Skin Autofluorescence as a Predictor of First Heart Failure Hospitalization in Patients With Heart Failure With Preserved Ejection Fraction

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Abstract

Background: An autofluorescence (AF) reader can be used to diagnose skin AF non-invasively by measuring local accumulation of advanced glycation end-products. A number of studies have investigated the relationships between skin AF and cardiovascular disease. However, data regarding the usefulness of skin AF as a predictor of chronic heart failure remain limited. This prospective study aimed to elucidate the usefulness of skin AF as a predictor of first heart failure (HF) hospitalization in patients with HF with preserved ejection fraction (HFpEF).

Methods: A total of 412 outpatients with HFpEF with no history of HF hospitalization were enrolled. Patients were assigned to either the low (group L; skin AF ≤ 2.9 arbitrary units (AU); n = 303) or the high (group H; skin AF ≥ 3.0 AU; n = 109) group according to optimal skin AF cut-off levels determined using receiver operating characteristic curves. Clinical parameters and the usefulness of skin AF as a predictor of first HF hospitalization were evaluated.

Results: The E/e' ratio as a marker of left ventricular diastolic function was significantly higher in group H patients than in group L patients at baseline (group H, 11.8 ± 3.8; group L, 10.6 ± 3.3; P = 0.002). During the 72.7-month follow-up period, 43 HF cases were hospitalized (group L, 15 cases; group H, 28 cases; P < 0.001, log-rank test). Multivariate Cox regression analyses revealed that group H exhibited a significantly higher risk of first HF hospitalization than did group L (hazard ratio, 2.26; 95% confidence interval, 1.21 - 3.52; P = 0.014).

Conclusions: The present study demonstrated that skin AF can predict the risk of first HF hospitalization in patients with HFpEF. Prospective studies, including intervention therapies, are required to validate our observations.

Keywords: Skin autofluorescence; Heart failure with preserved ejection fraction; First heart failure hospitalization; Left ventricular diastolic function; Cardio-ankle vascular index; Inflammation

Introduction

In recent years, extended life expectancy and other factors have led to an increase in the incidence of chronic heart failure (CHF) worldwide [1, 2]. Indeed, numerous patients with CHF, including those in asymptomatic phases, are encountered in daily clinical practice. Moreover, patients with CHF and a history of heart failure (HF) hospitalization reportedly have a poor prognosis because of re-hospitalization due to HF, cardiovascular diseases, or other adverse events [3, 4]. Thus, prompt diagnosis and therapy for patients with CHF are critical to reducing the incidence of HF hospitalization.

In the clinical setting, CHF can be divided into two or three types by left ventricular ejection fraction. In particular, recent studies have investigated patients with HF with preserved ejection fraction (HFpEF). Contrary to the remarkable advances in the development of therapeutic agents with proven benefit in HF with reduced ejection fraction (HFrEF), evidence-based therapeutic options lack for patients with HF-pEF [5, 6]. Moreover, similar to HFrEF, HFpEF also has a poor prognosis [5, 7]. Thus, it is imperative to investigate novel diagnostic and therapeutic options for HFpEF.

Advanced glycation end-products (AGEs) play an important role in the pathophysiology of cardiovascular disease. Among the methods used to evaluate AGEs, skin autofluorescence (AF) is known to be a simple and reliable marker *in vivo*, and recent clinical studies have indicated that skin AF levels are significantly associated with cardiovascular disease incidence and risk factors [8-10]. Moreover, several studies have found an association between skin AF and the pathogenesis of HF [11-13]. However, data on the usefulness of skin AF as a predictor of CHF are limited. Thus, this prospective study aimed to elucidate the usefulness of skin AF as a predictor of first HF hospitalization in patients with HFpEF.

Materials and Methods

Patients

Between August 2011 and July 2013, 436 patients with HF-pEF (left ventricular ejection fraction as estimated by echocardiography > 50%) and no history of HF hospitalization
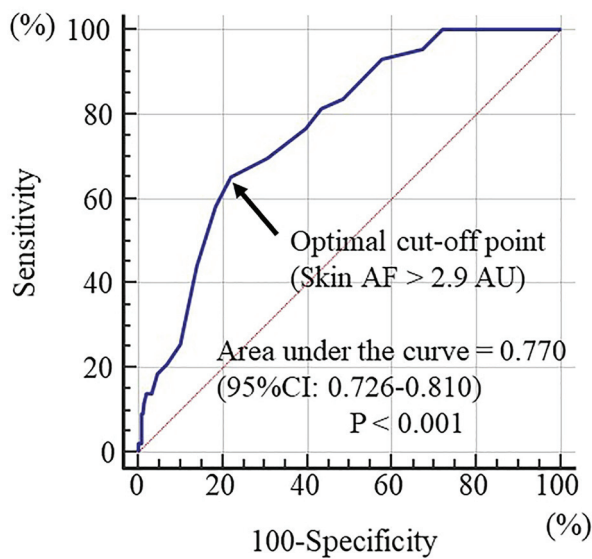
Figure 1. Prediction of first heart failure hospitalization at follow-up period using skin autofluorescence. Receiver operating characteristics to determine the optimal cut-off point of skin AF for the first heart failure hospitalization. The area under curve was 0.770 (P < 0.001). Maximum Youden index indicated that a skin AF > 2.9 arbitrary units was optimal cut-off point to predict the first heart failure hospitalization, indicating a sensitivity of 65.1% and a specificity of 78.1%. Arrow indicates the optimal cut-off point. AF: autofluorescence; AU: arbitrary units; CI: confidence interval.

presented to the Hitsumoto Medical Clinic, Yamaguchi, Japan. Of these, 24 patients with lack of baseline clinical data were excluded. The remaining 412 patients were prospectively included in this study. CHF was defined according to the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults [14], and patients with stage B (patients who are asymptomatic but demonstrate structural heart diseases such as left ventricular hypertrophy, ischemic heart disease and valvular heart disease) and stage C (patients with HF symptoms) were enrolled in this study. The enrolled patients included 105 (25.5%) males and 307 (74.5%) females (mean age, 73 ± 8 years). Patients were assigned to either the low group (group L; skin AF ≤ 2.9 arbitrary units (AU); n = 303) or the high group (group H; skin AF ≥ 3.0 AU; n = 109) according to the optimal skin AF cut-off levels determined using receiver operating characteristic curves (Fig. 1). The study protocol was approved by the Local Ethics Committee of the Hitsumoto Medical Clinic (approval number: HMC-2011-6).

Skin AF measurement

Skin AF was measured using a commercial device (AGE Reader™; DiagnOptics, Groningen, the Netherlands), as previously described [15, 16]. AF was defined as the average light intensity per nanometer in the spectrum between 300 and 420 nm. Skin AF levels were expressed in AU. All measurements were performed at the volar side of the lower arm, approxi-

mately 10 - 15 cm below the elbow, while the patients were in a sitting position. The value of pentosidine, a major AGEs component, was measured by skin biopsy taken at the volar side of the lower arm and has been found to correlate well with skin AF [17]. The validity and reliability of measuring skin AF levels in the Japanese population by this method were established previously [16].

Assessment of clinical parameters

The present study evaluated various clinical parameters, including classical risk factors for cardiovascular disease, history of ischemic heart disease, echocardiographic findings, hemoglobin levels, kidney function, brain natriuretic peptide (BNP) levels, high-sensitivity C-reactive protein (hs-CRP) levels as a marker of inflammation and cardio-ankle vascular index (CAVI) as a marker of arterial function. Obesity was identified using body mass index (BMI) data, with BMI calculated as the body weight (kg) divided by the squared body height (m^2). Smoking was defined as smoking at least one cigarette per day for the past 28 days. A history of ischemic heart disease was defined as having previous myocardial infarction and/or significant angiography-proven stenosis. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg and/or administration of antihypertensive medications. Dyslipidemia was defined as low-density lipoprotein cholesterol levels ≥ 140 mg/dL, high-density lipoprotein cholesterol levels ≤ 40 mg/dL, triglyceride levels ≥ 150 mg/dL and/or ongoing treatment for dyslipidemia. Diabetes mellitus was defined as having fasting blood glucose levels ≥ 126 mg/dL or hemoglobin A1c levels ≥ 6.5%, as stipulated by the National Glycohemoglobin Standardization Program, and/or taking antidiabetic treatment. Echocardiography was performed using a commercial device (HI VISION Avius, Hitachi Medical Corporation, Tokyo, Japan). Valvular heart disease comprised aortic or mitral valve disease (aortic stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation). Moreover, left ventricular wall thickness, extended period diameter, ejection fraction, left atrial dimension and E/e' ratio as a marker of left ventricular diastolic function were evaluated using echocardiography. Estimated glomerular filtration rate (eGFR) was calculated using the adjusted Modification of Diet in Renal Disease equation, as proposed by the Working Group of the Japanese Chronic Kidney Disease Initiative [18]. BNP levels were measured using a commercial kit (SHIONOSPOT Reader; Shionogi & Co., Osaka, Japan). CAVI was measured using VaSera VS-1000 (Fukuda Denshi Co. Ltd, Tokyo, Japan) according to a previously described method [19]. Briefly, the brachial and ankle pulse waves were determined using inflatable cuffs with the pressure maintained between 30 and 50 mm Hg to ensure that the cuff pressure had minimal effects on systemic hemodynamics. Following a 10-min rest in a quiet room, blood and pulse pressures were simultaneously measured with the participant in the supine position. Mean values for the left and right sides were used for the statistical evaluation of the CAVI. The CAVI was calculated using the following formula derived from the Bramwell-Hill equation: CAVI = a × ((2ρ/ΔP) × ln(Ps/Pd) ×

PWV^2) + b, where a and b are constants, ρ is blood density, ΔP is Ps - Pd, Ps is systolic blood pressure, Pd is diastolic blood pressure and PWV is pulse wave velocity. The CAVI may be less accurate in patients with a non-sinus rhythm or obstructive arteriosclerosis; therefore, patients with chronic atrial fibrillation and/or obstructive arteriosclerosis (ankle-brachial index < 0.9) were excluded. Reportedly, the average variation within the CAVI is < 5%, which is sufficiently small for clinical use, indicating good reproducibility [19].

Patient follow-up

The follow-up was terminated in December 2019. Patients were followed up for a median of 72.7 months (range, 6 - 100 months). The endpoint of this study was the incidence of HF hospitalization.

Statistical analysis

Data were analyzed using MedCalc for Windows (version 14.8.1; MedCalc Software, Ostend, Belgium) and StatView J5.0 (HULINKS, Tokyo, Japan). Receiver operating characteristic curves were constructed, and the maximum Youden index [20] was used to determine the optimal skin AF cut-off levels for predicting HF hospitalization. Data are presented as means and standard deviations. Between-group comparisons were performed using Student's t-test, the Mann-Whitney U-test, or the Chi-squared test. Event-free survival rate curves were plotted using Kaplan-Meier analysis, and differences between the curves were evaluated using the log-rank test. Multivariate analysis was performed using Cox regression. Probability (P) values of < 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

The characteristics of all patients at registration are summarized in Table 1. The mean skin AF for groups L and H was 2.4 and 3.3 AU, respectively. The following factors were significantly higher in group H than in group L: incidence of stage C, presence of diabetes mellitus, E/e' ratio, BNP levels, hs-CRP levels and CAVI. However, eGFR was significantly lower in group H than in group L.

Kaplan-Meier curve analysis

The Kaplan-Meier curve for the incidence of HF hospitalization is displayed in Figure 2. During the follow-up period, 43 HF cases were hospitalized (group L, 15 cases; group H, 28 cases). The Kaplan-Meier curve demonstrated that group H exhibited a significantly higher incidence of HF hospitalization than did group L (P < 0.001, log-rank test).

Clinical parameters at registration of patients with and without HF hospitalization

The clinical parameters at registration of all patients with and without HF hospitalization are summarized in Table 2. Age, incidence of stage C, smoking status, presence of diabetes mellitus, E/e' ratio, BNP levels, hs-CRP levels and CAVI were considerably higher, whereas eGFR and β-blocker use were considerably lower in patients with HF hospitalization than in patients not experiencing HF hospitalization.

Multivariate analysis

The results of multivariate Cox regression analysis of the incidence of HF hospitalization are summarized in Table 3. Eleven variables were included, which were all identified as significant factors for HF hospitalization in the univariate analysis. Among these, six variables (stage C, CAVI, group H, diabetes mellitus, hs-CRP levels and E/e' ratio) were associated with a considerable risk of HF hospitalization (Table 3, all patients). However, five variables (CAVI, group H, hs-CRP levels, diabetes mellitus and E/e' ratio) were associated with a considerable risk of HF hospitalization in patients with stage C (Table 3, stage C patients).

Discussion

Previous studies have reported an association between HF symptoms, diabetes mellitus and prognosis of CHF [21-23]. Similarly, this study demonstrated that these factors were predictors of first HF hospitalization in patients with HFpEF. Moreover, this study demonstrated that high skin AF (≥ 3.0 AU) was an important predictor of first HF hospitalization in patients with HFpEF. However, the E/e' ratio as a marker of left ventricular diastolic function, CAVI as a novel marker of arterial function and hs-CRP levels as an inflammation marker were also identified as predictors of first HF hospitalization.

Left ventricular diastolic function is considered one of the most important factors of HF prognosis in HFpEF patients [24]. The results of this study also revealed the E/e' ratio as a predictor of first HF hospitalization in patients with HFpEF. However, AGEs/AGE receptors (RAGEs) may affect left ventricular diastolic function through several pathways [25, 26]. Moreover, several clinical reports exist demonstrating a significant relationship of left ventricular diastolic function and skin AF [27, 28]. The results of this study also indicate that a high skin AF level reflects left ventricular diastolic dysfunction. Therefore, the reason why patients with high skin AF are at increased risk of HF hospitalization might be explained by left ventricular dysfunction caused by AGEs/RAGEs.

A couple of clinical studies have indicated the importance of myocardial injury in the prognosis of CHF, including HF hospitalization [29, 30]. Moreover, basic research studies have reported several pathways in which AGEs/RAGEs could be associated with myocardial injury, with evidence of

Table 1. Characteristics of Patients

	Overall	Group L	Group H	P value
n (male/female)	412 (105/317)	303 (79/224)	109 (26/83)	0.649
Age (years)	74 ± 8	73 ± 8	75 ± 9	0.108
Skin AF (arbitrary units)	2.7 ± 0.5	2.4 ± 0.3	3.3 ± 0.4	< 0.001
Stage B/stage C	246/166	213/90	33/76	< 0.001
Body mass index (kg/m^2)	22.9 ± 3.5	22.8 ± 3.5	22.9 ± 3.6	0.821
Current smoker, n (%)	100 (24)	73 (24)	27 (25)	0.887
Ischemic heart disease, n (%)	67 (16)	51 (17)	16 (15)	0.602
Hypertension, n (%)	302 (73)	218 (72)	84 (77)	0.302
Systolic blood pressure (mm Hg)	144 ± 27	144 ± 26	144 ± 30	0.911
Diastolic blood pressure (mm Hg)	86 ± 11	86 ± 11	85 ± 10	0.251
Pulse rate (/min)	66 ± 13	65 ± 13	66 ± 12	0.419
Dyslipidemia, n (%)	227 (55)	165 (55)	62 (57)	0.663
Diabetes mellitus, n (%)	104 (25)	63 (21)	41 (38)	0.002
Hear valvular disease, n (%)	317 (77)	230 (76)	87 (80)	0.254
IVsTd (mm)	9.6 ± 1.6	9.5 ± 1.7	9.6 ± 1.4	0.726
LVDd (mm)	49.7 ± 3.6	49.6 ± 3.5	49.8 ± 3.7	0.531
LVEF (%)	68.5 ± 8.3	68.3 ± 8.3	68.9 ± 8.1	0.509
LAD (mm)	42.3 ± 5.6	42.4 ± 5.6	42.0 ± 5.6	0.448
E/e'	10.9 ± 3.5	10.6 ± 3.3	11.8 ± 3.8	0.002
Hemoglobin (g/dL)	12.7 ± 1.5	12.7 ± 1.5	12.8 ± 1.6	0.570
eGFR (mL/min/1.73 m^2)	56.0 ± 22.5	58.0 ± 22.3	50.1 ± 22.1	0.001
Log-BNP (pg/mL)	2.0 ± 0.4	2.0 ± 0.4	2.1 ± 0.4	0.034
Log-hs-CRP (mg/dL)	-1.2 ± 0.5	-1.3 ± 0.5	-1.1 ± 0.4	0.001
CAVI	9.7 ± 1.2	9.4 ± 1.1	10.3 ± 1.2	< 0.001
Medication				
RAS inhibitor, n (%)	268 (65)	202 (67)	66 (61)	0.252
β-blocker, n (%)	71 (17)	54 (18)	17 (16)	0.598
Diureics, n (%)	88 (21)	67 (22)	21 (19)	0.535
Statin, n (%)	116 (28)	84 (28)	32 (29)	0.746

Continuous values are mean ± SD. AF: autofluorescence; IVSTd: interventricular septal thickness at end-diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-CRP: high-sensitivity C-reactive protein; CAVI: cardio-ankle vascular index; RAS: renin-angiotensin system.

significant increase in AGEs levels in the heart, particularly in the cardiomyocytes [31]. This research also indicated that AGEs-induced cardiomyocyte dysfunction might be linked to mitochondrial membrane depolarization and reduced GSK-3β inactivation, which are events that can be prevented by RNA interference knockdown of RAGEs expression. However, others have found that RAGEs affected ischemia/reperfusion injury in the myocardium [32]. Hofmann et al reported on the relationship between AGEs-modified cardiac tissue collagen levels and skin AF and found a significant relationship between cardiac tissue glycation and skin AF [33]. Moreover, they also clarified that the AGEs found at the volar side of the lower arm appear to reflect the level of AGEs/RAGEs in the cardiomyocytes. In fact, there are several clinical studies that show

significant relationships between skin AF and biomarkers of myocardial injury [13, 34]. Although markers of myocardial injury were not evaluated in the present study, previous studies have shown that AGEs/RAGEs are believed to play important roles in the progression of myocardial injury; consequently, HFpEF patients with high skin AF may be particularly prone to becoming hospitalized due to HF.

The CAVI is known as a proxy for systemic arterial stiffness which is independent of blood pressure levels [19]. Moreover, there is evidence that the CAVI also reflects endothelial function [35, 36]. Thus, previous studies have clarified that the CAVI is a useful physiological marker to evaluate arterial function in vivo. However, several clinical studies have reported an association between arterial dysfunction, including increased
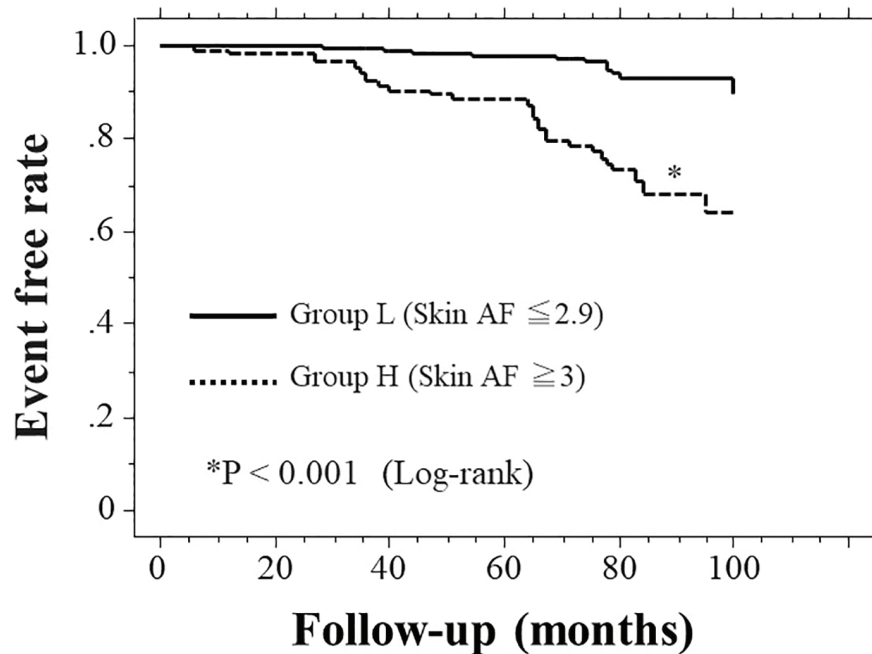
Figure 2. Kaplan-Meier curve for the incidence of first heart failure hospitalization. Patients were followed up for a median of 72.7 months (range, 6 - 100 months). During the follow-up period, 43 HF cases were hospitalized (group L, 15 cases; group H, 28 cases). The Kaplan-Meier curve demonstrated that group H exhibited a significantly higher incidence of first HF hospitalization than group L (P < 0.001, log-rank test). HF: heart failure; AF: autofluorescence; AU: arbitrary units.

arterial stiffness or endothelial dysfunction, and CHF prognosis, including HF re-hospitalization [37, 38]. The results of this study, which indicate a significant association between CAVI values and first HF hospitalization, can be interpreted so that arterial function is an essential factor in the prognosis of patients with HFpEF. However, patients with high skin AF levels showed significantly higher CAVI values than those with low skin AF levels in this study. Basic research studies have reported that AGEs/RAGEs are associated with vascular cell calcification, such as that of endothelial or smooth muscle cells, and functional arterial aging [39-41]. Moreover, clinical studies indicated that skin AF levels significantly correlated with physiological markers of arterial function [10, 42, 43]. Thus, the results of this and previous studies indicate that HFpEF patients with high skin AF levels can be considered a population at high risk of a poor prognosis from the perspective of arterial function.

A number of studies have clarified the importance of inflammation in pathogenesis of CHF. Among the inflammatory markers, hs-CRP levels are commonly used in clinical practice. Moreover, previous studies have reported hs-CRP levels to be independent predictors in CHF patients [44]. The results of this study also indicated that an increase in hs-CRP levels was an independent predictor of first HF hospitalization in patients with HFpEF. However, hs-CRP levels were significantly higher in patients with high skin AF than in those with low skin AF. Researchers have identified a close relationship between AGEs/RAGEs and inflammation in cardiac and vascular cells [45, 46]. Actually, several clinical studies have reported significant associations between inflammatory markers and skin AF [47, 48]. Therefore, the results of the previous and present studies indicate an association of inflammation and AGEs/RAGEs in the heart or blood vessels, consequently promoting the risk of first HF hospitalization in patients with HFpEF. However, previous studies indicated that both inflammation and AGEs/RAGEs were also associated with pathogenesis of HFrEF [49, 50]. The present study was not evaluated in patients with HFrEF. Therefore, furher research is required to clarify the relation of skin AF and inflammatory markers in patients with HFrEF.

Limitations

This study has several limitations. First, this study was conducted at a single center with a relatively small sample size. Thus, the findings cannot be generalized to all medical centers. Second, skin AF was measured only at one time point upon registration. Additional evaluations of correlations between serial changes in skin AF and HF hospitalization are required. Finally, further studies concerning patients with high skin AF are warranted to determine whether aggressive interventional therapy, such as improvements in physical activity or medication, reduces the incidence of first HF hospitalization in patients with HFpEF.

Conclusions

In conclusion, the present study demonstrated that skin AF

Table 2. Clinical Parameters at Registration of Patients With and Without Heart Failure Hospitalization

	Non-HF hospitalization (n = 369)	HF hospitalization (n = 43)	P value
Male/female	96/273	9/34	0.471
Age (years)	73 ± 8	79 ± 7	< 0.001
Stage B/stage C	241/128	5/38	< 0.001
Body mass index (kg/m^2)	22.9 ± 3.5	22.8 ± 4.0	0.880
Current smoker, n (%)	83 (23)	17 (40)	0.013
Ischemic heart disease, n (%)	58 (16)	9 (21)	0.382
Hypertension, n (%)	267 (72)	35 (81)	0.206
Systolic blood pressure (mm Hg)	146 ± 24	146 ± 45	0.922
Diastolic blood pressure (mm Hg)	86 ± 11	83 ± 10	0.067
Pulse rate (/min)	66 ± 13	65 ± 11	0.749
Dyslipidemia, n (%)	202 (55)	25 (58)	0.673
Diabetes mellitus, n (%)	83 (23)	21 (49)	< 0.001
Hear valvular disease, n (%)	280 (76)	37 (86)	0.135
IVsTd (mm)	9.6 ± 1.7	9.4 ± 1.1	0.279
LVDd (mm)	49.6 ± 3.3	50.6 ± 4.9	0.051
LVEF (%)	68.2 ± 8.2	65.9 ± 9.1	0.092
LAD (mm)	42.3 ± 5.6	42.2 ± 5.6	0.904
E/e'	10.7 ± 3.4	13.1 ± 3.5	< 0.001
Hemoglobin (g/dL)	12.7 ± 1.5	13.1 ± 1.7	0.056
eGFR (mL/min/1.73 m^2)	57.5 ± 22.3	42.9 ± 19.7	< 0.001
Log-BNP (pg/mL)	2.0 ± 0.4	2.2 ± 0.4	< 0.001
Log-hs-CRP (mg/dL)	-1.3 ± 0.5	-0.9 ± 0.5	< 0.001
CAVI	9.6 ± 1.2	10.4 ± 0.8	< 0.001
RAS inhibitor, n (%)	242 (66)	26 (60)	0.595
β-blocker, n (%)	69 (19)	2 (5)	0.021
Diureics, n (%)	81 (22)	7 (16)	0.392
Statin, n (%)	102 (28)	14 (33)	0.499

Continuous values are mean ± SD. HF: heart failure; IVSTd: interventricular septal thickness at end- diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-CRP: high-sensitivity C-reactive protein; CAVI: cardio-ankle vascular index; RAS: renin-angiotensin system.

can predict first HF hospitalization in patients with HFpEF. Further prospective studies, including studies investigating intervention therapies, are required to validate the results in this study.

Conflict of Interest

None to declare.

Informed Consent

All patients provided informed consent.

Author Contributions

The author was involved in preparing the study design as well as in the acquisition, analysis and interpretation of data.

Table 3. Multivariate Cox Regression Analysis for Heart Failure Hospitalization

	HR	95% CI	P value
Analysis in all patients			
Stage C	7.67	2.82 - 20.84	< 0.001
CAVI (≥ 10)	2.71	1.34 - 5.50	0.006
Group H	2.26	1.21 - 3.52	0.014
Diabetes mellitus	2.21	1.18 - 4.17	0.017
hs-CRP (≥ 0.1 mg/dL)	2.23	1.14 - 4.24	0.019
E/e' (≥ 15)	2.10	1.01 - 4.44	0.049
BNP (≥ 200 pg/mL)	1.32	0.96 - 2.62	0.076
Age (≥ 70 years)	2.04	0.91 - 4.62	0.085
eGFR (< 60 mL/min/1.73 m^2)	1.89	0.88 - 4.09	0.104
Current smoker	1.62	0.85 - 3.07	0.142
β-blocker	0.41	0.09 - 1.75	0.229
Analysis in patients with stage C			
CAVI (≥ 10)	2.85	1.33 - 6.09	0.007
Group H	2.36	1.15 - 4.86	0.019
hs-CRP (≥ 0.1 mg/dL)	2.30	1.14 - 4.63	0.020
Diabetes mellitus	2.09	1.14 - 4.24	0.034
E/e' (≥ 15)	2.11	1.01 - 4.46	0.048
BNP (≥ 200 pg/mL)	1.85	0.96 - 3.56	0.066
eGFR (< 60 mL/min/1.73 m^2)	1.70	0.86 - 3.58	0.127
Age (≥ 70 years)	1.67	0.72 - 3.54	0.144
β-blocker	0.25	0.03 - 1.91	0.183
Current smoker	1.20	0.47 - 3.07	0.227

HR: hazard ratio; CI: confidence interval; CAVI: cardio-ankle vascular index; hs-CRP: high-sensitivity C-reactive protein; BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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