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ORIGINAL RESEARCH

Plasma SMOC2 Predicts Prognosis in Patients with Heart Failure: A Prospective Cohort

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Background: Heart failure (HF) is a chronic disease with a poor prognosis, making it extremely important to assess the prognosis of patients with HF for accurate treatment. Secreted modular calcium-binding protein 2 (SMOC2) is a cysteine-rich acidic secreted protein that plays a pathophysiological role in many diseases, including regulation of vascular growth factor activity. It has previously been found that SMOC2 plays an essential role in cardiac fibrosis in our previous preclinical study, but whether it can be used as a clinical marker in heart failure patients remains unclear. The purpose of this research was to evaluate the correlation between plasma levels of SMOC2 and the prognosis for individuals with HF.

Methods: HF patients diagnosed with ischemic cardiomyopathy were enrolled from January to December 2021. Baseline plasma levels of SMOC2 were measured after demographic and clinical features were collected. Linear and nonlinear multivariate Cox regression models were used to determine the association between plasma SMOC2 and patient outcomes during follow-up. All analysis was performed using SPSS, EmpowerStats, and R software.

Results: The study included 188 patients, and the average follow-up time was 489.5±88.3 days. The plasma SMOC2 concentrations were positively correlated with N-terminal pro-B-type Natriuretic Peptide (NT-proBNP), left ventricular end-diastolic diameter (LVEDd), and length of hospital stay and were negatively correlated with left ventricular ejection fraction (LVEF) at baseline. A total of 53 patients (28.2%) were rehospitalized due to cardiac deterioration, 14 (7.4%) died, and 37 (19.7%) developed malignant arrhythmias. A fully adjusted multivariate COX regression model showed that SMOC2 is associated with readmission (HR = 1.02, 95% CI:1.012–1.655). A significant increase in rehospitalization risk was observed in group Q2 (HR =1.064, 95% CI: 1.037, 3.662, p=0.005) and group Q3 (HR =1.085, 95% CI:1.086, 3.792, p=0.009) in comparison with group Q1. The *p* for trend also shows a linear correlation across the three models (P < 0.001). SMOC2 was associated with the severity of HF in patients, but not with all-cause deaths and arrhythmias during follow-up.

Conclusion: Plasma SMOC2 is associated with the severity of HF and readmission rate, and is a good predictor of the risk of readmission in patients.

Keywords: SMOC2, heart failure, ischemic cardiomyopathy, readmission rate, myocardial fibrosis

Introduction

Heart failure (HF) is a complex clinical syndrome with high prevalence and mortality caused by physiological and neurohormonal changes caused by abnormal cardiac structure or function, which has seriously increased the global medical burden.[1] Wheezing, edema, arrhythmias, and cardiac enlargement are some of the clinical manifestations of HF.

Left ventricular ejection fraction (LVEF), ventricular structure, body mass index(BMI), and biomarkers such as brain natriuretic peptide, troponin, and C-reactive protein are commonly used clinically to assess heart disease.[2,3] There is still much to be discovered about the prognosis of HF, as it is an extremely complex pathophysiological process.

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Secreted modular calcium-binding protein 2 (SMOC2) is a member of the cysteine-rich acidic secretory protein (SPARC) in the stromal cell protein family, which contains an extracellular calcium-binding (EC) domain and a typical domain with 10 cysteines.[4] SMOC2 interacts with matrix proteins, cell surface receptors, cytokines, proteasomes, and other effector molecules, which can regulate the interaction of cells and cell matrix, as well as the activity of vascular growth factors.[5,6] The SMOC2 protein may serve as a marker for HF, and interventions targeting SMOC2 may be effective in treating heart disorders. For example, Wilk et al[7] in 2007 studied mRNA expressions in left and right ventricular samples without HF and right heart failure samples from patients with pulmonary arterial hypertension (PAH) and after LVAD implantation and revealed SMOC2 to be an interesting target for HF. Moreover, we have previously shown that SMOC2 was significantly increased in the process of myocardial fibrosis in mice, which could be reversed by SMOC2 down-regulation.[8]

There has yet to be a clinical study evaluating the association between plasma SMOC2 and HF severity and prognosis. The study presented here was undertaken to address the relationship between plasma SMOC2 levels and the severity of HF, as well as its diagnostic value in the prognosis of patients with end-stage heart abnormalities.

Study Design

In this prospective cohort study, inpatients that were diagnosed with ischemic heart disease in the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture were recruited from July 2020 to December 2021. Ethics approval was obtained from the Ethics Committee of the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture.

Participants

The demographic and clinical data of the patients were taken from their original medical records. The inclusion criteria of the present study were: 1. Those who were diagnosed with ischemic cardiomyopathy (ICM) with LVEF≤50%. 2. Those who were aged 18 or older. 3. Those who were willing to cooperate with our follow-up objective. Criteria for diagnosis of ICM: clinical diagnosis of coronary heart disease or angiography of coronary stenosis greater than 75% with left ventricular dilatation and reduced systolic function(LVEF≤50%), excluding other causes of left ventricular dilatation and reduced systolic function.[9] This study excluded patients with the following clinical conditions: acute myocardial infarction (MI), thyroid dysfunction, malignant tumors, inflammatory bowel disease, severe arrhythmias, etc. Clinical data were collected prospectively along with baseline characteristics. All patients were followed up.

Follow-Up and Study End Points

From discharge until the end of follow-up, patients were seen by outpatient clinical consultations or telephone interviews every 3 months. During follow-up, the primary endpoint event was all-cause re-hospitalization, and secondary endpoint events included all-cause death, new arrhythmias (including atrial fibrillation, ventricular premature, ventricular tachycardia, ventricular fibrillation), or heart rhythm abnormalities etc., and all these had been recorded by electrocardiogram or holter electrocardiogram. The telephone follow-up was conducted by a medical professional who had been trained for two weeks and had one year of experience. A second attempt was made to contact patients who were not reachable in the first round. Upon being unable to reach the patient's family members for a third time, treatment was discontinued and the patient was recorded as missing. In addition, a clinical endpoint event committee was established in order to ensure that endpoint events were objective and traceable.

Variables

The following information was collected and recorded: age, sex, height, weight, history of diabetes, history of arrhythmia, history of smoking, history of drinking wine, history of PCI heart failure duration, BMI, NYHA function class, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), medications(including anti-platelet therapy, Statins, β-blocker, ACEI/ARNI/ARB), and length of hospital stay. The blood was collected to detect the clinical biochemical parameters, consisting of high-density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol (TC), triglycerides (TG), creatinine (Cr), hemoglobin(Hb) and hemoglobin (Hb). Left atrial diameter (LA), left ventricle end-diastolic diameter (LVEDd), right ventricular end-diastolic diameter (RVEDd), right atrial diameter (RA), fractional shortening obtained from short axis images (FS), and Left ventricular ejection fraction (LVEF) were measured using

echocardiography. LVEF was measured using Modified Simpson's algorithm. All laboratory data was collected by the same laboratory to the same standard. Roche Elecsys ®NT-proBNP (Roche Diagnostics GmbH) was used for NT-proBNP determination. The SMOC2 was detected using a double antibody sandwich assay (Shanghai Enzyme-linked Biotechnology Co., Ltd., China).

Statistics Analysis

Participants were divided into three groups for further analysis according to the tertiles of SMOC2 concentration at admission. A continuous variable is presented as mean + standard deviation (SD) (Gaussian distribution) or median (range) (skewed distribution), and a categorical variable as Numbers and percentages. A one-way ANOVA, Chi-square test, and Kruskal–Wallis *H*-test were used to detect differences among three SMOC2 groups, where appropriate. The univariate and multivariate Cox proportional hazard models were employed to determine the correlation between the SMOC2 level and prognosis of the individuals included in the study. In model I, no variables were adjusted. In model II, age and sex were adjusted. All covariate adjustments were taken into account in model III. HR ratio and 95% confidence interval (CI) were calculated. The robustness of our results was verified by conducting a sensitivity analysis. We convert the SMOC2 level into a categorical variable and calculate the *p* for trend to verify the results obtained using the SMOC2 level as a continuous variable and check the possibility of nonlinearity. Since Cox proportional hazards regression model-based models are often associated with incapacity to handle nonlinear models, the nonlinearity between SMOC2 and the prognosis of HF was performed using a Cox proportional hazard regression model with cubic spline functions and smooth curve fitting (penalized spline method). Furthermore, a Pearson correlation analysis was performed on the relationship between SMOC2 and NT - proBNP, EF, LVEDd and length of hospital stay.

R statistical programming language (version 3.4.3), and EmpowerStats were applied to perform statistical analysis. A bilateral $p < 0.05$ was considered to be statistically significant.

Results

Patients Characteristics

During the study period of January to December 2021, 252 continuous participants with HF were enrolled, with 74 participants being excluded because of exclusion criteria. As a result, 188 participants were included in the study. Within an average follow-up time of 489.5 ± 88.3 days, 53 patients (28.2%) were all-cause re-hospitalization, 14(7.4%) patients died, and 37(19.7%) subjects developed malignant arrhythmias. Patients were categorized based on their SMOC2 tertiles into three groups. Table 1 presents their demographic and clinical characteristics.

Table 1 The Demographic and Clinical Characteristics of All Participants

SMOC2 tertiles	Low	Middle	High	P-value	P-value*
N	63	62	63		
Age(years)	58.556 ± 11.641	63.258 ± 11.914	63.127 ± 11.442	0.039	0.037
Height(cm)	160.825 ± 5.290	161.032 ± 4.231	160.698 ± 6.613	0.943	0.901
Weight(Kg)	61.268 ± 7.331	59.223 ± 6.121	58.703 ± 8.566	0.125	0.089
BMI(kg/m^2)	23.690 ± 2.452	22.803 ± 1.905	22.739 ± 3.002	0.060	0.056
SBP(mmHg)	132.460 ± 19.964	128.911 ± 21.321	125.381 ± 26.558	0.223	0.017
DBP(mmHg)	81.603 ± 11.211	79.161 ± 15.512	79.508 ± 19.600	0.653	0.129
LDL(mmol/L)	2.635 ± 0.540	2.720 ± 0.615	2.527 ± 0.635	0.198	0.143
HDL(mmol/L)	1.124 ± 0.292	1.064 ± 0.212	1.009 ± 0.243	0.038	0.069
TG(mmol/L)	1.536 ± 0.818	1.649 ± 1.496	1.900 ± 1.185	0.220	0.258
TC(mmol/L)	4.171 ± 1.093	4.146 ± 1.214	3.258 ± 1.627	<0.001	<0.001
HR(bpm)	71.667 ± 11.703	79.032 ± 22.478	84.730 ± 19.742	<0.001	<0.001
Duration of HF(year)	1.589 ± 1.615	3.010 ± 3.052	5.535 ± 4.667	<0.001	<0.001

(*Continued*)

Table 1 (Continued).

SMOC2 tertiles	Low	Middle	High	P-value	P-value*
Length of hospital stay(day)	6.413 ± 4.011	6.857 ± 3.354	9.286 ± 4.723	<0.001	<0.001
NT-proBNP (pg/mL)	578.316 ± 1003.068	4356.844 ± 3709.577	6134.663 ± 2961.459	<0.001	<0.001
SMOC2(pg/mL)	472.897 ± 230.167	934.817 ± 122.455	2529.015 ± 914.976	<0.001	<0.001
LA(cm)	3.588 ± 0.721	4.002 ± 0.765	4.389 ± 0.746	<0.001	<0.001
LVEDd(cm)	4.751 ± 0.643	5.260 ± 1.155	5.749 ± 1.256	<0.001	<0.001
RA(cm)	3.503 ± 0.444	3.690 ± 0.550	4.005 ± 0.796	<0.001	<0.001
RVEDd(cm)	3.322 ± 0.465	3.521 ± 0.566	3.764 ± 0.618	<0.001	<0.001
EF(%)	58.468 ± 11.728	49.963 ± 13.638	40.610 ± 15.441	<0.001	<0.001
FS(%)	31.308 ± 7.387	26.481 ± 8.118	22.260 ± 9.302	<0.001	<0.001
SEX				0.010	-
Female	34 (53.968%)	30 (48.387%)	18 (28.571%)		
Male	29 (46.032%)	32 (51.613%)	45 (71.429%)		
History of smoking				0.036	-
No	54 (85.714%)	49 (79.032%)	42 (66.667%)		
Yes	9 (14.286%)	13 (20.968%)	21 (33.333%)		
History of drinking				0.552	-
No	48 (76.190%)	52 (83.871%)	51 (80.952%)		
Yes	15 (23.810%)	10 (16.129%)	12 (19.048%)		
History of AF				0.016	-
No	60 (95.238%)	48 (77.419%)	53 (84.127%)		
Yes	3 (4.762%)	14 (22.581%)	10 (15.873%)		
NYHA function class				<0.001	-
I	35 (55.556%)	15 (24.194%)	10 (15.873%)		
II	21 (33.333%)	25 (40.323%)	18 (28.571%)		
III	6 (9.524%)	19 (30.645%)	31 (49.206%)		
IV	1 (1.587%)	3 (4.839%)	4 (6.349%)		
History of diabetes				0.064	-
No	60 (95.238%)	58 (93.548%)	53 (84.127%)		
Yes	3 (4.762%)	4 (6.452%)	10 (15.873%)		
History of PCI				0.530	
0	40 (63.49%)	40 (64.52%)	35 (55.56%)		
1	23 (36.51%)	22 (35.48%)	28 (44.44%)		
Medications					
Statins				0.201	
No	23 (36.51%)	20 (32.26%)	14 (22.22%)		
Yes	40 (63.49%)	42 (67.74%)	49 (77.78%)		
Anti-platelet therapy				0.798	
No	17 (26.98%)	19 (30.65%)	16 (25.40%)		
Yes	46 (73.02%)	43 (69.35%)	47 (74.60%)		
ACEI/ARNI/ARB				0.891	
No	28 (44.44%)	27 (43.55%)	30 (47.62%)		
Yes	35 (55.56%)	35 (56.45%)	33 (52.38%)		
β-blocker				0.263	
No	40 (63.49%)	39 (62.90%)	32 (50.79%)		
Yes	23 (36.51%)	23 (37.10%)	31 (49.21%)		
Hb	137.97±21.78	140.79±27.16	142.0±15.73	0.598	
Cr	86.37±33.93	86.25±32.98	84.42±27.69	0.926	

Notes: Data are presented as number (%), mean ± SD, or median (interquartile range). P value*: Kruskal Wallis Rank Test for continuous variables, Fisher Exact for categorical variables with Expects<10.

Abbreviations: SMOC2, secreted modular calcium-binding protein 2; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, Low Density Lipoprotein; HDL, high density lipoprotein; TG, Triglyceride; TC, Cholesterol; HR, heart rate; HF, heart failure; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; LA, left atrium; LVEDd, left ventricular end-diastolic diameter; RA, right atrium; RVEDd, right ventricular end-diastolic diameter; EF, ejection fraction; FS, fractional shortening; AF, atrial fibrillation; NYHA, new york heart association; CI, confidence interval; Cr, creatinine; Hb, hemoglobin.

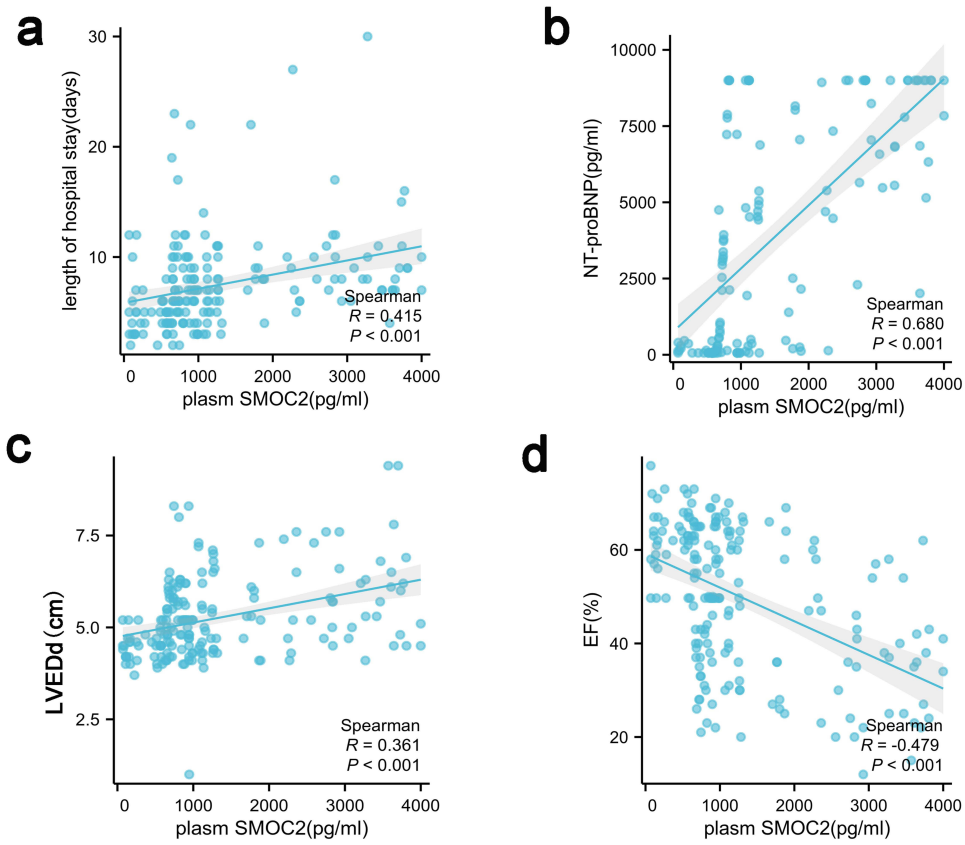

Figure 1 The correlation analysis of plasma SMOC2 between NT-proBNP, LVEDd, EF and length of hospital stay.

Correlation Analysis

A Pearson correlation analysis was performed to determine the correlation between SMOC2 and NT-proBNP, LVEDd, EF, length of hospital stay, etc., in HF. The results showed that the level of SMOC2 was positively correlated with NT-proBNP(R=0.680, p<0.001), LVEDd(R=0.361, p<0.001), and length of hospital stay(R=0.415, p<0.001) and was negatively correlated with EF(R=−0.479, p<0.001) at baseline. Figure 1 depicts the correlation analysis results.

Univariate Analysis of the Relationship Between Variables and Rehospitalization Rate

Rehospitalization rates and potential confounders were identified using a univariate analysis. According to the criterion of $p < 0.1$, the following variables were considered in multivariate Cox regression: age, sex, history of smoking, history of AF, history of diabetes mellitus, medications, Cr, Hb, NT-proBNP, EF, DBP, HR, heart failure duration, length of hospital stay, NYHA function class, SMOC2, LA, LVEDd, RA, and FS. The results of the Univariate analysis are shown in Table 2.

Multivariate COX Regression Analysis of SMOC2 and Readmission Risk of HF Patients

To examine the association between SMOC2 and the rate of readmission in HF patients, we used three models in multivariate COX regression analysis. A stable linear regression was observed when the SMOC2 level was a continuous variable. The fully adjusted model showed readmission risk increased by 2% (HR = 1.020, 95% CI:1.012–1.655, p=0.017). When SMOC2 was used as a categorical variable, we found a statistical difference between the Middle and High groups compared to the Low group in all three models ($p < 0.05$). In addition, the *p* for trend also showed a linear correlation across the three models ($p < 0.05$). The multivariate COX regression analysis is shown in Table 3. The Kaplan-Meier survival curve is shown in Figure 2.

Table 2 The Results of the Univariate Analysis

	Statistics	HR (95% CI) P-value
Age(years)	61.638 ± 11.809	1.036 (1.015, 1.056) 0.00053
SEX		
Female	82 (43.617%)	1.0
Male	106 (56.383%)	1.809 (1.109, 2.950) 0.01751
History of smoking		
No	145 (77.128%)	1.0
Yes	43 (22.872%)	1.832 (1.117, 3.004) 0.01642
History of drinking		
No	151 (80.319%)	1.0
Yes	37 (19.681%)	1.178 (0.677, 2.051) 0.56234
Height(cm)	160.851 ± 5.444	1.030 (0.987, 1.074) 0.17240
Weight(Kg)	59.734 ± 7.457	0.991 (0.957, 1.025) 0.58703
BMI(kg/m^2)	23.079 ± 2.521	0.923 (0.832, 1.023) 0.12697
SBP(mmHg)	128.918 ± 22.912	0.991 (0.979, 1.003) 0.13468
DBP(mmHg)	80.126 ± 15.778	0.982 (0.965, 0.999) 0.03749
LDL(mmol/L)	1.066 ± 0.254	0.341 (0.128, 1.007) 0.33108
HDL(mmol/L)	2.627 ± 0.600	0.844 (0.561, 1.270) 0.41676
TG(mmol/L)	1.695 ± 1.200	1.170 (0.830, 1.328) 0.21546
TC(mmol/L)	3.857 ± 1.391	0.731 (0.628, 1.851) 0.0865
HR(bpm)	78.473 ± 19.192	1.018 (1.008, 1.028) <0.001
History of AF		
No	161 (85.638%)	1.0
Yes	27 (14.362%)	1.943 (1.114, 3.387) 0.01923
Duration of HF(year)	3.380 ± 3.717	1.198 (1.146, 1.253) <0.001
NYHA function class		
I	60 (31.915%)	1.0
II	64 (34.043%)	11.634 (3.527, 38.382) <0.001
III	56 (29.787%)	22.811 (6.999, 74.349) <0.001
IV	8 (4.255%)	43.723 (11.187, 170.878) <0.001
Length of hospital stays(days)	7.544 ± 4.268	1.096 (1.054, 1.140) <0.001
NT-proBNP(pg/mL)	3907.278 ± 3632.791	1.000 (1.000, 1.000) <0.001
SMOC2(pg/mL)	1499.702 ± 1590.602	1.463 (1.022, 2.094) <0.001
LA(cm)	3.993 ± 0.810	2.124 (1.660, 2.718) <0.001
LVEDd(cm)	3.733 ± 0.646	1.830 (1.335, 2.508) <0.001
RA(cm)	5.253 ± 1.124	1.816 (1.514, 2.178) <0.001
RVEDd(cm)	3.536 ± 0.579	1.038 (1.091, 2.700) 0.0665
EF(%)	49.679 ± 15.462	0.946 (0.931, 0.960) <0.001
FS(%)	26.684 ± 9.060	0.909 (0.885, 0.933) <0.001
Anti-platelet therapy		
No	52 (27.660%)	1.0
Yes	13,672.340%)	1.2759(0.7124,2.2851) 0.4125
β-blocker		
No	111 (59.043%)	1.0
Yes	77(40.956%)	1.3357(0.4022,4.4364) 0.6364
ACEI/ARNI/ARB		
No	85 (45.213%)	1.0
Yes	103(54.787%)	0.8873(0.5532,1.4232) 0.6200
Statins		
No	57 (30.319%)	1.0
Yes	131(69.680)	1.0181(0.5831,1.7779)0.9496

(*Continued*)

Table 2 (Continued).

	Statistics	HR (95% CI) P-value
History of diabetes		
No	171 (90.957%)	1.0
Yes	17(9.043%)	0.6347(0.1880,2.1427)0.4640
Cr(μmol/L)	85.68±31.33	1.004(0.996,1.011)0.385
Hb(g/L)	140.26±22.0	1.010(0.999,1.021)0.065

Notes: Data are presented as number (%), mean ± SD, or median (interquartile range).
Abbreviations: CI, confidence interval; HR, heart rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, Low Density Lipoprotein; HDL, high density lipoprotein; TG, Triglyceride; TC, Cholesterol; HF, heart failure; NT-proBNP, N-terminal pro-B-type Natriuretic Peptide; SMOC2, secreted modular calcium-binding protein 2; LA, left atrium; LVEDd, left ventricular end-diastolic diameter; RA, right atrium; RVEDd, right ventricular end-diastolic diameter; EF, ejection fraction; FS, fractional shortening; AF, atrial fibrillation; NYHA, new york heart association; Cr, creatinine; Hb, hemoglobin.

Table 3 The Results of Multivariate COX Regression Analysis of SMOC2 and Readmission Risk of HF Patients

Exposure	Model I	Model II	Model III
SMOC2	1.463 (1.022, 2.094) <0.001	1.332 (1.045, 1.942) <0.001	1.020 (1.012, 1.655) 0.017
SMOC2 tertiles			
Low	1.0	1.0	1.0
Middle	2.825 (1.383, 5.771) 0.004	2.568 (1.253, 5.263) 0.009	1.064 (1.037, 3.662) 0.005
High	5.248 (2.674, 10.301) <0.001	4.281 (2.164, 8.469) <0.001	1.085 (1.086, 3.792) 0.009
p for trend	<0.001	<0.001	<0.001

Notes: In model I, no variables were adjusted. In model II, age and sex were adjusted. In model III: Age, sex, history of smoking, history of AF, NT-proBNP, EF, DBP, HR, heart failure duration, length of hospital stay, NYHA function class, SMOC2, LA, LVEDd, and RA were adjusted.
Abbreviations: SMOC2, secreted modular calcium-binding protein 2; HF, heart failure.

Smooth Curve Fitting and Threshold or Saturation Effect Analysis

Furthermore, we performed a smooth curve fit of a weighted generalized addition model to detect the nonlinear association between SMOC2 and readmission risk during follow-up and further confirmed the results. In patients with HF, plasma SMOC2 was not associated with readmission risk in a nonlinear manner. In addition, we compared two fitted models using threshold or saturation effect analysis to explain the association between SMOC2 and rehospitalization. Ultimately, we found no threshold or saturation effect (p = 0.082). The smooth curve fitting and threshold or saturation effect analysis were shown in Figure 3 and Table 4.

Multivariate COX Regression Analysis of SMOC2 and All-Cause Mortality/ New-Onset Arrhythmias in HF Patients

In order to further clarify the relationship between plasma SMOC2 and the prognosis of patients with HF, we analyzed the relationship between SMOC2 and all-cause mortality and new-onset arrhythmias in this cohort study. Cox regression analysis and Kaplan-Meier survival curve analysis showed that SMOC2 was not associated with the risk of mortality (p=0.42) or new arrhythmias (p=0.69) in patients with HF. The Kaplan-Meier survival curves are shown in Figures 4 and 5.

Discussion

Various outcomes result from HF, including heart failure recurrence, deterioration, arrhythmia, embolisms, and death. Numerous basic studies have identified SMOC2 as a member of SPARC that plays different roles in different systems. Studies on SMOC2, especially clinical studies, are scare, as are studies relating SMOC2 to heart diseases. SMOC2 is

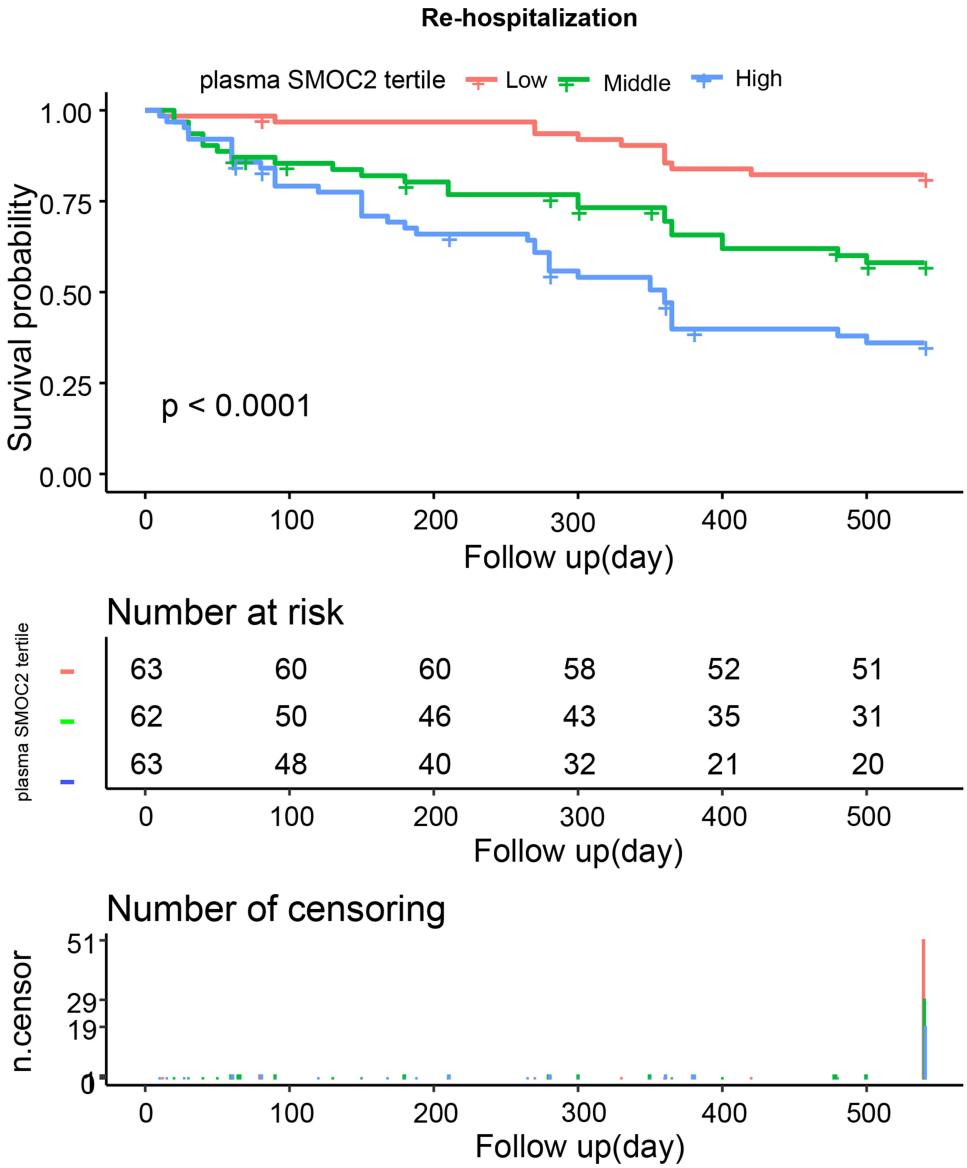

Figure 2 Kaplan–Meier curves demonstrating re-hospitalization stratified by tertiles of SMOC2.

currently associated with lung diseases, rheumatoid arthritis, renal cell carcinomas, thyroid tumors, and asthma,[10–13] and can be used as a predictive biomarker for a variety of diseases. A previous study had compared the gene expression profiles of patients with HF (n=177) and non-HF (n=136) through bioinformatics analysis and identified 38 HF characteristic genes, and their results suggested that SMOC2 plays a significant role in HF.[14] Additionally, SMOC2 is up-regulated in ISO-induced HF models, suggesting that SMOC2 may regulate myocardial remodeling.[8]

Main Findings

This prospective cohort study examined the association of plasma SMOC2 levels with severity and prognosis in 188 patients with ICM. During the 540-day follow-up, 28.2% of patients were re-hospitalized due to cardiac deterioration, 7.4% died, and 19.7% developed new-onset arrhythmias. There were three important findings from this study: Elevated plasma SMOC2 levels increased the risk of readmission in patients with HF (HR = 1.02, 95% CI:1.012–1.655). SMOC2 levels positively correlated with the severity of HF. SMOC2 was not associated with all-cause death or malignant arrhythmias during follow-up.

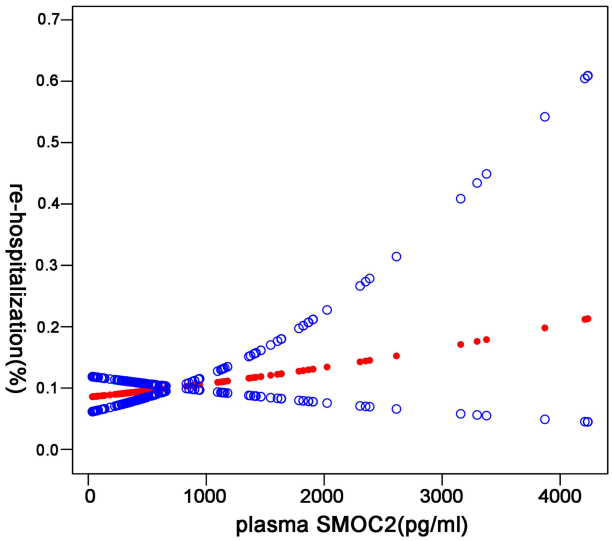

Figure 3 The smooth curve fitting analysis of plasma SMOC2 and re-hospitalization.
Notes: Relationship between plasma SMOC2 and re-hospitalization. The red line represents the smooth curve fit between variables. In comparison, blue bands represent the 95% CI. Age, sex, history of smoking, history of AF, NT-proBNP, EF, DBP, HR, heart failure duration, length of hospital stay, NYHA function class, SMOC2, LA, LVEDd, and RA were adjusted.

Firstly, to explore the utility of SMOC2 in evaluating and diagnosing the severity of HF, we used Pearson correlation analysis in order to examine the correlation between SMOC2 and indicators that represent the disease severity such as NT-proBNP, LVEDd, LA, EF, FS, and length of hospital stay. SMOC2 level was positively correlated with NT-proBNP, LVEDd, and length of hospital stay, and negatively correlated with EF and FS. This study showed that the higher the SMOC2 level, the more severe the decline of cardiac function, the more significant the enlargement of the left ventricle, and the longer the length of hospital stay in patients with heart disorders. SMOC2 is a marker of myocardial fibrosis,[8] and it was confirmed for the first time in this study that SMOC2 can be used to evaluate the severity of HF, which will provide an important reference for molecular markers of HF in practice.

Furthermore, three COX regression models were used to examine the relation between plasma SMOC2 and prognosis in patients with HF. The results showed that the risk of readmission increased for increase in SMOC2 in the fully adjusted model. In order to detect the nonlinear relationship between SMOC2 and readmission rate, we used trend test, weighted generalized addition model for smooth curve fitting, threshold saturation effect. The results showed that there was no nonlinear association between SMOC2 and the risk of rehospitalization. Our study is the first to suggest that plasma SMOC2 is associated with prognoses in patients with cardiac dysfunction. The potential role of SMOC2 in heart conditions has been suggested by previous studies. Zhou et al[15] used weighted gene co-expression network analysis (WGCNA) to identify new biomarkers and biological pathways and found that SMOC2 genes were highly correlated

Table 4 The Threshold or Saturation Effect Analysis

Outcome:	**HR (95% CI) P-value**
Fitting model by stand linear regression	1.148 (1.006, 1.824) 0.0133
Fitting model by two-piecewise linear regression	
Inflection point	984 (pg/mL)
<984	1.142 (1.000, 1.695) 0.0049
>984	1.104 (1.033, 1.749) 0.0176
P-value for the log-likelihood ratio test	0.082

Notes: Age, sex, history of smoking, history of AF, NT-proBNP, EF, DBP, HR, heart failure duration, length of hospital stay, NYHA function class, SMOC2, LA, LVEDd, and RA were adjusted.

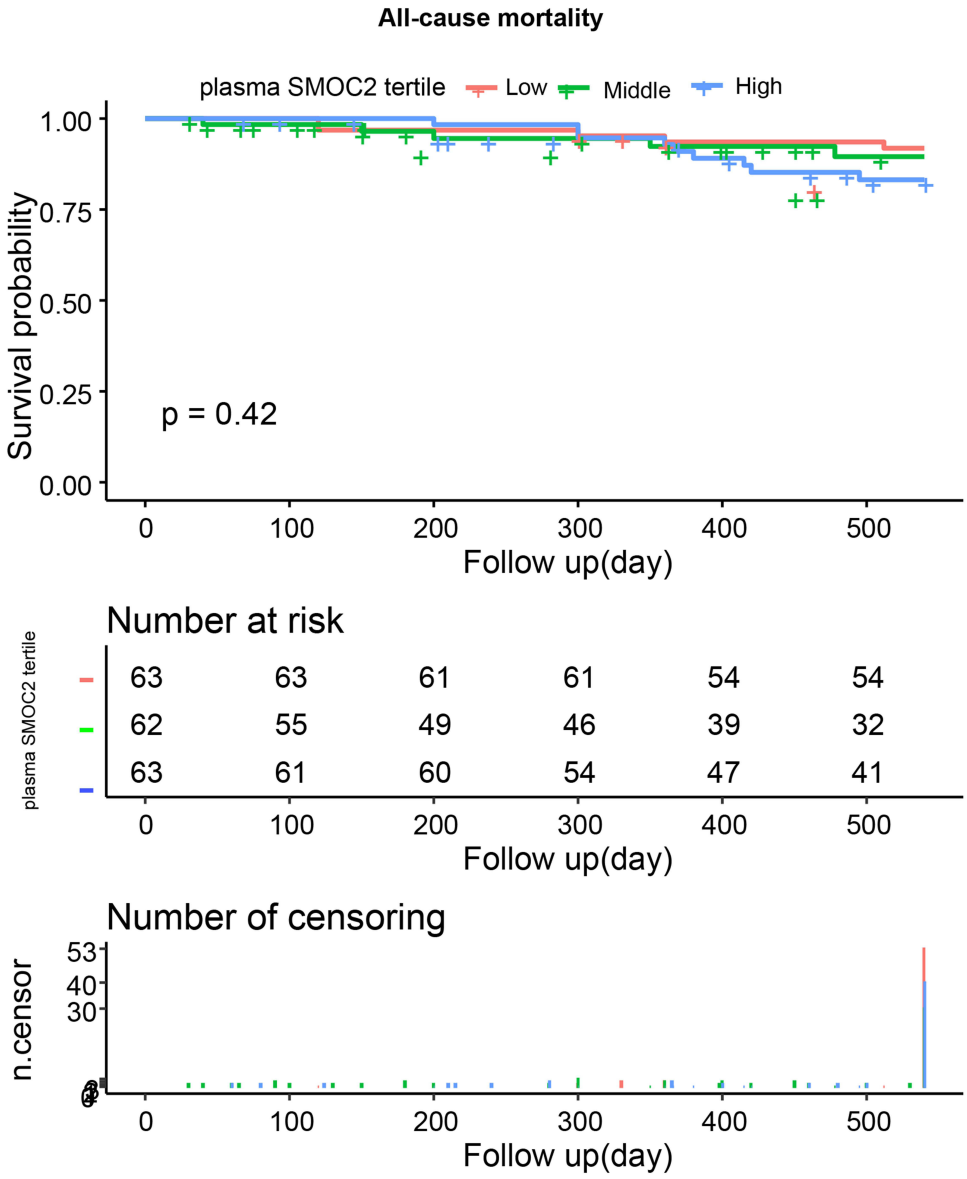

Figure 4 The smooth curve fitting analysis of plasma SMOC2 and all-cause mortality.
Notes: Age, sex, history of smoking, history of AF, NT-proBNP, EF, DBP, HR, heart failure duration, length of hospital stay, NYHA function class, SMOC2, LA, LVEDd, and RA were adjusted.

with HF caused by dilated cardiomyopathy. Previous reports also found that the high expression of SMOC2 was related to cardiac fibrosis in chronic Chagas disease cardiomyopathy.[16] In this study, we found that SMOC2 may be related to the prognosis of patients with ICM. It is suggested that in addition to detecting NT-proBNP and cardiac ultrasound, SMOC2 may also be of great significance in clinical practice.

Thirdly, we attempted to elucidate the association between SMOC2 and all-cause mortality and new-onset arrhythmia in ICM patients by using Cox regression analysis and Kaplan-Meier survival curve analysis, and found that SMOC2 was not associated with the risk of mortality (p=0.42) or new-onset arrhythmia (p=0.69) in patients with heart failure. A larger prospective study may be required to further confirm this finding due to the limited participants included in this study and the short period of follow-up.

SMOC2 has been used as a new biomarker to predict the severity and outcome of different diseases. Studies show that SMOC2 is independent of prognosis in colorectal cancer patients.[17] Schmidt et al[18] found that SMOC2 is a promising non-invasive biomarker for renal fibrosis. At the same time, many studies have confirmed that SMOC2

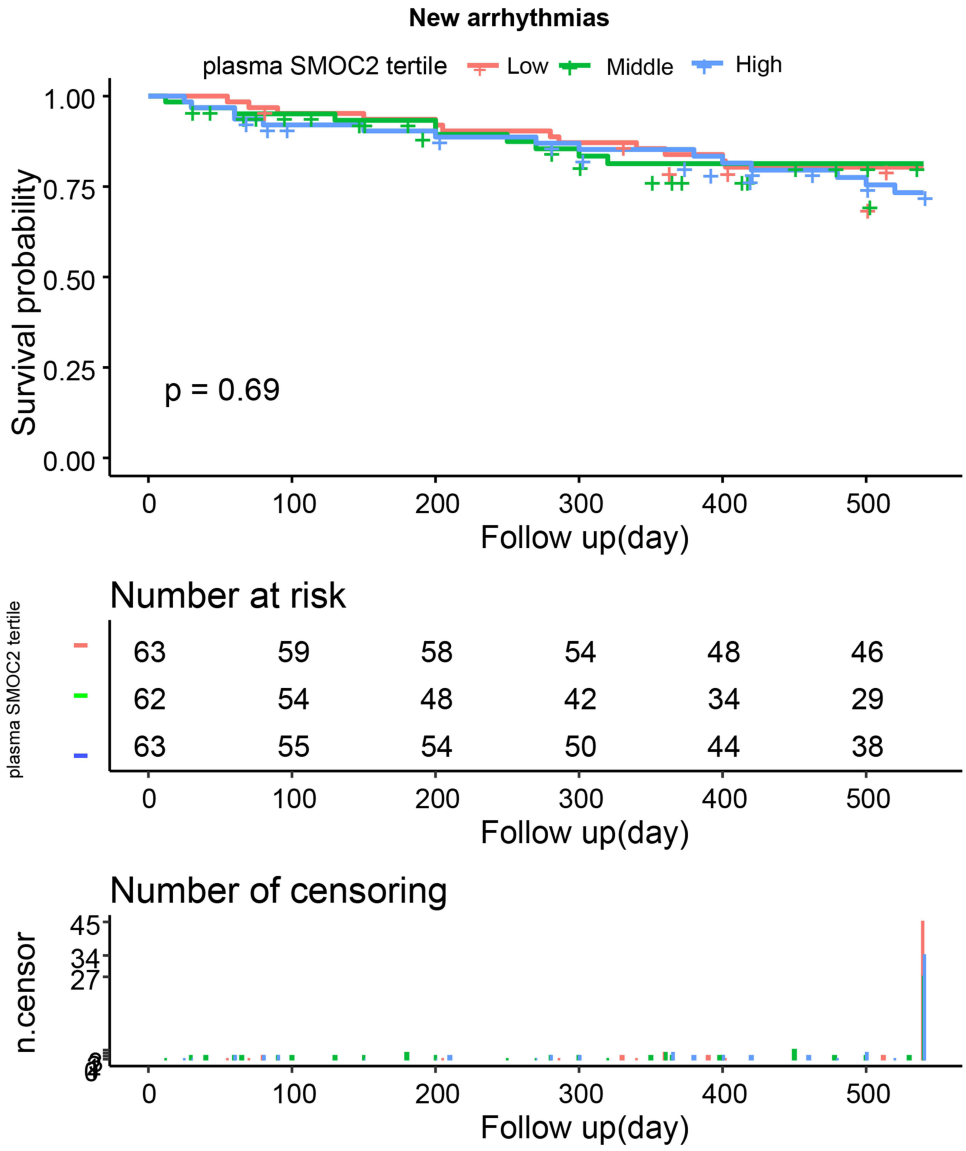

Figure 5 The smooth curve fitting analysis of plasma SMOC2 and new-onset arrhythmias.
Notes: Age, sex, history of smoking, history of AF, NT-proBNP, EF, DBP, HR, heart failure duration, length of hospital stay, NYHA function class, SMOC2, LA, LVEDd, and RA were adjusted.

can promote tissue fibrosis by regulating the transformation of fibroblasts into myofibroblasts, which can lead to fibrosis in lungs, kidneys, and other organs.[19,20] We also clearly elaborated that downregulation of SMOC2 can alleviate myocardial fibrosis by inhibiting the ILK/p38 signaling pathway through animal experiments, indicating that high expression of SMOC2 can lead to myocardial fibrosis.[8] In the pathophysiology and progression of HF, myocardial fibrosis is an important mechanism for the occurrence and development of the cardiac remodeling. Fibrosis of the myocardium can lead to abnormal cardiac structure and left ventricular dysfunction.[21] It has also been demonstrated in animal studies that inhibiting SMOC2 expression inhibits cardiomyocyte apoptosis, suggesting that high levels of SMOC2 can result in apoptosis in cardiomyocytes indirectly.[22] Similarly, cardiomyocyte apoptosis is also involved in the pathophysiological process of heart failure. The loss of cardiomyocytes caused by non-regenerative cardiomyocytes can result in severe heart failure if non-regenerative cardiomyocytes are lost through apoptosis.[23] At present, some relevant studies have found that SMOC2 has a certain role in inflammation-mediated reactions. According to the latest studies, SMOC2 has a significant anti-inflammatory effect on rheumatoid arthritis and nerve transmission.[11,24] In a study on SMOC2 and the prevention of renal function loss in a mouse model of chronic kidney disease,[25] it was found that

SMOC2 could play a central role in fibrogenesis and inflammation by activating a variety of signaling pathways and autophagy in vivo and in vitro, and therapeutic down-regulation of SMOC2 could play an anti-fibrosis and anti-inflammation role. The role of inflammation in cardiac remodeling has been studied for decades, and it has been confirmed that inflammation is involved in the occurrence and development of HF.[26]

We can therefore reasonably assume that SMOC2 is highly correlated with HF progression and deterioration. A high level of SMOC2 expression can cause inflammation, myocardial fibrosis, and apoptosis, ultimately leading to ventricular dysfunction, heart enlargement, and adverse cardiac remodeling. Clinical manifestations include worsening symptoms of heart failure and deterioration of the condition, complications, and increased hospitalization rates.

Clinical Implications

This study assessed the relationship between SMOC2 and HF by analyzing the expression of plasma SMOC2 in patients with ICM. As a result of these findings, we will be able to build on previous pre-clinical studies and advance our understanding of the relationship between SMOC2 and HF and other cardiac conditions in the future. In addition to its complex etiology, HF is characterized by variable conditions, a long course of disease with many adverse outcomes, and a very poor prognosis. There is still a need to explore more biomarkers to predict and evaluate the prognosis of patients with heart failure and guide treatment. As a secreted protein, SMOC2 is widely distributed in many organs and tissues, and its plasma concentration is easy to obtain in clinic. As a result of this study, we found that SMOC2 levels were positively correlated with rehospitalizations in HF sufferings during follow-up, making it a good predictor in clinical practice. In addition to providing new treatment options, these results lay the groundwork for future study of deeper pathogenesis of HF.

Limitations

In this study, our prospective cohort study included a small sample size of patients with ICM and a relatively short follow-up time, resulting in few endpoints such as death and malignant arrhythmias, and failed to find the association between SMOC2 and mortality and malignant arrhythmias. More large-scale data and prospective studies are needed to confirm this, as residual confounding could affect regression analysis.

Conclusion

Increased plasma SMOC2 levels increase the risk of readmission in HF. Plasma SMOC2 is associated with the severity and deterioration of HF and is a good predictor of the risk of readmission in patients.

Ethics Statement

This study was approved by the Biomedical Research Ethics Committee of The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture. We declare that the research on participants was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from study participants prior to commencement of the study.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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