

A Prospective Case-Control Study Examining the Relationship Between Frailty and Serum Myostatin in Older Persons with Chronic Heart Failure

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Background: Frailty affects the prognosis and management of patients with heart failure, and is often related with sarcopenia. Also, the serum myostatin (MSTN) involved in the development of sarcopenia and frailty. This study aimed to determine the connection between MSTN level and frailty in older adults with chronic heart failure (CHF).

Methods: This prospective case-control study enrolled older adult patients with CHF between May 2019 and May 2021, and analyzed their clinical data.

Results: In this study 75 older adults with CHF were included, 29 of whom were frail. The B-type natriuretic peptide (BNP) levels were significantly higher in frail older adults with CHF than in older adults with CHF who were not frail (316.82 ± 235.64 pg/mL vs 198.61 ± 112.58 pg/mL; $P = 0.016$). The MSTN levels were significantly higher in frail participants than in participants who were not frail (2.93 ± 1.35 ng/mL vs 2.24 ± 0.84 ng/mL; $P = 0.018$). Based on multivariable analysis the BNP (odds ratio [OR] = 1.004, 95% confidence interval [CI] = 1.001–1.008; $P = 0.018$) and MSTN (OR = 1.772, 95% CI = 1.079–2.912; $P = 0.024$) levels were independently associated with frailty in older adults with CHF.

Conclusion: MSTN is a promising biomarker of frailty in elderly patients with CHF.

Keywords: myostatin, B-type natriuretic peptide, frailty, chronic heart failure

Background

Frailty is defined as a clinical state of growing vulnerability and functional impairment caused by a cumulative decline in several bodily systems, which raises the likelihood of unfavorable health outcomes, such as falls, hospitalization, and death.^{1,2} Although old age increases the probability of acquiring frailty,^{1,2} frailty does not directly relate to chronologic age or impairment. A widely diverse population, older persons have varying levels of health and functional life spans. The scientific interest in fragility as a potential explanation for the disparity in health among older persons is growing.³ Frailty is thought to affect 15% of community-dwelling persons > 65 years of age in the USA.⁴ Frailty and/or functional decline are highly related with advanced age, poverty and/or isolation, polypharmacy, malnutrition and/or weight loss, cognitive impairment, and medical and/or psychiatric co-morbidities. Frailty is typically chronic and progressive, but interventions may improve outcomes or potentially reverse the frailty status.^{1,2} Frailty is becoming a silent killer that primarily affects elderly adults.^{1,2}

Frailty is linked to the negative effects of cardiovascular diseases in older adults.⁵ Heart failure (HF) is the final stage of many cardiac disorders. HF is significantly more common as individuals age, reaching up to 10% in those < 70 years of age.⁶ All HF patients, regardless of their chronologic age, should be assessed for the existence of frailty or the risk for developing frailty⁷ because frailty affects the prognosis and management of HF patients.

The prevalence of frailty in patients with Chronic heart failure (CHF) is estimated at 44.5%-46.0%.^{8,9} On one hand, CHF in older adult patients is often accompanied by reduced skeletal muscle mass and strength, making sarcopenia and frailty in these patients.^{10,11} A number of intricate pathogenic processes, such as abnormalities and dysregulation in the neuro-hormonal, muscular, immunologic, metabolic, and endocrine systems, as well as an up-regulation of inflammatory cytokines, contribute to worsening HF in frail patients,^{12–16} which generates an imbalance between anabolic and catabolic phases and may exacerbate the loss of strength and muscle mass while favoring the development of cachexia (characterized as a widespread wasting process affecting all bodily systems) and reduced lean muscle mass, also known as sarcopenia.^{17,18} On the other hand, frailty is also accompanied by loss of muscle mass and strength (sarcopenia). Sarcopenia often symptomizes as lower energy and exercise tolerance and diminished physiologic reserve, all of which contribute to poor health outcomes and a reduced ability to recover from acute stresses, disease, or treatments (frailty).^{1,2}

As stated above, bidirectional relationship consists between sarcopenia and frailty. Myostatin (MSTN) is a negative regulator of skeletal muscle mass.¹⁹ MSTN is involved in the development of sarcopenia and frailty.^{20,21} Therefore, inhibition of MSTN might serve as a treatment for sarcopenia and muscle mass loss.^{20,21} The exact role of MSTN in developing frailty in the context of CHF, however, is poorly understood.

Therefore, this study aimed to determine the association between the serum MSTN level and frailty in older adult patients with CHF.

Methods

Study Design and Participants

Participants in this prospective case-control study were elderly adults with CHF who received care in the Department of Cardiology of our medical center between May 2019 and May 2021. The study was conducted according to the current ethical practice standards and was approved by the Ethics Committee of the Sixth Medical Center, Chinese PLA General Hospital (HZKY-PJ-2020-9). All study participants signed informed consent forms.

The inclusion criteria were as follows: 1) ≥ 65 years of age; and 2) diagnosis of class II–IV CHF according to the New York Heart Association (NYHA) criteria.²² The exclusion criteria were as follows: 1) conditions that could affect the frailty evaluation, such as dementia, cognitive dysfunction, disturbance of consciousness, or mental illness; 2) acute coronary syndrome, acute inflammation, acute trauma, and/or malignant tumors; 3) muscle, thyroid, or other metabolic diseases, such as polymyositis or hyperthyroidism; or 4) severe liver (alanine aminotransferase [ALT] >3 times the upper limit of normal) or kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²).

Data Collection and Definition

Demographic and clinical data were collected, including gender, age, body mass index (BMI), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), and MSTN. Fasting venous blood samples (10 mL) were obtained in the morning and centrifuged for 15 min at 4°C at 3000 rpm. The supernatants were frozen at -80°C , and the serum MSTN levels were determined using the human MSTN enzyme-linked immunosorbent assay (ELISA) kit provided by Wuhan Hualianke Biotechnology Co., Ltd. (Wuhan, China). Automatic biochemical analyzer (HITACHI7600-020, Hitachi, Tokyo, Japan) was used to determine routine biochemical parameters, including TC, LDL-C, etc. BNP was determined by ELISA. LVEF was determined by GE E9 color Doppler ultrasonography (General Electric Co. Ltd, Boston, USA).

The patients with CHF were grouped according to the presence of frailty. Frailty was assessed using Fried's Frailty Scale-five criteria with a score range of 0–5,^{23,24} as follows: 1) weight decrease $> 5\%$ or 4.5 kg in the last year; 2) 4.57-m walking time (male patients, height >173 cm, ≥ 6 s and height ≤ 173 cm, ≥ 7 s; female patients, height >159 cm, ≥ 6 s and height ≤ 159 cm, ≥ 7 s); 3) male grasp strength, ≤ 29 –32 kg; female grip strength, ≤ 17 –21 kg; 4) physical activity, 383 kcal/week for male patients; 270 kcal/week for female patients; and 5) fatigue, a score of 2–3 on the Center for Epidemiological Studies-Depression scale (CES-DS) questionnaire. Older adult patients with ≥ 3 symptoms were defined as frailty. A score ≥ 3 is consistent with frailty.

Statistical Analysis

SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. A chi-square test was used to assess categorical data, which are expressed as n (%). A *t*-test was used to analyze continuous data with a normal distribution, which are expressed as the mean \pm standard deviation. Univariable and multivariable logistic regression analyses were used to identify factors related to frailty in older adult CHF patients. Variables with a $P < 0.05$ based on univariable analyses were included in the multivariable analysis. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Statistical significance was defined as a two-sided P -value < 0.05 .

Results

Seventy-five participants with CHF were enrolled in this study; 29 participants were frail and 46 patients were not frail. The BNP level was significantly higher in the participants with CHF and frailty than the participants with CHF without frailty (316.82 ± 235.64 pg/mL vs 198.61 ± 112.58 pg/mL; $P = 0.016$). The MSTN level was significantly higher in the participants with frailty compared to the participants without frailty (2.93 ± 1.35 ng/mL vs 2.24 ± 0.84 ng/mL; $P = 0.018$). There were no differences in gender, age, BMI, TC, LDL-C, and LVEF between the two groups (Table 1).

The multivariable analysis revealed that the BNP (odds ratio [OR] = 1.004, 95% confidence interval [CI] = 1.001–1.008; $P = 0.018$) and MSTN (OR = 1.772, 95% CI = 1.079–2.912; $P = 0.024$) levels were independently linked with frailty in participants with CHF (Table 2).

Table 1 Characteristics of the Patients

	CHF with Frailty (n=29)	CHF Without Frailty (n=46)	P
Sex, n (%)			0.875
Male	27 (93.1)	43 (93.5)	
Female	2 (6.9)	3 (6.5)	
Age (years), mean \pm SD	86.51 ± 5.42	84.21 ± 5.99	0.098
BMI (kg/m²), mean \pm SD	22.72 ± 3.49	23.95 ± 3.01	0.112
TC (mmol/L), mean \pm SD	3.39 ± 0.69	3.55 ± 0.83	0.396
LDL-C (mmol/L), mean \pm SD	1.84 ± 0.52	1.88 ± 0.63	0.771
BNP (pg/mL), mean \pm SD	316.82 ± 235.64	198.61 ± 112.58	0.016
LVEF (%), mean \pm SD	56.86 ± 5.2	58.13 ± 5.16	0.305
MSTN (ng/mL), mean \pm SD	2.93 ± 1.35	2.24 ± 0.84	0.018

Note: Data are presented as n (%) or mean \pm standard deviation.

Abbreviations: CHF, chronic heart failure; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; MSTN, myostatin.

Table 2 Logistic Regression Analyses of Factors Associated with Heart Failure with Frailty

	Univariable		Multivariable	
	OR (95% CI)	P	95% CI	P
Age	1.075 (0.986–1.172)	0.101		
Sex	0.942 (0.148–6.007)	0.949		
BMI	0.883 (0.757–1.031)	0.115		
TC	0.765 (0.414–1.412)	0.391		
LDL-C	0.887 (0.400–1.965)	0.767		
BNP	1.004 (1.001–1.008)	0.012	1.004 (1.001–1.008)	0.018
LVEF	0.953 (0.869–1.045)	0.305		
MSTN	1.846 (1.120–3.041)	0.016	1.772 (1.079–2.912)	0.024

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; MSTN, myostatin.

Discussion

MSTN is a well-known negative regulator of muscle development and a member of the transforming growth factor (TGF) family. Skeletal muscle (SM) contains MSTN, which has significant roles in several illnesses. As a result, MSTN is a key therapeutic target.²⁵ ZINC85592908, according to Ali et al,²⁶ may prevent downstream signaling by blocking the MSTN protein and increasing myogenesis in skeletal muscle tissues. ZINC85592908 also has anti-MSTN protein therapeutic potential. The results suggested that the MSTN level is positively associated with frailty in older adult patients with CHF.

Frailty is a complex clinical syndrome. Fried²³ defined frailty as a gradual decline in reserve and function of various physiologic systems. Frailty rates in patients with HF range from 15%–74%, depending on the research population, definitions, and evaluation techniques used.^{10,11,27} Studies have shown that frailty and HF are related. People with frailty also have a noticeably increased risk of developing HF than patients without frailty.²⁸ Reduced muscle mass, fatigue, and diminished energy are some of the clinical signs of frailty and HF.²⁸ The common symptoms and signs associated with frailty can be attributed to sarcopenia, a group of age-related syndromes, including loss of physical function, muscle mass, or strength.^{1,2} Older adult patients with CHF often have sarcopenia, which can eventually evolve into cardiac cachexia. Cardiac cachexia occurs in 5–15% of patients with HF, especially those with advanced HF and a low LVEF.^{29,30} Cardiac cachexia is a major factor of frequent hospitalizations and mortality among patients with CHF. Studies have revealed that muscle mass is one of the independent prognostic indicators of survival in patients with CHF.³¹

The TGF-family transforming growth factor, MSTN, is a potent inhibitor of skeletal muscle growth.¹⁹ MSTN is a skeletal muscle actin that binds to the type 2B activin receptor on skeletal muscle and activates multiple pathways of transcription factors associated with muscle-burning genes.¹⁹ MSTN inhibits skeletal muscle mass and regulates skeletal muscle fibrosis and lipogenesis.^{19–21} MSTN also affects skeletal muscle energy metabolism and exercise capacity.³² Therefore, MSTN is a crucial negative regulator of skeletal muscle mass.³³ Recently, satisfactory results have been achieved in the treatment of muscle loss caused by degenerative muscle diseases, hereditary myopathy, or other diseases using transgenic or blocker methods to inhibit the function of MSTN, which indicates that MSTN has emerged as a novel therapeutic target for skeletal muscle disorders.^{20,21}

MSTN is mainly expressed and secreted by skeletal muscle and is also abundantly produced in adipose tissue and the heart. MSTN is strongly upregulated under different cardiac pathologic conditions, such as myocardial infarction, cardiac hypertrophy, and HF.³⁴ Heineke et al³⁵ reported that the cardiomyocytes of mice with CHF release MSTN, which is involved in muscle atrophy. Serra-Prat et al³⁶ and Lenk et al³⁷ reported that the expression of MSTN mRNA is approximately 50% higher in lower limb muscle biopsies of patients with HF than healthy controls. These studies suggest that high expression of MSTN might be involved in skeletal muscle regulation in patients with CHF. Nevertheless, the role of MSTN in CHF are inconsistent. Indeed, Chen et al³⁸ divided patients with CHF into three groups (low, medium, and high) according to the NT-proBNP level. The serum MSTN levels were significantly higher in the medium and high NT-proBNP groups than the low NT-proBNP group (ie, the more severe the HF, the higher the MSTN level). Zamora et al³⁹ found no correlation between the MSTN level or MSTN propeptide and disease severity markers (eg, NYHA functional class, LVEF, and NT-proBNP) or prognosis in CHF patients. As reported, MSTN regulates mitochondrial function, inhibits AKT, and blocks insulin-like growth factor-induced cardiomyocyte hypertrophy.⁴⁰ The current investigation demonstrated a link between the MSTN level and frailty in older adult CHF patients. Perhaps MSTN is an indicator of a certain dysfunction and protective mechanism, which needs more explorations.

Expression of the BNP gene is stimulated by myocardial wall stress, cytokines, hormones, and ischemia.⁴¹ According to Ju et al,⁴² the plasma MSTN level is greater in COPD patients than in controls, and there is a significant association between the plasma BNP and MSTN levels in the COPD group ($r = 0.402$, $P < 0.001$). Plasma BNP levels are also greater in patients with COPD compared to controls and significantly higher in patients with cor pulmonale when MSTN and plasma BNP levels were determined in the current investigation. Significant connections between the BNP level and systolic pulmonary artery pressure (SPAP), tricuspid annular plane systolic excursion, and RV fractional area change (FAC) were also found by Pearson correlation analysis in the research participants. Recent investigations^{43,44} have

demonstrated elevated plasma BNP levels in patients with right ventricular (RV) dysfunction related to chronic respiratory illnesses.

Overall, the results of this study highlighted the merit of a higher plasma BNP level as a marker for RV stress. It is interesting to note that the BNP and MSTN levels in the COPD group had a positive association because increasing wall stress causes the myocardium to produce BNP and MSTN, both of which are capable of being released into the bloodstream. Therefore, a positive association between plasma BNP and MSTN levels is expected and logical. BNP is regarded as an RV dysfunction biomarker linked to chronic lung disease.⁴⁵ These findings indicate that increased MSTN might be a potential feedback regulation mechanism that improves abnormal energy metabolism, mitochondrial dysfunction, and myocardial hypertrophy in patients with HF. The overexpression of MSTN helps improve myocardial contractility and inhibits myocardial hypertrophy in patients with HF.⁴⁶ Additional in vitro and in vivo studies are necessary to understand the function of MSTN in muscle atrophy.

Limitations

This research had several restrictions. The sample was modest and only came from one center. The case-control study design does not allow a determination of causality; longitudinal studies are needed to analyze the results. Only LVEF was assessed as a heart variable. Other heart parameters (eg, strain) should be explored in future studies. Although the MSTN levels were elevated in CHF patients with frailty, the diagnostic or predictive value was not examined. Whether MSTN can identify patients who are at risk of developing HF in an early stage is unclear and should be evaluated in further studies. Due to the limited number of cases, this study did not reflect the impact of gender differences on the results, which is worth further studies.

Conclusion

MSTN is highly related with frailty, and could be a promising biomarker of frailty in elderly patients with CHF in the clinical practice.

Data Sharing Statement

The datasets generated and analysed during the current study are not publicly available due to patients' privacy but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Sixth Medical Center, Chinese PLA General Hospital (HZKY-PJ-2020-9). All study participants signed informed consent forms. This study was conducted under the principles of the Helsinki Declaration and local laws and regulations.

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Disclosure

The authors declare that they have no competing interests in this work.

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