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Soluble fibrin monomer complex is associated with cardio- and cerebrovascular events in patients with heart failure

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ABSTRACT

Background: A biomarker of fibrin formation, the soluble fibrin monomer complex (SFMC), is abnormally elevated in a variety of clinical situations of hypercoagulability. The aim of the present study was to examine the prognostic impact of SFMC, with regard to increased risk of major cardio- and cerebrovascular events (MACCE) and all-cause mortality, on patients with heart failure (HF).

Methods and Results: We conducted a prospective observational study where we analyzed data of 723 hospitalized patients with decompensated HF who were discharged alive and whose SFMC had been measured in a stable condition prior to discharge. The patients were divided into tertiles based on SFMC levels: the first (SFMC < 1.7 μg/ml, n = 250), second (≤1.8 SFMC < 2.9 μg/ml, n = 233), and third (3.0 μg/ml ≤ SFMC, n = 240) tertiles. The prevalence of chronic kidney disease and anemia was significantly higher in the third tertile than in the first and second tertiles. In contrast, age, sex, $CHADS_2$-Vasc score, left ventricular ejection fraction, and prevalence of hypertension, diabetes and atrial fibrillation did not differ among the tertiles. In the Kaplan-Meier analysis, accumulated event rates of both MACCE and all-cause mortality progressively increased from the first to third tertiles (log-rank P < 0.05, respectively). In the multivariate Cox proportional hazard analysis, the third tertile was found to be an independent predictor of MACCE (HR 2.014, P = 0.046) and all-cause mortality (HR 1.792, P = 0.036).

Conclusion: SFMC is an independent predictor of adverse prognosis in patients with HF.

1. Introduction

As a major cause of death among the elderly in many countries, heart failure (HF) has become a significant public health problem [1–3]. It is noteworthy that HF causes coagulation disorders, and is an important risk factor for thromboembolism through the fulfillment of the Virchow triad for thrombogenesis [4–6]. HF is associated with a pro-thrombotic state and disturbed blood coagulation system, regardless of the HF type (systolic or diastolic HF) [7,8]. Moreover, systemic activation of coagulation is a characteristic of HF, which may increase the risk of arterial and venous thromboembolic events, and is associated with an adverse prognosis [7,9–11]. D-dimer originates from the formation and degradation of cross-linked fibrin, reflects the activation of coagulation and fibrinolysis, increases in blood coagulation and degradation of fibrin, and could be a marker of thrombosis [12–14]. It has been reported that elevated D-dimer levels are determinant of the incidence of ischemic stroke, not only in the general population, but also in patients with atrial fibrillation (AF) [15]. Several studies have demonstrated that D-dimer is elevated in patients with HF, and elevated D-dimer was associated with poor outcome in patients with systolic or acute decompensated HF [16–19].

On the other hand, the soluble fibrin monomer complex (SFMC) is a novel biomarker of fibrin formation, produced by thrombin-mediated cleavage of fibrinogen in a hypercoagulable state, and thus could be considered a pre-thrombotic marker [20]. SFMC is abnormally elevated in various clinical situations of hypercoagulability, such as deep vein thrombosis or disseminated intravascular coagulation (DIC). SFMC is reportedly significantly elevated during the initial phase of thrombotic disease, such as myocardial infarction, [21,22] or deep vein thrombosis, [23] and is a better indicator of DIC than the fibrin degradation product (e.g. D-dimer) [24]. However, the association between SFMC and cardiovascular events in HF patients remains uncertain.

The aim of the current study was to examine the prognostic impact of SFMC, concerning increased risk of major cardio- and

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cerebrovascular events (MACCE) and all-cause mortality, on patients with HF. Second, we compared the predictive ability of SFMC with that of D-dimer and CHA_2DS_2-VASc score.

2. Methods

This was a prospective observational study of 723 decompensated HF patients who were discharged from Fukushima Medical University Hospital between January 2016 and April 2019, and whose SFMC was measured in a stable condition prior to discharge. The diagnosis of decompensated HF was made by several cardiologists based on the HF guidelines. [1–3] Blood samples were obtained at hospital discharge each morning, with the patients in a fasted state. Patients with acute coronary syndrome and dialysis were excluded. Patients were divided into tertiles based on levels of SFMC: first (SFMC < 1.7 μg/ml, n = 250), second (≤1.8 SFMC < 2.9 μg/ml, n = 233), and third (3.0 μg/ml ≤ SFMC, n = 240) tertiles. We compared the patient baseline characteristics, and their post-discharge prognosis, including MACCE and all-cause mortality among the tertiles.

We evaluated several co-morbidities, which often coexist and are associated with prognosis in HF patients. Comorbidities were defined in accordance with our previous studies [25–29]. Hypertension was defined as the recent use of antihypertensive drugs, a systolic blood pressure of ≥140 mmHg, and/or a diastolic blood pressure of ≥ 90 mmHg. Diabetes mellitus was defined as the recent use of antidiabetic drugs, a fasting glucose value of ≥ 126 mg/dl, a casual glucose value of ≥ 200 mg/dl, and/or a HbA1c percentage of ≥ 6.5% (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of ≥150 mg/dL, a low-density lipoprotein cholesterol value of ≥ 140 mg/dL, and/or a high-density lipoprotein cholesterol value of < 40 mg/dL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of<60 mL/min/1.73 m^2 using a three-variable Japanese equation [30,31]. Anemia was defined as hemoglobin levels of < 12.0 g/dL in females and < 13.0 g/dL in males [3]. AF was identified from medical records and/or by an electrocardiogram performed during hospitalization [11]. These assessments were performed within one week prior to hospital discharge.

The patients were followed up until January 2020 for MACCE and all-cause death. MACCE was defined as non-fatal and fatal cardio- and cerebrovascular events such as myocardial infarction and stroke. The status and/or dates of death of all patients were obtained from the patient medical records or the attending physicians at the patient referring hospital. We were able to follow up on all patients. Survival time was calculated from the date of hospitalization until the date of death or last follow-up. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University, and this study complied with the Declaration of Helsinki and the statement of STROBE (Strengthening the Reporting of Observational studies in Epidemiology) [32,33].

2.1. Measurement of plasma SFMC levels

SFMC was analyzed in a coagulometer (CS-5100, Sysmex, Co., Ltd., Kobe, Japan) using a latex immunoturbidimetry assay with an anti-SFC monoclonal antibody (Auto LIA FM, Nissui Pharmaceutical, Tokyo, Japan). The inter- and intra-assay variation coefficient was < 3%, and the lower limit of detection was 0.03 μg/ml. Plasma D-dimer level was measured using the reagent hexamate D-dimer (Medical and Biological Laboratories, Co., Ltd., Nagoya, Japan) on a STA-R EVOLUTION automated coagulation analyzer (Diagnostica Stago, Asnieres France). B-type natriuretic peptide (BNP) levels were measured using a specific immunoradiometric assay (Shionoria BNP kit, Shionogi, Osaka, Japan).

2.2. Echocardiography

Echocardiography was performed blindly by experienced echocardiographers using standard techniques [34]. The echocardiographic parameters investigated included left ventricular ejection fraction (LVEF), right ventricular fractional area change (RV-FAC), tricuspid valve regurgitation pressure gradient (TR-PG) and inferior vena cava (IVC). The LVEF was calculated using Simpson's method in a four-chamber view. The RV-FAC, defined as (end diastolic area - end systolic area)/end diastolic area × 100, was used as a measure of right ventricular systolic function. All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA).

2.3. Statistical analysis

Parametric variables are presented as mean ± SD, non-parametric variables (e.g. C-reactive protein and B-type natriuretic peptide) are presented as median and interquartile range, and categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables. We used the analysis of variance for continuous variables, followed by the Bonferroni post-hoc test. Kaplan-Meier analysis was used to evaluate the cardiac death and cardiac events, and the log-rank test was used for initial comparisons. Prognostic value was tested by univariate and multivariate Cox proportional hazard analyses. In the multivariate Cox proportional hazard analysis, to prepare for potential confounding, we considered the following clinical factors: age, gender, blood pressure, New York Heart Association functional class, ischemic etiology, BNP, LVEF, co-morbidities and medications, which are known to be associated with HF prognosis. In addition, receiver operating characteristic (ROC) curves were used to investigate predictive ability, and comparisons of ROC curves were carried out using the DeLong test [35]. Univariate parameters with P-values of < 0.10 were included in the multivariate analysis, and a p value of < 0.05 was considered statistically significant for all comparisons. All analyses were performed using a statistical software package (SPSS ver. 24.0, IBM, Armonk, NY, USA).

3. Results

Comparisons of the baseline patient characteristics are summarized in Table 1. Although age, body mass index and $CHA2DS_2$-VASc score tended to be higher, the prevalence of CKD and anemia was significantly higher, NYHA class III or IV tended to be higher, and the usage of diuretics was significantly higher in the third tertile, no significant difference in sex, blood pressure, heart rate, ischemic etiology, other co-morbidities or medications was observed among the tertiles. In the laboratory and echocardiographic data (Table 1), BNP and D-dimer were highest, and platelet count was lowest in the third tertile. In contrast, activated partial thromboplastin time, C-reactive protein, and sodium did not differ among the groups. Echocardiographic parameters showed no statistical differences among the tertiles.

In the follow-up period (mean 422 days, range 4–939 days), there were 61 MACCEs (17 S, 11 coronary events and 33 cardiac deaths) and 82 deaths (42 cardiac deaths and 40 non-cardiac deaths). In the Kaplan-Meier analysis (Fig. 1), the accumulated event rates of MACCE and all-cause death progressively increased from the first to third tertiles (log-rank P = 0.014, P < 0.001, respectively). In the Cox proportional hazard analysis (Table 2), after

Table 1
Comparisons of clinical features.

	First tertile SFMC < 1.7 μg/ml N = 250	Second tertile ≤1.8 SFMC < 2.9 μg/ml N = 233	Third tertile SFMC ≥ 3.0 μg/ml N = 240	P-value
SFMC (μg/ml)	1.3 (1.0–1.5)	2.2 (2.0–2.5)	6.2 (3.9–26.2) **††	<0.001
Age	66.3 ± 13.6	67.1 ± 15.2	69.3 ± 16.0	0.082
Male gender (n, %)	141 (56.4)	136 (58.4)	139 (57.9)	0.899
Body mass index (kg/m^2)	23.5 ± 4.2	23.4 ± 4.4	22.9 ± 4.5	0.184
Systolic BP (mmHg)	125.6 ± 24.8	125.5 ± 23.2	126.0 ± 26.5	0.975
diastolic BP (mmHg)	72.4 ± 17.3	69.9 ± 14.8	70.8 ± 20.3	0.298
Heart rate (bpm)	77.3 ± 24.9	76.3 ± 21.9	79.5 ± 22.0	0.314
NYHA III or IV (n, %)	16 (6.4)	14 (6.0)	27 (11.3)	0.068
Ischemic etiology (n, %)	53 (21.2)	59 (25.3)	49 (20.4)	0.388
CHA_2DS_2-VASc score	4.0 ± 1.7	4.1 ± 1.8	4.3 ± 1.7	0.096
Co-morbidity				
Atrial fibrillation (n, %)	99 (39.6)	75 (32.2)	78 (32.5)	0.150
Hypertension (n, %)	149 (59.6)	147 (63.1)	156 (65.0)	0.456
Diabetes (n, %)	85 (34.0)	86 (36.9)	98 (40.8)	0.292
Dyslipidemia (n, %)	170 (68.0)	156 (67.0)	150 (62.5)	0.399
CKD (n, %)	140 (56.0)	119 (51.1)	150 (62.5)	0.042
Anemia (n, %)	113 (45.2)	102 (43.8)	143 (59.6)	0.001
Stroke (n, %)	38 (15.2)	38 (16.3)	35 (14.6)	0.870
PAD (n, %)	32 (12.8)	21 (9.0)	31 (12.9)	0.321
Medication				
RAS inhibitors (n, %)	171 (68.4)	152 (65.2)	154 (64.2)	0.588
β-blockers (n, %)	167 (66.8)	150 (64.4)	162 (67.5)	0.753
Diuretics (n, %)	175 (70.0)	152 (65.2)	186 (77.5)	0.012
Inotropic (n, %)	24 (9.6)	32 (13.7)	36 (15.0)	0.171
Antiplatelets (*n*, %)	116 (46.4)	122 (52.4)	100 (41.7)	0.066
Anti-coagulations (*n*, %)	177 (70.8)	111 (47.6)	122 (50.8)	<0.001
-Vitamin K antagonists (*n*, %)	100 (40.0)	56 (24.0)	60 (25.0)	≤0.001
-DOACs (*n*, %)	77 (30.8)	55 (23.6)	62 (25.8)	0.186
-Factor X blockers (*n*, %)	62 (24.8)	45 (19.3)	49 (20.4)	0.297
-Dabigatran (*n*, %)	15 (6.0)	10 (4.3)	13 (5.4)	0.696
Laboratory data				
Platelet count (10^3/μL)	215.3 ± 70.5	205.3 ± 63.8	197.4 ± 84.5*	0.031
PT-INR	1.4 ± 0.8	1.2 ± 0.6*	1.4 ± 1.1	0.044
APTT (sec)	35.7 ± 12.3	34.2 ± 20.5	35.1 ± 15.8	0.625
CRP (mg/dl)	0.14 (0.05–0.615)	0.14 (0.07–0.38)	0.38 (0.11–1.21)	0.113
Sodium (mEq/l)	139.5 ± 3.4	139.5 ± 3.1	139.4 ± 4.8	0.944
BNP (pg/ml) §	164.0 (73.0–417.6)	220.8 (72.9–528.0)	484.8 (190.5–1067.4)**††	<0.001
D-dimer (mg/l)	0.5 (0.5–0.7)	0.7 (0.5–1.5)	2.8 (1.3–5.5)**††	<0.001
Echocardiographic data				
LVEF (%)	51.1 ± 17.0	52.2 ± 16.2	50.0 ± 16.8	0.520
RV-FAC (%)	39.1 ± 12.1	40.0 ± 14.6	39.9 ± 16.5	0.890
TR-PG (mmHg)	30.0 ± 17.9	28.3 ± 18.6	27.9 ± 15.5	0.446
IVC (mm)	15.8 ± 5.0	15.0 ± 4.4	15.6 ± 5.0	0.196

*P < 0.05 and **P < 0.01 vs second tertile; †P < 0.05 and ††P < 0.01 vs third tertile.
SFMC, soluble fibrin monomer complex; BP, blood pressure; NYHA, New York Heart Association; CKD, chronic kidney disease; PAD, peripheral artery disease; RAS, renin-angiotensin system; DOAC, direct oral anticoagulants; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; CRP, C-reactive protein; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change; TR-PG, tricuspid valve regurgitation pressure gradient; IVC, inferior vena cava.

adjusting for other confounding factors, high SFMC was an independent predictor of MACCE (hazard ratio 2.014, 95% confidence interval 1.014–4.004, P = 0.046) and all-cause mortality (hazard ratio 1.792, 95%CI 1.046–3.395, P = 0.036) in the HF patients.

ROC analysis (Fig. 2) demonstrated that a SFMC cut-off value of 2.0 μg/ml predicted MACCE with a sensitivity of 76% and a specificity of 62% (AUC 0.67, 95% confidence interval, 0.60–0.74; P < 0.01), and all-cause mortality with a sensitivity of 78% and a specificity of 65% (AUC 0.70, 95% confidence interval, 0.64–0.76; P < 0.01), and that the predictive value of SFMC was superior or comparable to that of D-dimer and CHA_2DS_2-VASc score.

4. Discussion

The present study is the first to report that high SFMC level, which is a marker of fibrin formation, in patients with HF is associated with high MACCE and all-cause mortality, and that the predictive ability of SFMC is superior or comparable to that of D-dimer and CHA_2DS_2-VASc score.

HF patients have elevated levels of coagulation markers such as D-dimer [10]. Hypercoagulability in HF could be derived from many causes, such as blood stasis, hemodynamic disorders, [36–38] impaired cardiac structure and/or function, dilatation of cardiac chambers, reduced myocardial contractility, low cardiac output, mobility limitation, [39] increased intra-cardiac and central venous pressure, inflammation activation, [40] neurohormonal activation, impaired endothelial function, and arrhythmias such as AF [5,7,38,40–42]. The hypercoagulability status predisposes the patients to embolic events, and anticoagulation therapy could be associated with better clinical outcomes [11].

Previous studies have shown that elevated D-dimer level predicted the development of incident systolic HF [43]. It has recently been reported that high admission D-dimer level is associated with adverse in-hospital and poor mid-term prognosis in patients with

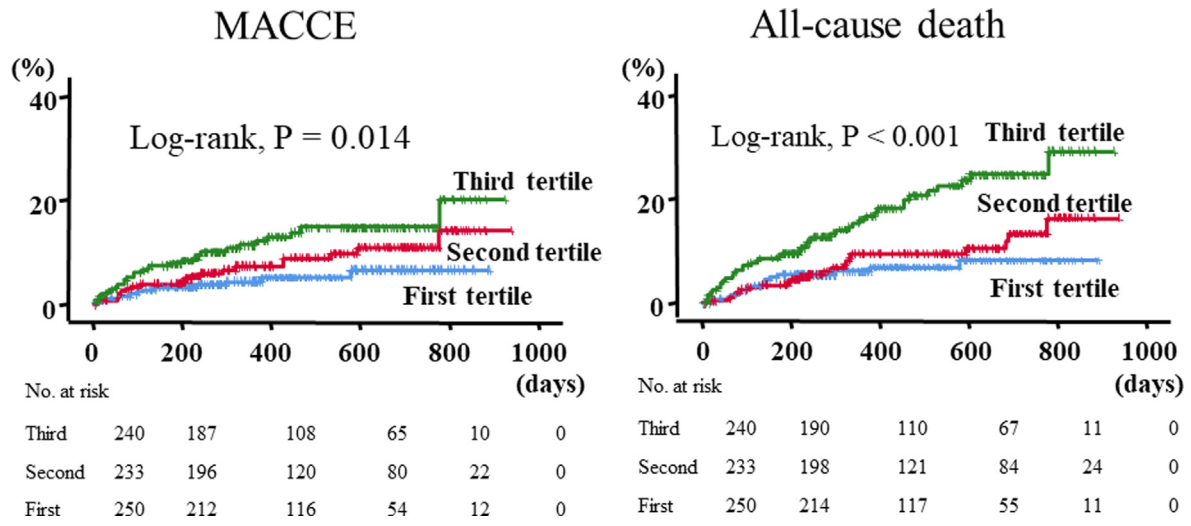


Fig. 1. Accumulated event rates stratified by SFMC. SFMC, Soluble fibrin monomer complex; MACCE, major cardio- and cerebrovascular events.

Table 2
Cox proportional hazard analysis: the prognostic impact of SFMC.

	Unadjusted		Adjusted*	
	HR (95% CI)	P value	HR (95% CI)	P value
MACCE				
First tertile	Reference			
Second tertile	1.690 (0.825–3.461)	0.151	1.587 (0.771–3.267)	0.209
Third tertile	2.608 (1.331–5.113)	0.005	2.014 (1.014–4.004)	0.046
All-cause mortality				
First tertile	Reference			
Second tertile	1.363 (0.715–2.600)	0.346	1.156 (0.602–2.220)	0.663
Third tertile	2.938 (1.657–5.207)	≤ 0.001	1.792 (1.046–3.395)	0.036

HR, hazard ratio; CI, confidence interval; MACCE, major cardio- and cerebrovascular events.
* Adjusted for age, gender, body mass index, systolic blood pressure, New York Heart Association functional class, left ventricular ejection fraction, B-type natriuretic peptide, presence or absence of ischemic etiology, atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, anemia, stroke, peripheral artery disease, use of renin-angiotensin system inhibitors, β-blockers, diuretics and inotoropics.

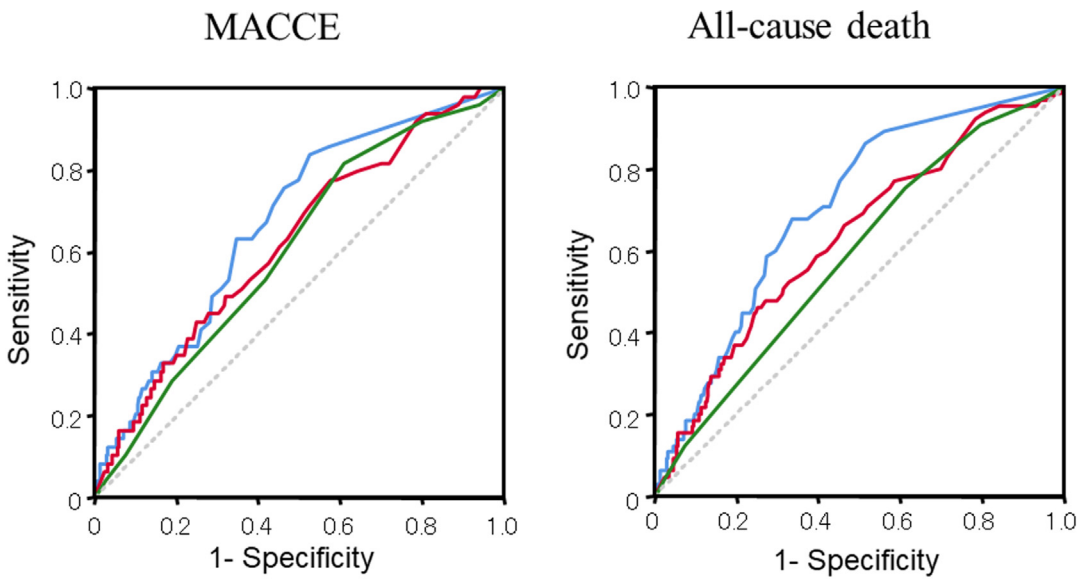
acute decompensated HF [17]. Another study reported that elevated D-dimer independently predicts increased cardiovascular mortality [19]. The precise mechanisms of elevated coagulation markers (e.g. D-dimer level) as an independent risk factor for adverse prognosis in patients with HF are not well understood. There are some possible explanations. Firstly, hemostatic abnormalities may reflect the integrated effect of cardiac and non-cardiac functional status, such as in coronary artery disease, stroke, vascular dementia [16,44]. Hemostatic abnormalities may represent the integrated effect of insufficient systemic organ perfusion, organ congestion and cardiac structural, functional, and electrophysiological abnormalities. Secondly, it is known that either thrombotic or hemorrhagic events are associated with increased risk of poor outcome. [2,16] Furthermore, previous studies have shown that D-dimer can promote inflammatory reactions by inducing the synthesis and release of some inflammatory cytokines such as interleukin-1β and interleukin-6, [45] resulting in increased mortality.

The SFMC is produced by thrombin-mediated cleavage of fibrinogen in a hypercoagulable state, and could be considered a pre-thrombotic marker [20]. It has been recently reported that, in patients with AF taking the vitamin K antagonist, high SFMC levels were associated with the risk of adverse cardiovascular events, and that the addition of SFMC to the CHA_2DS_2-VASc score improved the score's predictive performance [46]. On the other hand, in another study that included patients with AF who were being treated with vitamin K antagonist, elevated SFMC levels during anticoagulant treatment were not useful as predictors of thromboembolic events [47]. We found in the present study, for predicting thromboembolic events or worse prognosis in HF patients, that SFMC, a biomarker of fibrin formation, might be more sensitive and could be superior to D-dimer as a fibrin degradation product [24].

5. Study strengths and limitations

Our study has several strengths. For example, this is the first study to show the association of increased serum SFMC with adverse prognosis in HF patients, taking into consideration a multifaceted background including laboratory data and echocardiographic data within a given population. Second, the current study's population was larger than those of previous studies, [16,48] and we were able to follow up on all patients.

The present study has several limitations. First, as a prospective cohort study of a single center with a relatively small number of patients, the present results may not be representative of a general population. Although we performed multivariate Cox proportional hazard analysis with several confounding factors, we cannot rule out residual confounding variables, and the effects of differences in the backgrounds among the groups might not be completely



	AUC	95%CI	P-value	vs.CHADS$_2$	vs. D-dimer	AUC	95%CI	P-value	CHADS$_2$	vs. D-dimer
CHADS$_2$	0.60	0.53–0.68	P = 0.02	Reference	P = 0.42	0.59	0.52–0.66	P = 0.02	Reference	P = 0.11
D-dimer	0.62	0.54–0.70	P < 0.01	P = 0.42	Reference	0.63	0.56–0.70	P < 0.01	P = 0.11	Reference
SFMC	0.67	0.60–0.74	P < 0.01	P = 0.04	P=0.17	0.70	0.64–0.76	P < 0.01	P = 0.02	P = 0.04

Fig. 2. Receiver operating curve (ROC) to predict MACCE and all-cause mortality in patients with heart failure. MACCE, major cardio- and cerebrovascular events.

adjusted. Second, since the present study included variables during hospitalization for decompensated HF, without taking into consideration changes in medical parameters and post-discharge treatment, we should pay attention to extrapolation of our findings to patients with stable chronic HF. Third, since this was a prospective observational study, the causal relationships and mechanisms of increased SFMC and worse prognosis could not be fully explained. Additionally, we did not measure other markers of procoagulant states such as thrombin generation, platelet reactivity or proacoagulant microvesicles, and could not compare their utility to those of SFMC. Therefore, the present results should be viewed as preliminary, and further studies with a larger population are needed.

6. Conclusion

Increased serum levels of SFMC, a marker of fibrin formation, are associated with adverse prognosis in HF patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H. Tsutsui, M. Isobe, H. Ito, H. Ito, K. Okumura, M. Ono, et al., JCS 2017/JHFS 2017 Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure- Digest Version, Circ. J. 83 (2019) 2084–2184.
[2] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 37 (2016) 2129–2200.
[3] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., M.H. Drazner, et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 62 (2013) e147–e239.
[4] Abdul-Rahim AH, Perez AC, Fulton RL, Jhund PS, Latini R, Tognoni G, et al. Risk of Stroke in Chronic Heart Failure Patients Without Atrial Fibrillation: Analysis of the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) Trials. Circulation. 2015;131:1486-94; discussion 94
[5] T.M. Ng, F. Tsai, N. Khatri, M.N. Barakat, U. Elkayam, Venous thromboembolism in hospitalized patients with heart failure: incidence, prognosis, and prevention, Circ Heart Fail. 3 (2010) 165–173.
[6] G.Y. Lip, C.R. Gibbs, Does heart failure confer a hypercoagulable state? Virchow's triad revisited, J. Am. Coll. Cardiol. 33 (1999) 1424–1426.
[7] B. Jug, N. Vene, B.G. Salobir, M. Sebestjen, M. Sabovic, I. Keber, Procoagulant state in heart failure with preserved left ventricular ejection fraction, Int Heart J. 50 (2009) 591–600.
[8] G.Y. Lip, L.A. Pearce, B.S. Chin, D.S. Conway, R.G. Hart, Effects of congestive heart failure on plasma von Willebrand factor and soluble P-selectin concentrations in patients with non-valvar atrial fibrillation, Heart 91 (2005) 759–763.
[9] S.G. Wannamethee, P.H. Whincup, O. Papacosta, L. Lennon, G.D. Lowe, Associations between blood coagulation markers, NT-proBNP and risk of incident heart failure in older men: The British Regional Heart Study, Int. J. Cardiol. 230 (2017) 567–571.
[10] A. Mebazaa, T.E. Spiro, H.R. Buller, L. Haskell, D. Hu, R. Hull, et al., Predicting the risk of venous thromboembolism in patients hospitalized with heart failure, Circulation 130 (2014) 410–418.
[11] A. Yoshihisa, Y. Sato, T. Sato, S. Suzuki, M. Oikawa, Y. Takeishi, Better clinical outcome with direct oral anticoagulants in hospitalized heart failure patients with atrial fibrillation, BMC Cardiovasc. Disord. 18 (2018) 11.
[12] J.I. Weitz, J.C. Fredenburgh, J.W. Eikelboom, A Test in Context: D-Dimer, J. Am. Coll. Cardiol. 70 (2017) 2411–2420.
[13] G.P. Koracevic, Pragmatic classification of the causes of high D-dimer, Am. J. Emerg. Med. 27 (1016) (2009) e5–e7.
[14] K. Yamamoto, U. Ikeda, K. Furuhashi, M. Irokawa, T. Nakayama, K. Shimada, The coagulation system is activated in idiopathic cardiomyopathy, J. Am. Coll. Cardiol. 25 (1995) 1634–1640.
[15] T. Sadanaga, M. Sadanaga, S. Ogawa, Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy, J. Am. Coll. Cardiol. 55 (2010) 2225–2231.
[16] B. Huang, Y.J. Li, J. Shen, Y. Yang, G. Liu, S.X. Luo, D-dimer level and long-term outcome in patients with end-stage heart failure secondary to idiopathic dilated cardiomyopathy, J. Geriatr. Cardiol. 16 (2019) 621–629.
[17] Y. Minami, S. Haruki, K. Jujo, R. Itani, K. Shimazaki, H. Arashi, et al., Elevated D-dimer levels predict an adverse outcome in hospitalized patients with acute decompensated heart failure, Int. J. Cardiol. 204 (2016) 42–44.
[18] A. Zorlu, M.B. Yilmaz, H. Yucel, G. Bektasoglu, M. Refiker Ege, I. Tandogan, Increased d-dimer levels predict cardiovascular mortality in patients with systolic heart failure, J. Thromb. Thrombolysis 33 (2012) 322–328.

[19] U. Alehagen, U. Dahlstrom, T.L. Lindahl, Elevated D-dimer level is an independent risk factor for cardiovascular death in out-patients with symptoms compatible with heart failure, Thromb. Haemost. 92 (2004) 1250–1258.
[20] H. Hou, Z. Ge, P. Ying, J. Dai, D. Shi, Z. Xu, et al., Biomarkers of deep venous thrombosis, J. Thromb. Thrombolysis 34 (2012) 335–346.
[21] L.V. Lee, G.A. Ewald, C.R. McKenzie, P.R. Eisenberg, The relationship of soluble fibrin and cross-linked fibrin degradation products to the clinical course of myocardial infarction, Arterioscler. Thromb. Vasc. Biol. 17 (1997) 628–633.
[22] M. Saigo, D.D. Waters, S. Abe, S. Biro, S. Minagoe, I. Maruyama, et al., Soluble fibrin, C-reactive protein, fibrinogen, factor VII, antithrombin, proteins C and S, tissue factor, D-dimer, and prothrombin fragment 1 + 2 in men with acute myocardial infarction </=45 years of age, Am. J. Cardiol. 94 (2004) 1410–1413.
[23] V. Dopsaj, N. Bogavac-Stanojevic, D. Vasic, D. Vukosavljevic, J. Martinovic, J. Kotur-Stevuljevic, et al., Excluding deep venous thrombosis in symptomatic outpatients: is fibrin monomer aid to D-dimer analysis?, Blood Coagul. Fibrinol. 20 (2009) 546–551.
[24] N. Singh, H.P. Pati, S. Tyagi, A.D. Upadhyay, R. Saxena, Evaluation of the Diagnostic Performance of Fibrin Monomer in Comparison to d-Dimer in Patients With Overt and Nonovert Disseminated Intravascular Coagulation, Clin. Appl. Thromb. Hemost. 23 (2017) 460–465.
[25] A. Yoshihisa, Y. Ichijo, K. Watanabe, Y. Sato, Y. Kanno, M. Takiguchi, et al., Prior History and Incidence of Cancer Impacts on Cardiac Prognosis in Hospitalized Patients With Heart Failure, Circ. J. 83 (2019) 1709–1717.
[26] A. Yoshihisa, Y. Sato, Y. Kanno, M. Takiguchi, T. Yokokawa, S. Abe, et al., Prognostic impacts of changes in left ventricular ejection fraction in heart failure patients with preserved left ventricular ejection fraction, Open Heart. 7 (2020) e001112.
[27] A. Yoshihisa, M. Takiguchi, T. Shimizu, Y. Nakamura, H. Yamauchi, S. Iwaya, et al., Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease, J. Cardiol. 64 (2014) 256–264.
[28] A. Sato, A. Yoshihisa, Y. Kanno, M. Takiguchi, S. Miura, T. Shimizu, et al., Associations of dipeptidyl peptidase-4 inhibitors with mortality in hospitalized heart failure patients with diabetes mellitus, ESC Heart Fail. 3 (2016) 77–85.
[29] A. Yoshihisa, S. Watanabe, Y. Kanno, M. Takiguchi, A. Sato, T. Yokokawa, et al., The CHA2 DS2 -VASc score as a predictor of high mortality in hospitalized heart failure patients, ESC Heart Fail. 3 (2016) 261–269.
[30] A.S. Levey, K.U. Eckardt, Y. Tsukamoto, A. Levin, J. Coresh, J. Rossert, et al., Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO), Kidney Int. 67 (2005) 2089–2100.
[31] S. Matsuo, E. Imai, M. Horio, Y. Yasuda, K. Tomita, K. Nitta, et al., Revised equations for estimated GFR from serum creatinine in Japan, Am. J. Kidney Dis. 53 (2009) 982–992.
[32] Rickham PP. Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki. Br Med J. 1964;2:177
[33] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gotzsche, J.P. Vandenbroucke, et al., Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, BMJ 335 (2007) 806–808.
[34] R.M. Lang, M. Bierig, R.B. Devereux, F.A. Flachskampf, E. Foster, P.A. Pellikka, et al., Recommendations for chamber quantification, Eur J Echocardiogr. 7 (2006) 79–108.
[35] E.R. DeLong, D.M. DeLong, D.L. Clarke-Pearson, Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach, Biometrics 44 (1988) 837–845.
[36] E. Tanai, S. Frantz, Pathophysiology of Heart Failure, Compr Physiol. 6 (2015) 187–214.
[37] C.J. Davis, P.A. Gurbel, W.A. Gattis, S.Y. Fuzaylov, G.V. Nair, C.M. O'Connor, et al., Hemostatic abnormalities in patients with congestive heart failure: diagnostic significance and clinical challenge, Int. J. Cardiol. 75 (2000) 15–21.
[38] S.M. Jafri, Hypercoagulability in heart failure, Semin. Thromb. Hemost. 23 (1997) 543–545.
[39] M. Albabtain, M.J. Brenner, J.M. Nicklas, S.L. Hummel, M.P. McCormick, J.L. Pawlowski, et al., Hyponatremia, Cognitive Function, and Mobility in an Outpatient Heart Failure Population, Med. Sci. Monit. 22 (2016) 4978–4985.
[40] Y. Zhang, J. Bauersachs, H.F. Langer, Immune mechanisms in heart failure, Eur. J. Heart Fail. 19 (2017) 1379–1389.
[41] R. Marcucci, A.M. Gori, F. Giannotti, M. Baldi, V. Verdiani, S. Del Pace, et al., Markers of hypercoagulability and inflammation predict mortality in patients with heart failure, J. Thromb. Haemost. 4 (2006) 1017–1022.
[42] R. Itani, Y. Minami, S. Haruki, E. Watanabe, N. Hagiwara, Prognostic impact of disseminated intravascular coagulation score in acute heart failure patients referred to a cardiac intensive care unit: a retrospective cohort study, Heart Vessels 32 (2017) 872–879.
[43] R.A. de Boer, M. Nayor, C.R. deFilippi, D. Enserro, V. Bhambhani, J.R. Kizer, et al., Association of Cardiovascular Biomarkers With Incident Heart Failure With Preserved and Reduced Ejection Fraction, JAMA Cardiol. 3 (2018) 215–224.
[44] B.S. Chin, A.D. Blann, C.R. Gibbs, N.A. Chung, D.G. Conway, G.Y. Lip, Prognostic value of interleukin-6, plasma viscosity, fibrinogen, von Willebrand factor, tissue factor and vascular endothelial growth factor levels in congestive heart failure, Eur. J. Clin. Invest. 33 (2003) 941–948.
[45] S.C. Robson, E.G. Shephard, R.E. Kirsch, Fibrin degradation product D-dimer induces the synthesis and release of biologically active IL-1 beta, IL-6 and plasminogen activator inhibitors from monocytes in vitro, Br. J. Haematol. 86 (1994) 322–326.
[46] J.M. Rivera-Caravaca, V. Roldan, M. Romera, M.A. Esteve-Pastor, M. Valdes, G.Y. H. Lip, et al., Soluble Fibrin Monomer Complex and Prediction of Cardiovascular Events in Atrial Fibrillation: The Observational Murcia Atrial Fibrillation Project, J. Gen. Intern. Med. 33 (2018) 847–854.
[47] T. Sadanaga, H. Mitamura, Soluble fibrin monomer complex levels during oral anticoagulant therapy do not predict subsequent thromboembolic events in patients with permanent atrial fibrillation, Int. J. Cardiol. 168 (2013) 578–580.
[48] Y. Hamatani, T. Nagai, M. Nakai, K. Nishimura, Y. Honda, H. Nakano, et al., Elevated Plasma D-Dimer Level Is Associated With Short-Term Risk of Ischemic Stroke in Patients With Acute Heart Failure, Stroke 49 (2018) 1737–1740.