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

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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 < 1.7µg/ml, n = 250), second (1.7 ≤ SFMC < 2.9µg/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, CHADS2-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.

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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
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 CHA2DS2-VASc score.

2. Methods

This was a prospective observational study of 723 decompensated HF patients who were discharged from Fukushima Medical University 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 [11–3]. 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 m² 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 (RVFAC), 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, comorbidities 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 CHA2DS2-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
Comparisons of clinical features.

| SFMC (μg/ml) | Age | Male gender (n, %) | Body mass index (kg/m²) | Systolic BP (mmHg) | Diastolic BP (mmHg) | Heart rate (bpm) | NYHA III or IV (n, %) | Ischemic etiology (n, %) | CHA2DS2-VASc score |
|-------------|-----|--------------------|-------------------------|--------------------|-------------------|-----------------|---------------------|------------------------|---------------------|
| 1.3 (1.0–1.5) | 66.3 ± 13.6 | 141 (56.4) | 23.5 ± 4.2 | 125.6 ± 24.8 | 72.4 ± 17.3 | 77.3 ± 24.9 | 16 (6.4) | 53 (21.2) | 4.0 ± 1.7 |
| 2.2 (2.0–2.5) | 67.1 ± 15.2 | 136 (58.4) | 23.4 ± 4.4 | 125.5 ± 23.2 | 69.9 ± 14.8 | 76.3 ± 21.9 | 14 (6.0) | 59 (25.3) | 4.1 ± 1.1 |
| 6.2 (3.9–26.2)** | 69.3 ± 16.0 | 139 (57.9) | 22.9 ± 4.5 | 126.0 ± 26.5 | 70.8 ± 20.3 | 79.5 ± 22.0 | 27 (11.3) | 49 (20.4) | 4.3 ± 1.7 |

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.

Table 1
Comparisons of clinical features.

| SFMC (μg/ml) | Age | Male gender (n, %) | Body mass index (kg/m²) | Systolic BP (mmHg) | Diastolic BP (mmHg) | Heart rate (bpm) | NYHA III or IV (n, %) | Ischemic etiology (n, %) | CHA2DS2-VASc score |
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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 1.79 μg/ml predicted MACCE with a sensitivity of 76% and a specificity of 65% (AUC 0.70, 95% confidence interval, 0.64–0.76; P < 0.01), and all-cause mortality with a sensitivity of 78% and a specificity of 62% (AUC 0.67, 95% confidence interval, 0.60–0.74; P < 0.01), and that the predictive value of SFMC was superior or comparable to that of D-dimer and CHA2DS2-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 CHA2DS2-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] neuro-hormonal 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
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 CHA2DS2-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 background among the groups might not be completely...
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 procoagulant 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.

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