Serum Chemerin as a Novel Prognostic Indicator in Chronic Heart Failure

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Background—It has been documented that circulating chemerin is associated with inflammation, metabolic syndrome, and coronary artery disease. The present study was aimed to evaluate the prognostic value of serum chemerin in patients with chronic heart failure.

Methods and Results—We included 834 patients with chronic heart failure in a prospective cohort study and investigated the association between serum chemerin and clinical outcomes using multivariate Cox regression analysis. Patients with higher chemerin levels tended to be older and women and were more likely to experience hypertension, diabetes mellitus, and hyperlipemia. Cox regression analysis showed that chemerin was a significant predictor of major adverse cardiac events (hazard ratio, 1.83; 95% CI, 1.31–2.96) after adjustment for conventional risk factors. Net reclassification and integrated discrimination improvements for major adverse cardiac events were markedly improved by addition of chemerin to the reference model. In addition, chemerin was an independent predictor of all-cause mortality (hazard ratio, 1.67; 95% CI, 1.21–2.73) after multivariable adjustment. Furthermore, the Kaplan–Meier survival analysis revealed that chemerin was a prognostic indicator of major adverse cardiac events in patients with chronic heart failure and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels above and below the median.

Conclusions—Our study suggests that chemerin is a novel serum marker for predicting major adverse cardiac events in patients with chronic heart failure. (*J Am Heart Assoc.* 2019;8:e012091. DOI: 10.1161/JAHA.119.012091.)

Key Words: chemerin • chronic heart failure • major adverse cardiac events

Chronic heart failure (CHF), a complex clinical syndrome characterized by ventricular remodeling, cardiac dysfunction, and hemodynamic abnormality, is the end-stage manifestation of various cardiovascular diseases. The clinical applications of renin-angiotensin system inhibitors, aldosterone antagonists, and β blockers have significantly reduced hospitalization and mortality in patients with CHF. In recent years, several biomarkers have been identified associated with the diagnosis and prognosis of CHF, which may facilitate the treatment and risk stratification in patients with CHF.[1]

Chemerin is a newly discovered adipokine that can regulate adipocyte differentiation and stimulate chemotaxis of dendritic cells and macrophages.[2] Increasing evidence has demonstrated that circulating chemerin was closely associated with inflammation, obesity, metabolic syndrome, and coronary artery disease (CAD).[3–6] A previous prospective study by Leiherer et al showed that high chemerin levels were associated with renal dysfunction and were predictive for cardiovascular events in patients with stable CAD.[7] Menzel et al conducted a case-cohort study and found that chemerin was strongly related to the risk of CHF after multivariable adjustment.[8] However, it remains unclear whether chemerin is associated with the prognosis of CHF. We, therefore, performed a prospective cohort study to assess the prognostic value of serum chemerin in patients with CHF.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

A total of 834 consecutive patients with CHF who were admitted to the affiliated hospitals of Soochow University and Nanjing Medical University from May 2014 to August 2017 were prospectively included in this study. The diagnosis of CHF was based on manifestations of dyspnea, fatigue, fluid

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Clinical Perspective

What Is New?

- Cox regression analysis shows that chemerin is a significant predictor of major adverse cardiac events in chronic heart failure.
- Chemerin is also an independent predictor of all-cause mortality after multivariable adjustment.
- Kaplan–Meier survival analysis indicates that patients with chronic heart failure and increased chemerin levels have a high incidence of major adverse cardiac events.

What Are the Clinical Implications?

- Serum chemerin is a novel prognostic indicator of major adverse cardiac events in chronic heart failure.
- Circulating chemerin can improve early risk stratification for patients with chronic heart failure.

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retention, and left ventricular dysfunction by echocardiography. Patients with malignancy or end-stage renal disease were excluded. Demographic, clinical, and biochemical data were obtained from the medical records. This study was conducted in agreement with the Declaration of Helsinki and approved by the Clinic Institutional Review Board. Written informed consent was obtained from each patient enrolled in this study.

Detection of Serum Chemerin

Fasting blood samples were collected from patients with CHF on admission. Serum was obtained by centrifugation at 1000*g* for 10 minutes and then stored at −80°C until analysis. The human chemerin ELISA kit was purchased from R&D Systems (Minneapolis, MN), and serum levels of chemerin were determined according to the manufacturer's instructions.

End Points

The primary end point was major adverse cardiac events (MACEs), including all-cause mortality and rehospitalization for heart failure (HF). The secondary end point was all-cause mortality. HF rehospitalization was defined as a hospital readmission attributable to HF requiring treatment with intravenous diuretics, inotropes, or vasodilators. End points were obtained by reviewing the hospital records and contacting patients or their families.

Statistical Analysis

The study population was divided into 2 groups, according to the median levels of chemerin. Continuous variables were expressed as median with interquartile range and compared

with the Mann-Whitney U test. Categorical variables were presented as proportions and compared with the χ^2 test. The normality of continuous variables was evaluated by the Kolmogorov-Smirnov test. Multivariate Cox regression analysis was conducted to assess the association between serum chemerin and cardiovascular outcomes. Chemerin levels were divided into quartiles for a more comprehensive analysis. Adjustments were made for conventional risk factors, including age, sex, hypertension, diabetes mellitus, hyperlipidemia, left ventricular ejection fraction, NT-proBNP (N-terminal pro-B-type natriuretic peptide), estimated glomerular filtration rate, and high-sensitivity C-reactive protein, to predict MACEs and all-cause mortality. Kaplan–Meier analysis was undertaken to compare the survival rate among patients with different levels of chemerin using the log-rank test. Patients who survived without MACEs at the end of follow-up were censored in the statistical analysis. Integrated discrimination improvement and net reclassification improvement were calculated to determine the incremental value of chemerin in the prognosis of CHF. $P<0.05$ was considered statistically significant in this study.

Results

Patient Characteristics

The baseline characteristics of the study cohort are presented in Table 1. Patients with CHF were assigned into 2 groups, according to the median levels of chemerin (195 ng/mL). Patients with higher chemerin levels tended to be older and women and were more likely to experience hypertension, diabetes mellitus, and hyperlipemia. Chemerin seemed to be positively associated with NT-proBNP and high-sensitivity C-reactive protein, whereas it was inversely correlated with left ventricular ejection fraction, estimated glomerular filtration rate, and β-blocker use.

There were no missing data for any variable used in this study. The median length of follow-up was 524 days. A total of 834 patients with CHF were enrolled in this study. Among them, 436 patients who survived without MACEs were censored. During the follow-up period, 142 patients died and 256 patients were readmitted with HF. None of the patients were lost to follow-up.

Serum Chemerin and MACE

As shown in Table 2, elevated chemerin levels were associated with an increased risk for MACEs (quartile 4 versus 1: unadjusted hazard ratio [HR], 3.25; 95% CI, 2.18–4.97). After adjustment for demographic variables, traditional risk factors, estimated glomerular filtration rate, and high-sensitivity C-reactive protein, serum chemerin remained a significant predictor of MACEs (model 1: HR, 2.80; 95% CI, 1.92–4.26; model 2: HR, 2.16; 95% CI, 1.40–3.39; model 3: HR, 1.83;

Table 1. Baseline Characteristics of Patients With CHF

Characteristics	All Patients (n=834)	Chemerin <195 ng/mL	Chemerin ≥195 ng/mL	P Value
Age, y	66 (58–75)	64 (57–73)	69 (63–78)	<0.001
Men	493 (59.1)	275 (65.9)	218 (52.3)	<0.001
Ischemic cause	561 (67.3)	273 (65.5)	288 (69.1)	NS
Hypertension	352 (42.2)	145 (34.8)	207 (49.6)	<0.001
Diabetes mellitus	179 (21.5)	70 (16.8)	109 (26.1)	0.001
Hyperlipidemia	316 (37.9)	136 (32.6)	180 (43.2)	0.002
LVEF	37 (32–43)	42 (36–49)	31 (27–36)	<0.001
NT-proBNP, pg/mL	1845 (1263–3152)	1371 (830–2516)	2459 (1904–4038)	0.017
hsCRP, mg/L	3.6 (2.5–5.3)	1.7 (0.8–3.2)	5.3 (4.0–7.8)	<0.001
eGFR, mL/min per 1.73 m^2	67 (53–84)	76 (64–90)	60 (43–75)	0.005
Medical treatment				
Loop diuretics	729 (87.4)	357 (85.6)	372 (89.2)	NS
ACEI/ARB	640 (76.7)	328 (78.7)	312 (74.8)	NS
β Blocker	575 (68.9)	302 (72.4)	273 (65.5)	0.030
Spironolactone	387 (46.4)	186 (44.6)	201 (48.2)	NS

Values are median (interquartile range) or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NS, not significant; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

95% CI, 1.31–2.96). In addition, integrated discrimination improvement and net reclassification improvement for MACEs were significantly improved by addition of chemerin to the model of traditional risk factors (integrated discrimination improvement, 0.108 [95% CI, 0.073–0.156]; net reclassification improvement, 0.132 [95% CI, 0.094–0.205]). No significant interaction was found in this study. The risks for MACEs were similar between ischemic and nonischemic patients with CHF, as well as other clinical subgroups (Figure 1).

Serum Chemerin and All-Cause Mortality

As shown in Table 3, elevated chemerin levels were related to an increased risk for all-cause mortality (quartile 4 versus 1: unadjusted HR, 3.06; 95% CI, 2.10–4.65). After adjusting for demographic variables, traditional risk factors, estimated glomerular filtration rate, and high-sensitivity C-reactive protein, serum chemerin remained a significant predictor of all-cause mortality (model 1: HR, 2.75; 95% CI, 1.84–4.02; model 2: HR, 2.08; 95% CI, 1.30–3.24; model 3: HR, 1.67; 95% CI, 1.21–2.73).

Kaplan–Meier Survival Analysis

Patients with CHF were divided into 4 groups, according to the median levels of chemerin and NT-proBNP. The Kaplan–Meier survival analysis indicated that chemerin was a significant predictor of MACEs in patients with NT-proBNP levels above and below the median (Figure 2). For patients above the median levels of chemerin, they had a higher incidence of MACEs compared with those below the median (log-rank test, P<0.001).

Table 2. HR of Serum Chemerin Levels for MACEs

Model	Quartile 1 (<132 ng/mL)	Quartile 2 (132–195 ng/mL)	Quartile 3 (195–243 ng/mL)	Quartile 4 (>243 ng/mL)
Unadjusted model	1	1.36 (0.83–2.08)	2.13 (1.32–3.20)*	3.25 (2.18–4.97)*
Adjusted model 1	1	1.28 (0.79–2.01)	1.89 (1.16–2.85)*	2.80 (1.92–4.26)*
Adjusted model 2	1	1.19 (0.72–1.93)	1.45 (0.91–2.28)	2.16 (1.40–3.39)*
Adjusted model 3	1	1.15 (0.68–1.84)	1.32 (0.87–2.15)	1.83 (1.31–2.96)*

Data are given as HR (95% CI). Model 1, adjusted for age and sex. Model 2, adjusted for model 1 plus hypertension, diabetes mellitus, hyperlipidemia, left ventricular ejection fraction, and NT-proBNP (N-terminal pro-B-type natriuretic peptide). Model 3, adjusted for model 2 plus estimated glomerular filtration rate and high-sensitivity C-reactive protein (log transformed). HR indicates hazard ratio; MACE, major adverse cardiac event.
*P<0.01.

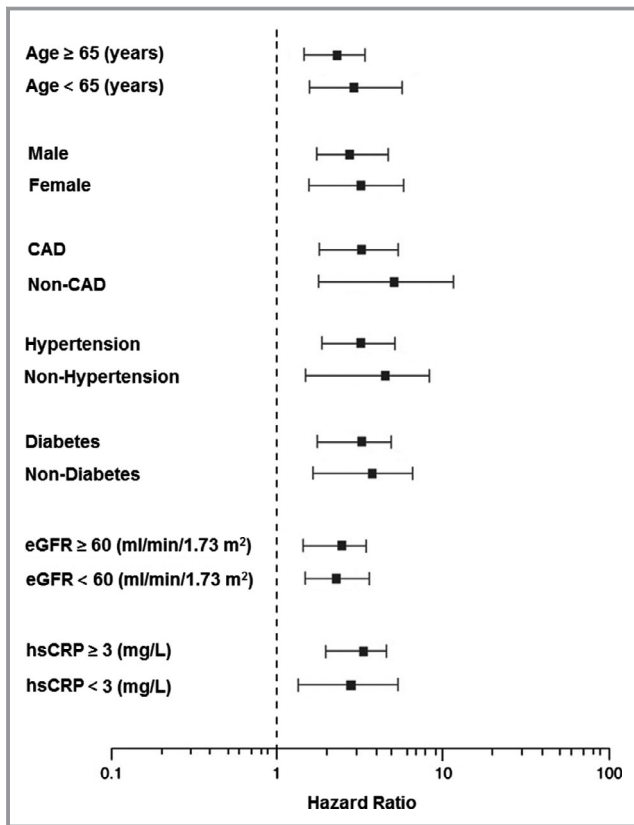**Figure 1.** Relationship between serum chemerin levels and major adverse cardiac events (MACEs), stratified according to baseline characteristics. Forest plot of the hazard ratio of MACEs, comparing first and fourth quartiles of serum chemerin levels. CAD indicates coronary artery disease; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein.

Discussion

The past decades have witnessed significant progress in the treatment of CHF. However, CHF remains a leading cause of hospitalization and death all over the world. The adipokine chemerin is an immune system regulator that functions primarily through its receptor chemokine-like receptor 1, and it also plays critical roles in the metabolic and inflammatory processes.[9] The present cohort study was conducted to investigate the prognostic value of serum chemerin in patients with CHF using Cox proportional hazards regression analysis. Our results suggested that chemerin might be a useful indicator for the prediction of MACEs and could provide independent information for risk stratification in patients with CHF.

Previous experimental research has revealed the pathophysiological function of chemerin both in vivo and in vitro. Gao et al found that the mRNA and protein expression levels of chemerin were significantly upregulated in epicardial adipose tissue from patients with CAD and the severity of coronary atherosclerosis was positively related to the chemerin expression.[10] In addition, Rodríguez-Penas et al reported that chemerin was regulated by metabolic and inflammatory mediators at the cardiac level, and it could induce apoptosis and inhibit protein kinase B phosphorylation in cardiomyocytes.[11] Furthermore, chemerin promoted adhesion of macrophages to vascular cell adhesion molecule 1 and fibronectin by clustering VLA-4 ($\alpha4\beta1$) and VLA-5 ($\alpha5\beta1$), thereby contributing to inflammation.[12] It has been documented that inflammation is actively involved in the development of various cardiovascular diseases, including hypertension, CAD, and CHF.[13–15] Therefore, we speculate that chemerin may participate in the pathogenesis of cardiovascular diseases through inflammatory mechanisms.

In recent years, numerous epidemiological studies have explored the relationship between chemerin and cardiovascular diseases. Xiaotao et al showed that elevated chemerin levels were correlated with the presence of CAD and serum chemerin may reflect the extent of coronary atherosclerosis.[6] Zhang et al indicated that plasma chemerin concentration was increased in patients with dilated cardiomyopathy and chemerin was markedly associated with inflammatory response and left ventricular dysfunction.[16] Moreover, a recent study by Menzel et al provided first evidence for a strong positive correlation between chemerin and HF risk.[8] In the present study, our results suggested that patients with high chemerin levels were more likely to be accompanied by hypertension, diabetes mellitus, and hyperlipemia. Cox regression analysis revealed that serum chemerin was a significant predictor for the primary end point of MACE and the secondary end point of all-cause mortality after multivariable adjustment. Addition of chemerin to the traditional

Table 3. HR of Serum Chemerin Levels for All-Cause Mortality

Model	Quartile 1 (<132 ng/mL)	Quartile 2 (132–195 ng/mL)	Quartile 3 (195–243 ng/mL)	Quartile 4 (>243 ng/mL)
Unadjusted model	1	1.27 (0.78–2.05)	1.98 (1.26–3.12)*	3.06 (2.10–4.65)*
Adjusted model 1	1	1.24 (0.73–1.96)	1.81 (1.15–2.79)*	2.75 (1.84–4.02)*
Adjusted model 2	1	1.12 (0.65–1.78)	1.39 (0.87–2.21)	2.08 (1.30–3.24)*
Adjusted model 3	1	1.06 (0.59–1.61)	1.23 (0.82–2.06)	1.67 (1.21–2.73)*

Data are given as HR (95% CI). Model 1, adjusted for age and sex. Model 2, adjusted for model 1 plus hypertension, diabetes mellitus, hyperlipidemia, left ventricular ejection fraction, and NT-proBNP (N-terminal pro-B-type natriuretic peptide). Model 3, adjusted for model 2 plus estimated glomerular filtration rate and high-sensitivity C-reactive protein (log transformed). HR indicates hazard ratio.
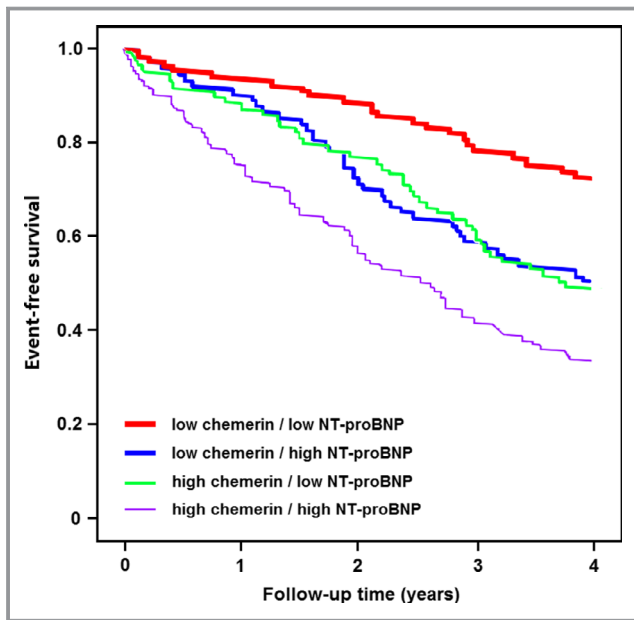*P<0.01.

Figure 2. Kaplan–Meier survival analysis. The event-free survival for major adverse cardiac events in patients with chronic heart failure, stratified according to the median levels of chemerin and NT-proBNP (N-terminal pro-B-type natriuretic peptide).

model could lead to an improvement in integrated discrimination improvement and net reclassification improvement for MACE prediction in patients with CHF.

Our study had several limitations. First, we did not perform serial measurements of serum chemerin during the follow-up period. Second, we did not have complete information about New York Heart Association functional class and atrial fibrillation in this study population. Third, because it is not a randomized study, residual confounding cannot be ruled out.

In summary, our study demonstrates that serum chemerin is a significant prognostic indicator of MACEs in CHF. The addition of chemerin to traditional risk factors may improve early risk stratification for patients with CHF. However, long-term prospective cohort studies are still needed to confirm the prognostic value of chemerin.

Sources of Funding

Disclosures

None.

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