was defined as cardiovascular death and rehospitalization due to worsening CHF. The secondary endpoints were the individual components of the primary outcome, including cardiovascular mortality and CHF rehospitalization. Endpoints were obtained by reviewing the hospital database and by contacting each patient individually.

Statistical analysis

Normality of distribution was assessed using Kolmogorov–Smirnov test. Skewed data were expressed as median and quartile ranges, and comparisons of two and more than two independent groups were analysed by Mann–Whitney U test and Kruskal–Wallis test, respectively. Pearson χ^2 test was used to compare qualitative variables represented as frequencies. Univariate analysis and multivariate logistic regression analysis were taken to determine the variables that independently contributed to weight loss in patients with CHF. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The correlations between serum Metrnl

levels and cardiac function variables were calculated using Spearman correlation coefficient. The association between baseline variables and MACEs was evaluated using univariable and multivariable Cox proportional hazards analysis. Hazard ratios (HRs) and 95% CIs were calculated. The factors entered into the multivariable regression model were age, sex, body mass index (BMI), ischaemic aetiology, hypertension, diabetes, left ventricular ejection fraction (LVEF), NT-proBNP, eGFR, medical treatments, and Metrnl. Kaplan–Meier analysis was conducted to compare the differences of survival rates between patients with different quartile range of serum Metrnl levels using the log-rank test. All tests were two sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using PASW 18.0 (IBM SPSS, Inc., Chicago, USA).

Results

Baseline characteristics

The baseline characteristics of the participants are shown in *Table* 1. The median value of LVEF in patients with CHF was 41% (35–49%). There were 227, 242, and 462 patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction, respectively. According to New York Heart Association functional class, there were 182, 285, 310, and 154 patients with New York Heart Association Classes I–IV, respectively. No significant differences were observed between CHF patients and control subjects with respect to age, sex, BMI, rates of smoking, hypertension and diabetes, fasting blood glucose, and lipid parameters. By contrast, serum levels of Metrnl were lower in CHF patients when compared with those control subjects [168.68 (103.15–197.54) pg/mL vs. 201.31 (184.95–261.16) pg/mL, $P < 0.001$]. We further divided the elderly patients with CHF into four subgroups according to the quartile values of serum Metrnl concentrations (*Table* 2). We found that patients with the lowest levels of Metrnl had higher NT-proBNP levels but lower LVEF and eGFR ($P < 0.001$).

Serum Metrnl and weight loss

Patients from the lowest Metrnl quartile were more prone to have >5% weight loss over a period of 12 months (*Figure* 1A, $P < 0.001$). The changes in weight were increased as the levels of Metrnl decreased (*Figure* 1B, $P < 0.001$). As shown in *Table* 3, lower serum Metrnl concentration was a significant predictor of weight loss at 12 months (adjusted OR = 6.13, 95% CI = 2.57–14.62 per log decrease, $P < 0.001$). Similar results were obtained by using serum Metrnl as a ranked variable (first quartile vs. fourth quartile: adjusted OR = 1.44, 95% CI = 1.19–1.73, $P < 0.001$) (*Table* 3).

Serum Metrnl and cardiac function

As shown in *Figure* 2A, serum Metrnl levels were decreased as LVEF decreased, with 181.93 (125.16–205.78) pg/mL in pa-

Table 1 Baseline characteristics of the participants

Variables	Control (*n* = 135)	CHF (*n* = 931)	*P* value
Age (years)	69 (65–76)	68 (66–75)	0.322
Male, *n* (%)	93 (68.9)	609 (65.4)	0.426
BMI (kg/m²)	24.51 (22.66–27.00)	24.69 (22.50–26.67)	0.953
Smoking, *n* (%)	53 (39.3)	411 (44.1)	0.285
Hypertension, *n* (%)	58 (43.0)	392 (42.1)	0.850
Diabetes, *n* (%)	50 (37.0)	402 (43.2)	0.177
FBG (mmol/L)	5.39 (5.00–6.19)	5.43 (5.06–6.07)	0.745
TC (mmol/L)	4.64 (3.74–5.41)	4.59 (3.90–5.20)	0.108
TG (mmol/L)	1.34 (1.03–1.82)	1.50 (1.07–2.04)	0.085
HDL-C (mmol/L)	1.05 (0.88–1.18)	1.07 (0.91–1.24)	0.093
LDL-C (mmol/L)	2.64 (2.17–3.42)	2.68 (2.26–3.28)	0.711
Metrnl (pg/mL)	201.31 (184.95–261.16)	168.68 (103.15–197.54)	<0.001
LVEF (%)	/	41 (35–49)	/
HFpEF, *n* (%)	/	227 (24.4)	/
HFmrEF, *n* (%)	/	242 (26.0)	/
HFrEF, *n* (%)	/	462 (49.6)	/
NYHA class			
I, *n* (%)	/	182 (19.6)	/
II, *n* (%)	/	285 (30.6)	/
III, *n* (%)	/	310 (33.3)	/
IV, *n* (%)	/	154 (16.5)	/

BMI, body mass index; CHF, chronic heart failure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; Metrnl, Meteorin-like; NYHA, New York Heart Association; TC, total cholesterol; TG, triglyceride.
Data are presented as median with interquartile range or number with percentage in parenthesis.

Table 2 Baseline characteristics of the chronic heart failure patients according to quartile levels of serum Metrnl

Variables	First quartile (*n* = 233)	Second Quartile (*n* = 233)	Third quartile (*n* = 233)	Fourth quartile (*n* = 232)	P value
Age (years)	69 (67–75)	68 (66–75)	68 (67–74)	66 (67–73)	0.741
Male, *n* (%)	149 (63.9)	154 (66.1)	150 (64.4)	157 (67.7)	0.826
Weight (kg)	60.0 (54.0–68.0)	61.6 (56.0–69.0)	62.0 (55.5–69.0)	61.5 (55.0–68.0)	0.472
BMI (kg/m^2)	24.65 (22.12–26.53)	24.56 (22.87–26.65)	24.80 (22.53–26.71)	24.67 (22.55–26.81)	0.719
Smoking, *n* (%)	97 (41.6)	100 (42.9)	108 (46.4)	106 (45.7)	0.700
Hypertension, *n* (%)	101 (43.3)	103 (44.2)	100 (42.9)	87 (37.5)	0.449
Diabetes, *n* (%)	116 (49.8)	103 (44.2)	89 (38.2)	93 (40.1)	0.057
Ischaemic aetiology, *n* (%)	111 (47.6)	106 (45.5)	103 (44.2)	98 (42.2)	0.694
LVEF (%)	37 (33–43)	40 (34–50)	41 (35–50)	44 (37–52)	<0.001
NT-proBNP (pg/mL)	1452.99 (1115.00–1805.23)	1374.41 (951.74–1674.44)	1351.98 (954.25–1562.74)	1074.23 (786.62–1466.87)	<0.001
eGFR (mL/min/1.73 m^2)	66.0 (56.5–78.0)	73.0 (58.5–80.0)	75.0 (68.0–88.0)	81.0 (69.0–88.0)	<0.001
TC (mmol/L)	4.53 (3.91–5.20)	4.35 (3.84–5.05)	4.65 (3.93–5.23)	4.77 (3.97–5.38)	0.044
TG (mmol/L)	1.52 (1.06–2.21)	1.46 (1.07–2.23)	1.50 (1.04–1.97)	1.51 (1.13–2.02)	0.702
HDL-C (mmol/L)	1.07 (0.92–1.26)	1.07 (0.92–1.28)	1.08 (0.90–1.23)	1.07 (0.93–1.22)	0.937
LDL-C (mmol/L)	2.73 (2.26–3.30)	2.67 (2.28–3.28)	2.63 (2.18–3.16)	2.77 (2.31–3.37)	0.377
FBG (mmol/L)	5.33 (4.88–6.24)	5.40 (5.11–5.90)	5.39 (5.06–5.98)	5.49 (5.15–6.20)	0.147
Metrnl (pg/mL)	81.32 (69.85–93.02)	127.83 (118.04–157.78)	181.93 (173.62–188.89)	226.85 (205.78–264.95)	<0.001
Medical treatment					
Diuretics, *n* (%)	219 (94.0)	220 (94.4)	228 (97.9)	226 (97.4)	0.069
Spironolactone, *n* (%)	176 (75.5)	175 (75.1)	186 (79.8)	182 (78.4)	0.559
ACEI/ARB, *n* (%)	196 (84.1)	198 (85.0)	207 (88.8)	210 (90.5)	0.121
Beta-blocker, *n* (%)	88 (37.8)	135 (57.9)	143 (61.4)	130 (56.0)	<0.001

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor antagonist; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular eject fraction; Metrnl, Meteorin-like; NT-proBNP, N-terminal pro brain natriuretic peptide; TC, total cholesterol; TG, triglyceride.
Data are presented as median with interquartile range or number with percentage in parenthesis.
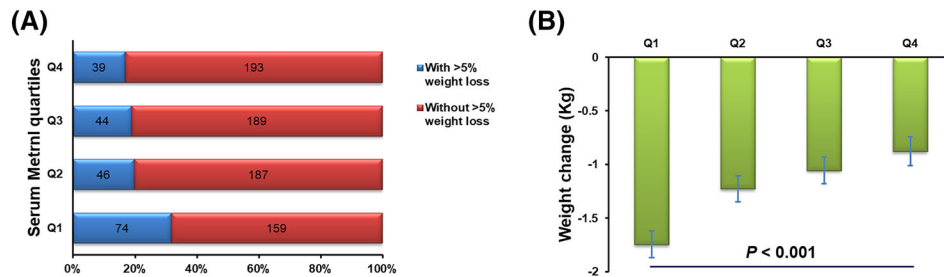
Figure 1 Correlation of serum Metrnl with weight loss in elderly patients with CHF. Patients were divided into four subgroups according to the quartile values of serum Metrnl concentrations. *(A)* Percentage of patients with or without more than 5% weight loss (in 12 months) per quartile of serum Metrnl. *(B)* Changes of body weight in 12 months per quartile of serum Metrnl. CHF, chronic heart failure; Metrnl, Meteorin-like.

Table 3 Associations of baseline serum Metrnl with weight loss

	Univariable		Multivariable[a]	
	OR (95% CI)	P value	OR (95% CI)	P value
Metrnl per log decrease	4.50 (2.04–9.93)	< 0.001	6.13 (2.57–14.62)	<0.001
Metrnl per rank decrease				
Quartile 4	1.00	/	1.00	/
Quartile 3	1.15 (0.72–1.85)	0.559	1.25 (0.76–2.06)	0.380
Quartile 2	1.10 (0.87–1.40)	0.414	1.21 (0.93–1.58)	0.157
Quartile 1	1.32 (1.14–1.53)	<0.001	1.44 (1.19–1.73)	<0.001

CI, confidence interval; Metrnl, Meteorin-like; OR, odds ratio.
[a]Variables in the multivariable logistical analysis: age, BMI, diabetes, NT-proBNP, LVEF, eGFR, and diuretics use at baseline.
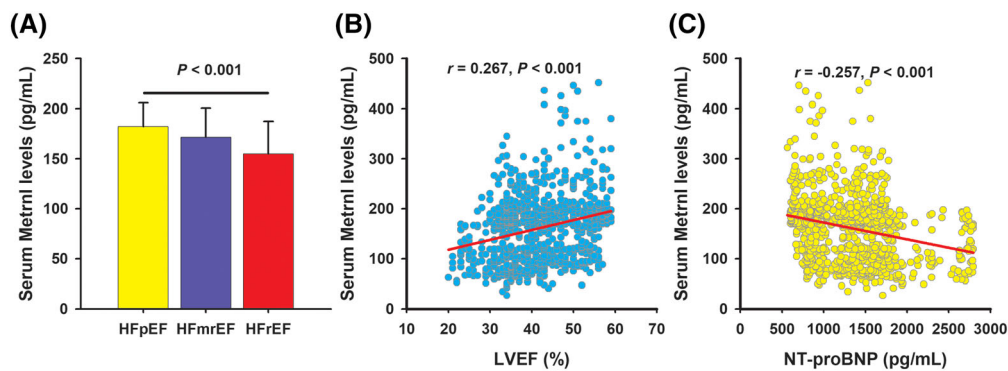

Figure 2 Correlation of serum Metrnl with cardiac dysfunction in elderly patients with CHF. *(A)* Changes of serum Metrnl in different subgroups according to LVEF. *(B)* Correlation of serum Metrnl levels with LVEF. *(C)* Correlation of serum Metrnl levels with NT-proBNP. CHF, chronic heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular eject fraction; Metrnl, Meteorin-like; NT-proBNP, N-terminal pro brain natriuretic peptide.

tients with heart failure with preserved ejection fraction, 171.54 (110.28–200.45) pg/mL in heart failure with mid-range ejection fraction, and 154.81 (93.02–187.30) pg/mL in heart failure with reduced ejection fraction. Moreover, serum Metrnl levels were positively correlated with LVEF ($r = 0.267$, $P < 0.001$, *Figure* 2B) and negatively correlated with NT-proBNP levels ($r = -0.257$, $P < 0.001$, *Figure* 2C).

Serum Metrnl and clinical outcomes

The median length of follow-up was 732 days (range 102 to 1591 days). During the follow-up period, 207 patients died, and 360 patients were readmitted due to CHF. In a univariable Cox regression model, lower serum Metrnl was associated with higher cardiovascular mortality

(HR = 6.71, 95% CI = 3.41–13.18 per log decrease; *P* < 0.001), CHF rehospitalization (HR = 3.07, 95% CI = 1.82–5.17 per log decrease; *P* < 0.001), and the combined MACEs (HR = 5.38, 95% CI = 3.51–8.25 per log decrease; *P* < 0.001). However, the association did not remain significant after adjustment for age, sex, BMI, LVEF, NT-proBNP, and other traditional factors (*Table* 4). Similar results were obtained by using serum Metrnl as a ranked variable (*Table* 5). The cumulative MACEs prevalence stratified by serum Metrnl is shown in *Figure* 3. A higher MACEs

Table 4 Associations of log Metrnl with clinical outcomes in chronic heart failure patients

	Univariable		Multivariable	
Outcomes	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary endpoint				
MACEs	5.38 (3.51–8.25)	<0.001	1.58 (0.99–2.52)	0.056
Secondary endpoints				
Cardiovascular mortality	6.71 (3.41–13.18)	<0.001	2.01 (0.96–4.21)	0.063
Rehospitalization	3.07 (1.82–5.17)	<0.001	0.99 (0.56–1.77)	0.996

CI, confidence interval; HR, hazard ratio; Metrnl, Meteorin-like.
The factors entered into the multivariable Cox regression model were age, sex, BMI, ischaemic aetiology, hypertension, diabetes, LVEF, and NT-proBNP at baseline.

Table 5 Associations of rank of Metrnl level with clinical outcomes in chronic heart failure patients

Outcomes	Fourth quartile	Third quartile	Second quartile	First quartile
MACEs				
Crude model	1	1.30 (1.00–1.68)*	1.18 (1.03–1.34)*	1.31 (1.21–1.42)*
Adjusted model	1	1.01 (0.77–1.32)	1.02 (0.88–1.19)	1.03 (0.93–1.14)
Cardiovascular mortality				
Crude model	1	1.16 (0.77–1.74)	1.11 (0.91–1.37)	1.28 (1.13–1.46)*
Adjusted model	1	0.90 (0.58–1.38)	0.99 (0.77–1.27)	0.91 (0.77–1.07)
Rehospitalization				
Crude model	1	1.48 (1.10–1.99)*	1.11 (0.94–1.30)	1.23 (1.11–1.36)*
Adjusted model	1	1.20 (0.89–1.64)	0.94 (0.78–1.13)	1.01 (0.90–1.14)

MACEs, major adverse cardiac event(s); Metrnl, Meteorin-like.
Data are presented as hazard ratio (95% confidence interval). The factors entered into the adjusted model were age, sex, BMI, ischaemic aetiology, hypertension, diabetes, LVEF, and NT-proBNP at baseline.
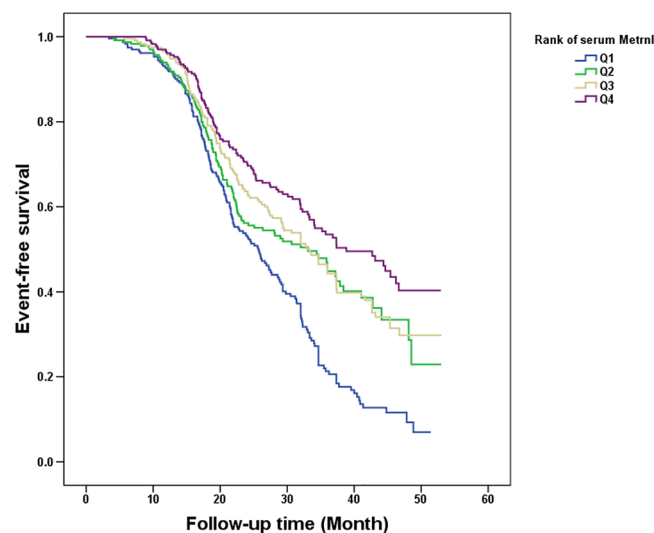*P < 0.05.

Figure 3 Kaplan–Meier survival analysis. The event-free survival for MACEs in elderly patients with CHF, stratified according to the quartile values of serum Metrnl concentrations. CHF, chronic heart failure; MACEs, major adverse cardiac event(s); Metrnl, Meteorin-like.

prevalence rate was observed in the lowest Metrnl group (log-rank test, $P < 0.001$).

Stratified analyses were conducted according to sex, diabetes, and coronary artery disease status. We noted that serum Metrnl levels were lower in patients with diabetes than those without diabetes [155.74 (94.43–195.99) pg/mL vs. 171.00 (113.50–198.79) pg/mL, $P = 0.002$]. By contrast, no significant difference of serum Metrnl concentrations was observed between male and female patients [168.89 (104.27–199.26) pg/mL vs. 168.66 (102.87–199.26) pg/mL, $P = 0.983$] as well as CHF patients with and without coronary artery disease [167.37 (101.11–196.83) pg/mL vs. 169.81 (107.78–198.20) pg/mL, $P = 0.242$]. Multivariable Cox regression analyses indicated that lower serum Metrnl was correlated to high risk of MACEs (HR = 2.09, 95% CI = 1.13–3.86 per log decrease; $P = 0.019$) and cardiovascular mortality in CHF patients with coronary artery disease (HR = 3.10, 95% CI = 1.38–6.98 per log decrease; $P = 0.006$) even after adjustment for age, BMI, hypertension, LVEF, and NT-proBNP (Table 6).

Discussion

In the present study, we showed that lower serum Metrnl concentrations were associated with weight loss and the severity of cardiac dysfunction in elderly patients with CHF. Furthermore, lower serum Metrnl levels were associated with worse outcome in elderly patients with CHF, especially in those with coronary artery disease.

Metrnl is a secretory protein mainly produced by muscle and adipose tissue.[4,16] Lower circulating Metrnl levels have been linked to obesity,[17–19] diabetes,[12,20–23] and coronary artery disease.[12,13] Consistently, we also demonstrated that serum Metrnl levels were lower in patients with diabetes when compared with those without diabetes. Intriguingly, lower levels of serum Metrnl were noticed in the elderly

patients with CHF. Moreover, lower serum Metrnl levels were associated with the severity of cardiac dysfunction. Our results, however, are contradicted with a recent study showing that plasma levels of Metrnl were higher in patients with CHF and were correlated with increased risk of death in CHF patients.[11] The discrepancies might partly attribute to the heterogeneity in study design. Our study population was restricted to elderly patients (>60 years) who were hospitalized for CHF, while the study of Rupérez et al.[11] was composed of both elderly and young patients. Indeed, ageing could lead to a significant reduction in circulating Metrnl levels.[11] Another potential confounder might be different blood collection tubes, as we examined Metrnl concentration in serum samples while Rupérez et al.[11] tested in plasma samples. Another possibility that may account for the observed inconsistencies might be the different race of subjects enrolled in different studies. Therefore, studies with much larger sample sizes and different races should be carried out before a credible conclusion can be drawn.

The exact mechanism for linking Metrnl to the pathogenesis and progression of CHF is yet to be clarified. Besides muscle and adipose tissue, heart is also a source of expression and release of Metrnl.[10,11] Results from experimental studies have shown that Metrnl can attenuate doxorubicin-induced cardiotoxicity via activating cyclic AMP/protein kinase A/Sirtuin1 pathway and reduce ischemia/reperfusion injury-induced cardiomyocyte apoptosis via activation of AMP-activated protein kinase/p21 activated kinase 2 signalling,[9,10] indicating that Metrnl may play important roles in cardiac repair in response to various types of injury. Intriguingly, although expression of Metrnl is increased in response to hypertrophic stimuli both in vivo and in vitro; however, cardiac dysfunction is enhanced in Metrnl knockout mice.[11] Reciprocally, cardiac-specific overexpression of Metrnl prevents the development of cardiac hypertrophy and fibrosis via promoting fatty acid oxidation and activating alternatively activated (M2) macrophages in cardiac tissue.[11] Based on these findings, we speculate that Metrnl might be a novel cardiokine that is required for main-

Table 6 Stratification analyses of serum Metrnl and clinical outcomes in patients with chronic heart failure

Variables	MACEs		Cardiovascular mortality		Rehospitalization	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Diabetes						
With	1.62 (0.81–3.27)	0.175	2.46 (0.84–7.15)	0.099	1.00 (0.42–2.40)	0.996
Without	1.56 (0.83–2.94)	0.171	1.52 (0.55–4.22)	0.418	1.04 (0.48–2.23)	0.930
Coronary artery disease						
With	2.09 (1.13–3.86)	0.019	3.10 (1.38–6.98)	0.006	1.03 (0.44–2.42)	0.953
Without	1.05 (0.52–2.12)	0.899	0.28 (0.06–1.38)	0.118	1.00 (0.47–2.15)	0.994
Sex						
Male	1.59 (0.87–2.91)	0.134	1.75 (0.68–4.49)	0.247	1.09 (0.52–2.28)	0.827
Female	1.44 (0.67–3.07)	0.352	2.35 (0.70–7.89)	0.169	0.73 (0.29–1.84)	0.502

CI, confidence interval; HR, hazard ratio; Metrnl, Meteorin-like; MACEs, major adverse cardiac event(s).
The factors entered into the multivariable Cox regression model were age, BMI, hypertension, LVEF, and NT-proBNP at baseline.

taining the physiological microenvironment in hearts, thereby may serve as a promising therapeutic target for the treatment of CHF. However, additional in-depth investigation is required to elucidate the precise mechanism governing the pathological effect of Metrnl on the progression of CHF.

Another interesting finding of our study is the association of low Metrnl concentrations with significant weight loss in the elderly patients with CHF. There is plenty of evidence that decreased body weight is correlated with a higher mortality risk in patients with CHF.[3] Skeletal muscle wasting, also known as sarcopenia, is one of the most important reasons of weight loss that contributes to poor prognosis in CHF.[3] As a novel myokine, Metrnl expression in muscle and blood is decreased in mice fed with high-fat diet,[6] while Metrnl administration improves high-fat diet-induced glucose tolerance and attenuates lipid-induced inflammation and insulin resistance.[4,6,24] Metrnl also seems to exert protective effects on skeletal muscle as it facilitates skeletal muscle repair after muscle injury through a stat3/IGF-1 mechanism.[7] These results may shed light on the potential mechanisms associated with the dramatic weight loss in patients with lower Metrnl concentrations. However, we here can only hypothesize that circulating Metrnl may serve as a potential biomarker for weight loss in CHF. Further studies are needed to analyse the exact cause and effect relationship between low Metrnl concentration and muscle wasting during the pathogenesis of CHF. Emerging evidence has proved exercise as a therapeutic strategy for sarcopenia in heart failure.[25] Indeed, increased Metrnl expression has been reported in the skeletal muscle after downhill running,[4] treadmill training,[26,27] and other types of exercise.[28] This would allow us to apply circulating Metrnl as a biomarker for monitoring the efficiency of exercise training on patients with CHF.

Study limitations

Firstly, our present study only analysed an association between Metrnl and body weight loss without differentiating the tissues affected, that is, skeletal muscle, body fat, and bones. Secondly, the association of Metrnl with other elements of cardiac cachexia, for example, muscle strength reduction and markers of systemic inflammation, was not evaluated in our study. Thirdly, we only enrolled Chinese elderly patients; further studies are needed in more diverse groups with different ages as well as with different regions and ethnicities. Furthermore, considering that expression of skeletal Metrnl is increased in the early phase after muscle injury, the change and role of Metrnl concentrations in patients with acute heart failure need to be further delineated. Finally, our present study only measured baseline Metrnl levels but did not dynamically monitor the levels of Metrnl during the follow-up period.

Conclusions

In summary, our findings demonstrate that lower serum Metrnl level is correlated with weight loss and the severity of cardiac dysfunction in elderly patients with CHF. Addition of Metrnl to the traditional risk factors may not only help the risk stratification for the elderly patients with CHF but also may serve as an easily accessible marker to assess cachexia in CHF. However, long-term prospective cohort studies are still needed to confirm the prognostic value of Metrnl in heart failure.

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Conflict of interest

The authors declare no conflict of interest.

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References

1. Dharmarajan K, Rich MW. Epidemiology, pathophysiology, and prognosis of heart failure in older adults. *Heart Fail Clin* 2017;**13**:417–426.

2. Konishi M, Akiyama E, Matsuzawa Y, Sato R, Kikuchi S, Nakahashi H, et al. Prognostic impact of muscle and fat mass in patients with heart failure. *J Cachexia Sarcopenia Muscle* 2021;**12**:568–576.

3. Bielecka-Dabrowa A, Ebner N, Dos Santos MR, Ishida J, Hasenfuss G, von Haehling S. Cachexia, muscle wasting, and frailty in cardiovascular disease. *Eur J Heart Fail* 2020;**22**:2314–2326.

4. Rao RR, Long JZ, White JP, Svensson KJ, Lou J, Lokurkar I, et al. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell* 2014;**157**:1279–1291.

5. Ronn T, Volkov P, Gillberg L, Kokosar M, Perfilyev A, Jacobsen AL, et al. Impact of age, BMI and HBA1c levels on the genome-wide DNA methylation and mrna expression patterns in human adipose tissue and identification of epigenetic biomarkers in blood. *Hum Mol Genet* 2015;**24**:3792–3813.

6. Jung TW, Lee SH, Kim HC, Bang JS, Abd El-Aty AM, Hacimuftuoglu A, et al. METRNL attenuates lipid-induced inflammation and insulin resistance via AMPK or PPARdelta-dependent pathways in skeletal muscle of mice. *Exp Mol Med* 2018;**50**:1–11.

7. Baht GS, Bareja A, Lee DE, Rao RR, Huang R, Huebner JL, et al. Meteorin-like facilitates skeletal muscle repair through a Stat3/IGF-1 mechanism. *Nat Metab* 2020;**2**:278–289.

8. Miao ZW, Hu WJ, Li ZY, Miao CY. Involvement of the secreted protein metrnl in human diseases. *Acta Pharmacol Sin* 2020;**41**:1525–1530.

9. Xu L, Cai Y, Wang Y, Xu C. Meteorin-like (METRNL) attenuates myocardial ischemia/reperfusion injury-induced cardiomyocytes apoptosis by alleviating endoplasmic reticulum stress via activation of AMPK-PAK2 signaling in h9c2 cells. *Med Sci Monit* 2020;**26**:e924564.

10. Hu C, Zhang X, Song P, Yuan YP, Kong CY, Wu HM, et al. Meteorin-like protein attenuates doxorubicin-induced cardiotoxicity via activating CAMP/PKA/SIRT1 pathway. *Redox Biol* 2020;**37**:101747.

11. Rupérez C, Ferrer-Curriu G, Cervera-Barea A, Florit L, Guitart-Mampel M, Garrabou G, et al. Meteorin-like/meteorin-beta protects heart against cardiac dysfunction. *J Exp Med* 2021;**218**:e20201206.

12. Dadmanesh M, Aghajani H, Fadaei R, Ghorban K. Lower serum levels of meteorin-like/subfatin in patients with coronary artery disease and type 2 diabetes mellitus are negatively associated with insulin resistance and inflammatory cytokines. *PLoS ONE* 2018;**13**:e0204180.

13. Liu ZX, Ji HH, Yao MP, Wang L, Wang Y, Zhou P, et al. Serum metrnl is associated with the presence and severity of coronary artery disease. *J Cell Mol Med* 2019;**23**:271–280.

14. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the american college of cardiology/american heart association task force on clinical practice guidelines and the Heart Failure Society of America. *Circulation* 2017;**136**:e137–e161.

15. Code of ethics on human experimentation adapted from the Helsinki Declaration of the World Medical Association. *Am J Orthopsychiatry* 1968;**38**:589–590.

16. Li ZY, Song J, Zheng SL, Fan MB, Guan YF, Qu Y, et al. Adipocyte metrnl antagonizes insulin resistance through ppargamma signaling. *Diabetes* 2015;**64**:4011–4022.

17. Pellitero S, Piquer-Garcia I, Ferrer-Curriu G, Puig R, Martinez E, Moreno P, et al. Opposite changes in meteorin-like and oncostatin m levels are associated with metabolic improvements after bariatric surgery. *Int J Obes (Lond)* 2018;**42**:919–922.

18. Du Y, Ye X, Lu A, Zhao D, Liu J, Cheng J, et al. Inverse relationship between serum metrnl levels and visceral fat obesity (VFO) in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2020;**161**:108068.

19. Sobieh BH, Kassem DH, Zakaria ZM, El-Mesallamy HO. Potential emerging roles of the novel adipokines adipolin/CTRP12 and meteorin-like/METRNL in obesity-osteoarthritis interplay. *Cytokine* 2021;**138**:155368.

20. Lee JH, Kang YE, Kim JM, Choung S, Joung KH, Kim HJ, et al. Serum meteorin-like protein levels decreased in patients newly diagnosed with type 2 diabetes. *Diabetes Res Clin Pract* 2018;**135**:7–10.

21. Fadaei R, Dadmanesh M, Moradi N, Ahmadi R, Shokoohi Nahrkhalaji A, Aghajani H, et al. Serum levels of subfatin in patients with type 2 diabetes mellitus and its association with vascular adhesion molecules. *Arch Physiol Biochem* 2020;**126**:335–340.

22. El-Ashmawy HM, Selim FO, Hosny TAM, Almassry HN. Association of low serum meteorin like (Metrnl) concentrations with worsening of glucose tolerance, impaired endothelial function and atherosclerosis. *Diabetes Res Clin Pract* 2019;**150**:57–63.

23. Wang R, Hu D, Zhao X, Hu W. Correlation of serum meteorin-like concentrations with diabetic nephropathy. *Diabetes Res Clin Pract* 2020;**169**:108443.

24. Lee JO, Byun WS, Kang MJ, Han JA, Moon J, Shin MJ, et al. The myokine meteorin-like (metrnl) improves glucose tolerance in both skeletal muscle cells and mice by targeting AMPKalpha2. *FEBS J* 2020;**287**:2087–2104.

25. Cho J, Choi Y, Sajgalik P, No MH, Lee SH, Kim S, et al. Exercise as a therapeutic strategy for sarcopenia in heart failure: insights into underlying mechanisms. *Cell* 2020;**9**.

26. Bae JY, Woo J, Kang S, Shin KO. Effects of detraining and retraining on muscle energy-sensing network and meteorin-like levels in obese mice. *Lipids Health Dis* 2018;**17**:97.

27. Bae JY. Aerobic exercise increases meteorin-like protein in muscle and adipose tissue of chronic high-fat diet-induced obese mice. *Biomed Res Int* 2018;**2018**:6283932.

28. Eaton M, Granata C, Barry J, Safdar A, Bishop D, Little JP. Impact of a single bout of high-intensity interval exercise and short-term interval training on interleukin-6, FNDC5, and METRNL mRNA expression in human skeletal muscle. *J Sport Health Sci* 2018;**7**:191–196.

29. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the journal of cachexia, sarcopenia and muscle: update 2019. *J Cachexia Sarcopenia Muscle* 2019;**10**:1143–1145.