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ORIGINAL ARTICLE
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# Impact of Modified H2FPEF Score on Chronic Limb-Threatening Ischemia in Patients With Lower Extremity Artery Disease Who Underwent Endovascular Therapy

Taku Shikama, MD; Yoichiro Otaki, MD, PhD; Tetsu Watanabe, MD, PhD; Hiroki Takahashi, MD, PhD; Tasuku Kurokawa, MD; Harutoshi Tamura, MD, PhD; Shigehiko Kato, MD, PhD; Satoshi Nishiyama, MD, PhD; Takanori Arimoto, MD, PhD; Masafumi Watanabe, MD, PhD

***Background:*** Lower extremity artery disease (LEAD) is an arterial occlusive disease characterized by an insufficient blood supply to the lower limb arteries. The H2FPEF score, comprising Heavy, Hypertensive, atrial Fibrillation, Pulmonary hypertension, Elder, and Filling pressure, has been developed to identify patients at high risk of heart failure (HF) with preserved ejection fraction. This study assessed the impact of modified H2FPEF scores on chronic limb-threatening ischemia (CLTI) in patients with LEAD.

***Methods and Results:*** This study was a prospective observational study. Because the definition of obesity differs by race, we calculated the modified H2FPEF score using a body mass index >25 kg/m$^2$ to define obesity in 293 patients with LEAD who underwent first endovascular therapy. The primary endpoints were newly developed and recurrent CLTI. The secondary endpoint was a composite of events, including mortality and rehospitalization due to worsening HF and/or CLTI. The modified H2FPEF score increased significantly with advancing Fontaine classes. Multivariate Cox proportional hazard analysis revealed that the modified H2FPEF score was an independent predictor of newly developed and recurrent CLTI and composite events. The net reclassification index and integrated discrimination improvement were significantly improved by adding the modified H2FPEF score to the basic predictors.

***Conclusions:*** The modified H2FPEF score was associated with LEAD severity and future CLTI development, suggesting that it could be a feasible marker for patients with LEAD.

**Key Words:** Chronic limb-threatening ischemia; H2FPEF score; Lower extremity artery disease

Lower extremity artery disease (LEAD) is an arterial occlusive disease of the lower limb arteries associated with increased morbidity and mortality.[1–5] Despite advances in revascularization of LEAD, chronic limb-threatening ischemia (CLTI) in end-stage LEAD remains an important medical issue, resulting in limb amputation and extremely high mortality rates. Therefore, patients with high-risk LEAD for CLTI should be identified early and stratified according to risk. Although several risk factors predisposing patients to CLTI have been reported,[6,7] useful markers have not yet been fully elucidated.

LEAD is considered a Stage A heart failure (HF), indicating that patients with LEAD are at risk of developing HF.[8] A meta-analysis demonstrated that the prevalence of HF was 1.9-fold higher in patients with LEAD.[9] Conversely, LEAD was reported in approximately 10% of patients with HF with preserved ejection fraction (HFpEF), suggesting that it is a common comorbidity in these patients.[10–12] Furthermore, the prevalence of left ventricular diastolic dysfunction was reported to be higher in patients with than without LEAD.[13] These findings suggest a close relationship between LEAD and cardiac diastolic dysfunction.

The H2FPEF score is a non-invasive scoring system developed to discriminate HFpEF from non-cardiac causes of dyspnea that reflects the degree of diastolic dysfunction.[14] The H2FPEF score comprises 6 variables involved in HFpEF, namely heavy (H), hypertensive (H), atrial fibrillation (F), pulmonary hypertension (P), elder (E), and filling pressure (F).[15] Regarding the H2FPEF score, research attention has shifted from diagnostic markers for HFpEF to prognostic markers in a broad spectrum of heart diseases.[16–18] In addition, the Atherosclerosis Risk in Communities (ARIC) study used the H2FPEF score with community participants with no other common cardiopulmonary causes of dyspnea and found increase in the incidence of HF hospitalization or deaths with increasing

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Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan
Mailing address: Yoichiro Otaki, MD, PhD, Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan. E-mail: y-otaki@med.id.yamagata-u.ac.jp

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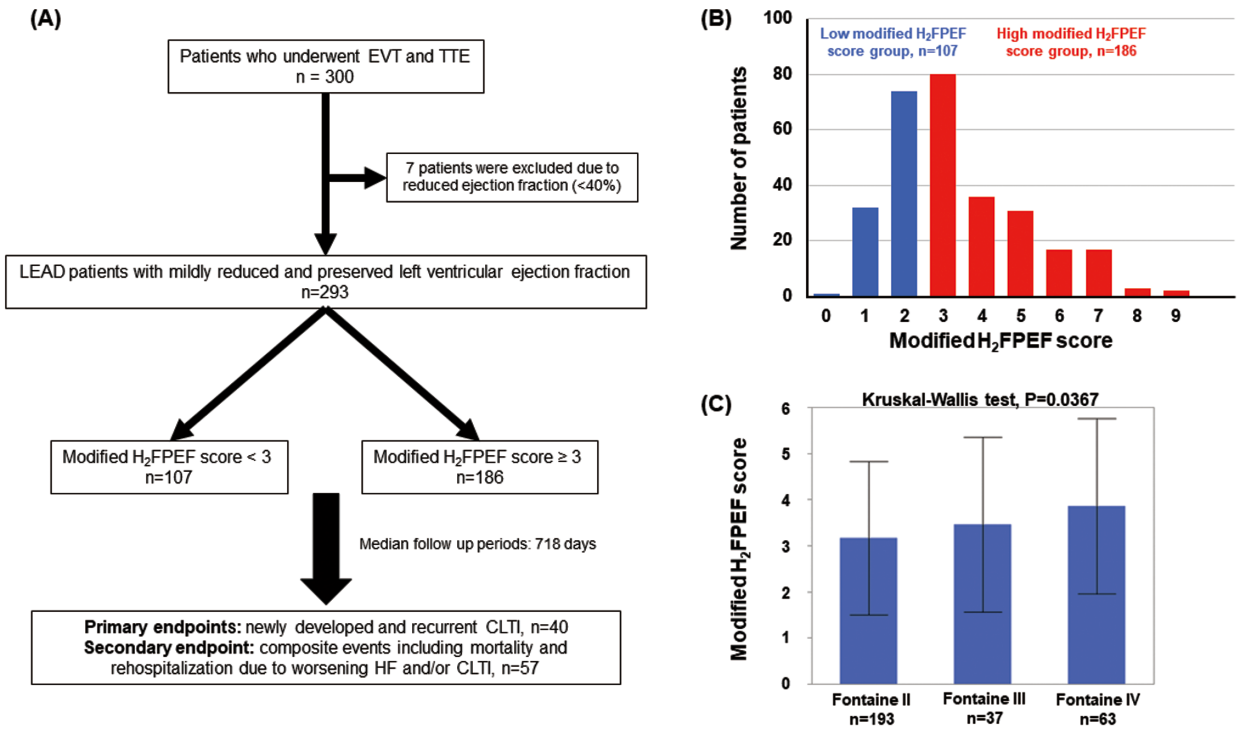


**Figure 1.** (**A**) Flow chart of the study population. CLTI, chronic limb-threatening ischemia; EVT, endovascular therapy; HF, heart failure; LEAD, lower extremity artery disease; TTE, transthoracic echocardiography. (**B**) Distribution of modified H2FPEF scores. (**C**) Association between Fontaine class and modified H2FPEF scores. Data are the mean±SD.

H2FPEF score.[19] To date, there has been no report examining the prognostic usefulness of the H2FPEF score in patients with LEAD.

Because obesity is defined as a body mass index (BMI) >25 kg/m² in the Asian population, we calculated a modified H2FPEF score by substituting Asian obesity in place of "heavy". Overall, the aim of this study was to investigate whether modified H2FPEF scores are associated with the severity of LEAD and the development of CLTI in patients with LEAD.

## Methods

### Study Population

The flowchart of the study population is shown in **Figure 1A**. This was a single-center prospective observational study of 300 patients admitted to our hospital for their first endovascular therapy (EVT) between 2010 and 2020. Of these 300 patients, 7 were excluded because of a reduced ejection fraction (left ventricular ejection fraction <40%), leaving 293 patients included in the present study.

LEAD was diagnosed based on an ankle brachial index (ABI) <0.9, and peripheral artery stenosis or occlusion was detected using computed tomographic angiography. Experienced cardiologists performed EVT according to the recommendations of the American College of Cardiology/American Heart Association guidelines and the European Society of Cardiology/European Society of Vascular Surgery guidelines.[20,21] Experienced cardiologists and sonographers performed echocardiography. Echocardiographic parameters, including left ventricular ejection fraction, pulmonary artery systolic pressure, and the ratio of the mitral inflow E wave to the tissue Doppler e' wave (E/e') ratio, were assessed by an experienced cardiologist and sonographer who were blinded to the EVT data. Optimized medical therapy was independently administered by physicians based on symptom improvement.

Demographic and clinical data, including age, sex, smoking history, cardiovascular risk factors, ABI, and medications, were collected from patients' medical records and through interviews.

### Ethics Statement

The study protocol was approved by the Institutional Ethics Committee of Yamagata University School of Medicine (No. 2020-344), and all participants provided written informed consent. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

### Definitions

Hypertension was defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg, or the use of antihypertensive medications.[22] Hyperlipidemia was defined as total cholesterol ≥220 mg/dL, triglyceride ≥150 mg/dL, or the use of antihyperlipidemic medications. Diabetes was defined as fasting blood sugar ≥126 mg/dL and HbA1c ≥6.5%.

### H2FPEF and Modified H2FPEF Scores

The H2FPEF score comprised 6 variables involved in

HFpEF: "heavy" (H), defined as a BMI >30 kg/m$^2$; hypertensive (H), defined as ≥2 or more antihypertensive medications; the presence of atrial fibrillation (F); pulmonary hypertension (P), defined as pulmonary artery systolic pressure >35 mmHg; elder (E), defined as age >60 years; and elevated filling pressures (F), defined as E/e' >9. The scores assigned to these 6 variables were as follows: atrial fibrillation, 3 points; heavy, 2 points; and all others, 1 point each.[15]

Generally, obesity in Asian populations is defined as BMI >25 kg/m$^2$. Therefore, we also calculated a modified $H_2$FPEF score using obesity instead of "heavy", because the definition of obesity differs by race.

### Malnutrition

The controlling nutritional status (CONUT) score was calculated using serum albumin, total lymphocyte count, and total cholesterol values, as reported previously.[23] Patients with CONUT scores of 0–1 were categorized having a normal nutritional status, whereas those with CONUT scores of 2–4, 5–8, and 9–12 were categorized as having mild, moderate, and severe risk of malnutrition, respectively. Malnutrition was defined as a CONUT score ≥5 or moderate-to-severe malnutrition.[24]

### Biochemical Markers

Blood samples were obtained early in the morning before the first EVT. These samples were transferred to chilled tubes containing 4.5 mg EDTA disodium salt and aprotinin (500 U/mL) and centrifuged at 1,000 g for 15 min at 4°C. The clarified plasma samples were frozen, stored at −70°C, and thawed immediately before the assay was performed. B-Type natriuretic peptide (BNP) concentrations were measured using a commercially available radioimmunoassay specific for human BNP (Shiono RIA BNP assay kit; Shionogi, Tokyo, Japan).

Estimated glomerular filtration rate (eGFR) was calculated using the following equations:[25]

$$eGFR = 194 \times sCr - 1.094 \times Age - 0.287 \text{ in men}$$
$$eGFR = 194 \times sCr - 1.094 \times Age - 0.287 \times 0.739 \text{ in women}$$

where sCr is serum creatinine.

C-reactive protein (CRP), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, and HbA1c levels were measured simultaneously.

### Severity of LEAD

The severity of LEAD was determined using the Fontaine class.[26] According to the global vascular guidelines,[27] CLTI is a clinical syndrome defined by the presence of LEAD in combination with rest pain, gangrene, or a lower limb ulceration >2 weeks duration.

### Endpoints and Follow-up

All participants were followed up for a median period of 718 days (interquartile range [IQR] 373–1,441 days; longest follow-up 1,825 days) through telephone interviews or reviewing medical records twice a year. Follow-up was performed until the end of December 2021. The primary endpoints were newly developed and recurrent CLTI, which were defined as the first-ever onset of CLTI and the recurrence of CLTI, respectively. The secondary endpoint was a composite of events, including mortality and rehospitalization due to worsening HF and/or CLTI.

### Statistical Analysis

Continuous data are expressed as the mean±SD or the median with IQR. Continuous and categorical variables were compared using t-tests and Chi-squared tests, respectively. Data that were not normally distributed were compared using the Mann-Whitney U test.

Associations between Fontaine class and modified $H_2$FPEF scores were analyzed using the Kruskal-Wallis test. Associations between baseline CLTI and components of the modified $H_2$FPEF score were assessed using Chi-squared tests. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test.

Cox proportional hazard analysis was performed to identify independent predictors of the primary and secondary endpoints. Significant ($P<0.05$) predictors in the univariate Cox proportional hazard regression analysis were screened using the Bayesian method. The selected predictors were analyzed using multivariate analysis. Multicollinearity was assessed using the variance inflation factor. Multivariate analysis was performed to evaluate independent predictors of the primary and secondary endpoints. Statistical significance was set at $P<0.05$.

The net reclassification index (NRI) and integrated discrimination improvement (IDI) were calculated to measure the quality of improvement for correct reclassification after adding the modified $H_2$FPEF score to the current model.

All statistical analyses were performed using JMP version 14 (SAS Institute, Cary, NC, USA) and R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) with additional packages, including Rcmdr, Epi, pROC, and PredictABEL.

## Results

### Baseline Characteristics of Patients With LEAD

Baseline patient characteristics are presented in **Table 1**. Of the 293 patients in this study, 220 (75%) were men. Hypertension, diabetes, and hyperlipidemia were identified in 251 (86%), 138 (47%), and 192 (66%) patients, respectively. In all, 98 patients (33%) had previous ischemic heart disease and 67 (23%) underwent hemodialysis. With regard to LEAD severity, 193 patients were in Fontaine Class II, 37 were in Fontaine Class III, 63 were in Fontaine Class IV. The mean $H_2$FPEF and modified $H_2$FPEF scores were 3.0 and 3.4, respectively. Individual components of heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, and filling pressure were identified in 11 (4%), 196 (67%), 48 (17%), 31 (11%), 269 (92%), and 212 (72%) patients, respectively. Obesity was identified in 65 (22%) patients.

The success rate of the first EVT was 100%. All patients with CLTI at baseline were completely cured through EVT and/or amputation. The modified $H_2$FPEF scores were normally distributed (**Figure 1B**). The modified $H_2$FPEF score increased significantly with advancing Fontaine class (**Figure 1C**). Patients with CLTI at baseline had a higher rate of atrial fibrillation, pulmonary hypertension, and elevated filling pressure than those without CLTI (**Figure 2**).

### Clinical Characteristics in Patients With High and Low Modified $H_2$FPEF Scores

Patients were divided into 2 groups based on the median modified $H_2$FPEF score of 3 points, namely patients with

**Table 1. Clinical Characteristics of All Patients and Those With High (≥3) and Low (<3) Modified $H_2FPEF$ Scores Separately**

| | All patients (n=293) | Modified $H_2FPEF$ score <3 (n=107) | Modified $H_2FPEF$ score ≥3 (n=186) | P value |
|---|---|---|---|---|
| Age (years) | 74±9 | 73±10 | 75±9 | 0.0474 |
| Male sex | 220 (75) | 84 (79) | 136 (73) | 0.3011 |
| BMI (kg/m$^2$) | 22.3±3.6 | 20.6±2.6 | 23.3±3.8 | <0.0001 |
| Hypertension | 251 (86) | 82 (77) | 169 (91) | 0.0010 |
| Diabetes | 138 (47) | 41 (38) | 97 (52) | 0.0219 |
| Hyperlipidemia | 192 (66) | 76 (71) | 116 (62) | 0.1305 |
| Hemodialysis | 67 (23) | 13 (12) | 54 (29) | 0.0006 |
| Smoking | 226 (77) | 96 (90) | 130 (70) | <0.0001 |
| Previous ischemic heart disease | 98 (33) | 35 (33) | 63 (34) | 0.8392 |
| Previous cerebrovascular disease | 96 (33) | 33 (31) | 63 (34) | 0.5939 |
| Fontaine Class II/III/IV (n) | 193/37/63 | 78/11/18 | 115/26/45 | 0.1507 |
| Endovascular therapy data | | | | |
| Iliac artery | 152 (52) | 64 (60) | 88 (47) | 0.0392 |
| Femoropopliteal artery | 143 (49) | 45 (42) | 98 (53) | 0.0796 |
| Tibial or peroneal artery | 43 (15) | 11 (10) | 32 (17) | 0.1068 |
| Pre-ABI | 0.58 [0.44–0.69] | 0.57 [0.45–0.68] | 0.59 [0.44–0.70] | 0.9928 |
| Nutritional status | | | | |
| Serum albumin (mg/dL) | 3.7±0.5 | 3.7±0.5 | 3.6±0.5 | 0.9447 |
| Lymphocyte count (/mm$^3$) | 1,550±620 | 1,587±594 | 1,525±635 | 0.4183 |
| Total cholesterol (mg/dL) | 170±41 | 170±41 | 169±41 | 0.8314 |
| CONUT score | 2 (1–4) | 2 (1–3) | 2 (1–4) | 0.4706 |
| Malnutrition | 50 (17) | 17 (16) | 33 (18) | 0.6834 |
| Biochemical data | | | | |
| BNP (pg/mL) | 54 (21–167) | 31 (15–70) | 81 (31–257) | 0.0274 |
| eGFR (mL/min/1.73 m$^2$) | 56.9±40.6 | 70.3±36.6 | 49.2±40.9 | <0.0001 |
| CRP (mg/dL) | 0.22 [0.11–0.86] | 0.25 [0–1.22] | 0.22 [0.11–0.81] | 0.1172 |
| LDL-C (mg/dL) | 98±34 | 97±33 | 98±35 | 0.7393 |
| HDL-C (mg/dL) | 50±15 | 52±18 | 48±13 | 0.0394 |
| Triglyceride (mg/dL) | 124±64 | 117±55 | 128±69 | 0.1545 |
| HbA1c (%) | 6.4±1.1 | 6.3±1.2 | 6.5±1.0 | 0.3248 |
| Medication | | | | |
| ACEIs and/or ARBs | 169 (58) | 42 (39) | 127 (68) | <0.0001 |
| $\beta$-blockers | 95 (32) | 21 (20) | 74 (40) | 0.0003 |
| CCBs | 173 (59) | 49 (46) | 124 (67) | 0.0005 |
| Statins | 197 (67) | 80 (75) | 117 (63) | 0.0352 |
| Aspirin | 203 (69) | 72 (67) | 131 (70) | 0.5757 |
| Clopidogrel | 265 (90) | 98 (92) | 167 (90) | 0.6101 |
| Cilostazol | 78 (27) | 31 (29) | 47 (25) | 0.4914 |
| Warfarin | 19 (6) | 6 (6) | 13 (7) | 0.6404 |
| OACs | 33 (11) | 8 (7) | 25 (13) | 0.1100 |
| $H_2FPEF$ score components | | | | |
| Heavy[A] | 11 (4) | 0 (0) | 11 (6) | 0.0014 |
| Obesity[A] | 65 (22) | 25 (19) | 40 (25) | 0.2241 |
| Hypertensive | 196 (67) | 35 (33) | 161 (87) | <0.0001 |
| Atrial fibrillation | 48 (17) | 0 (0) | 48 (26) | <0.0001 |
| Pulmonary hypertension | 31 (11) | 1 (1) | 30 (16) | <0.0001 |
| Elder | 269 (92) | 94 (88) | 175 (94) | <0.0001 |
| Filling pressure | 212 (72) | 50 (47) | 162 (87) | <0.0001 |
| $H_2FPEF$ score | 3.0±1.1 | 1.7±0.5 | 3.7±1.5 | <0.0001 |
| Modified $H_2FPEF$ score | 3.4±1.4 | 1.7±0.5 | 4.3±1.5 | <0.0001 |

Unless indicated otherwise, data are expressed as the mean±SD, or n (%), or median [interquartile range]. [A]Heavy and obesity indicate a body mass index (BMI) of >30 and >25 kg/m$^2$, respectively. ABI, ankle brachial index; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BNP, B-type natriuretic peptide; CCBs, calcium channel blockers; CONUT, controlling nutritional status; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; OACs, oral anticoagulants.

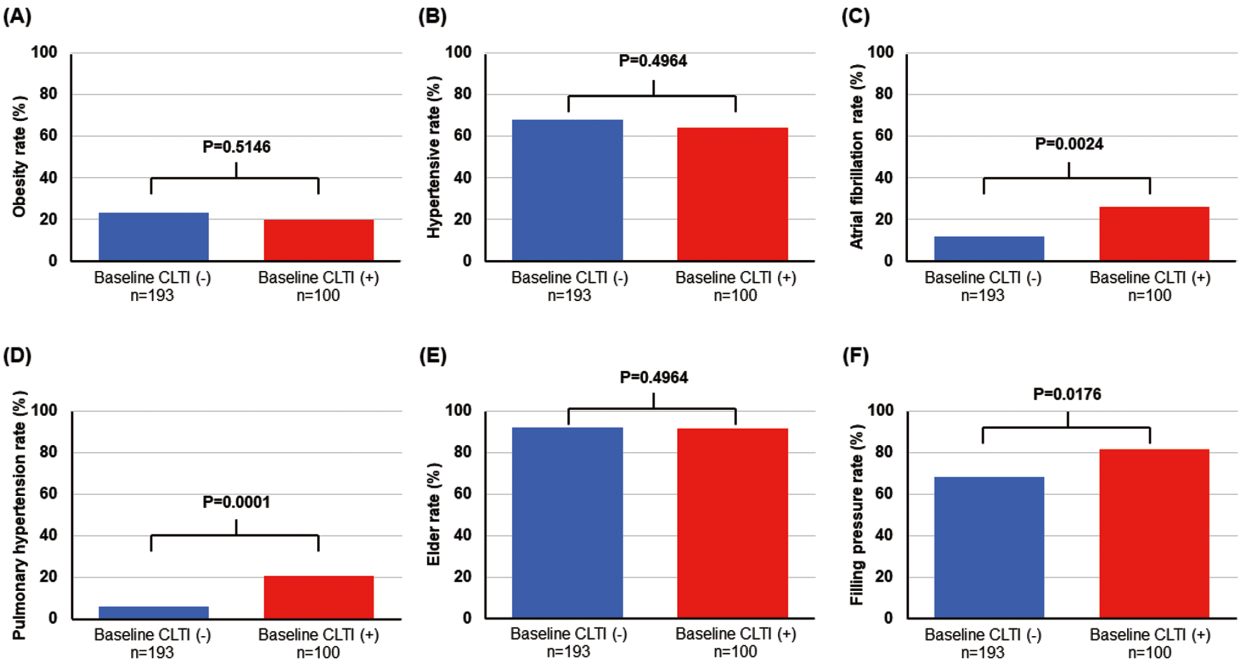


**Figure 2.** Association of chronic limb-threatening ischemia (CTLI) at baseline with (**A**) obesity, (**B**) hypertension, (**C**) atrial fibrillation, (**D**) pulmonary hypertension, (**E**) elder, and (**F**) filling pressure.

a high modified H2FPEF score (≥3 points; n=186) and those with a low modified H2FPEF score (<3 points; n=107). Compared with patients with low modified H2FPEF scores, those with high modified H2FPEF scores were older and had a higher prevalence of hypertension, diabetes, and hemodialysis and a lower prevalence of smoking (**Table 1**). Patients with high modified H2FPEF scores also had higher BMI and BNP concentrations and lower eGFR and HDL-C concentrations than those with low modified H2FPEF scores. Patients with high modified H2FPEF scores took more antihypertensive medications than those with low modified H2FPEF scores, but fewer statins. There were no significant differences between patients with high and low modified H2FPEF scores in terms of sex, previous ischemic heart disease, previous cerebrovascular disease, target lesion excluding the iliac artery, pre-ABI, nutritional status, CRP, lipid profiles, excluding HDL-C, and HbA1c.

### Modified H2FPEF Score and Clinical Outcomes

During the follow-up period, 40 newly developed and recurrent CLTIs and 57 composite events were observed. Kaplan-Meier analysis showed that rates of newly developed and recurrent CLTI were higher in patients with a high compared with low modified H2FPEF score (**Figure 3A**). In addition, Kaplan-Meier analysis showed that patients with high modified H2FPEF scores had a higher rate of composite events than those with low modified H2FPEF scores (**Figure 3B**). Furthermore, Kaplan-Meier analysis demonstrated that, for LEAD patients without baseline CLTI, the incidence of newly developed CLTI and composite events was higher in the group with a high compared with low modified H2FPEF score (**Supplementary Figure**).

Univariate and multivariate Cox proportional hazard regression analyses were performed to examine the impact of modified H2FPEF scores on newly developed and recurrent CLTI in patients with LEAD. Univariate Cox proportional hazards regression analysis demonstrated that the modified H2FPEF score was significantly associated with newly developed and recurrent CLTI in patients with LEAD. Moreover, there was a significant relationship between newly developed or recurrent CLTI and sex, smoking, hemodialysis, baseline CLTI, BNP, CRP, eGFR, CONUT score, and malnutrition (**Table 2**). In the multivariate Cox proportional hazard regression, Model 1 included hemodialysis, smoking, baseline CLTI, and malnutrition, whereas Model 2 included hemodialysis, baseline CLTI, malnutrition, and BNP concentrations. Multivariate Cox proportional hazard regression analyses demonstrated that the modified H2FPEF score was an independent predictor of newly developed and recurrent CLTI after adjusting for confounding risk factors (**Table 3**). Next, to examine the impact of components of the H2FPEF score on newly developed and recurrent CLTI, we calculated hazard ratios and event rates for the newly developed and recurrent CLTI for each component separately. As shown in **Figure 4**, atrial fibrillation, pulmonary hypertension, and filling pressure exacerbated the risk of newly developed and recurrent CLTI.

We also performed univariate and multivariate Cox proportional hazard regression analyses to examine the impact of modified H2FPEF scores on composite events in patients with LEAD. Univariate Cox proportional hazards regression analysis demonstrated that the modified H2FPEF score was significantly associated with composite events in

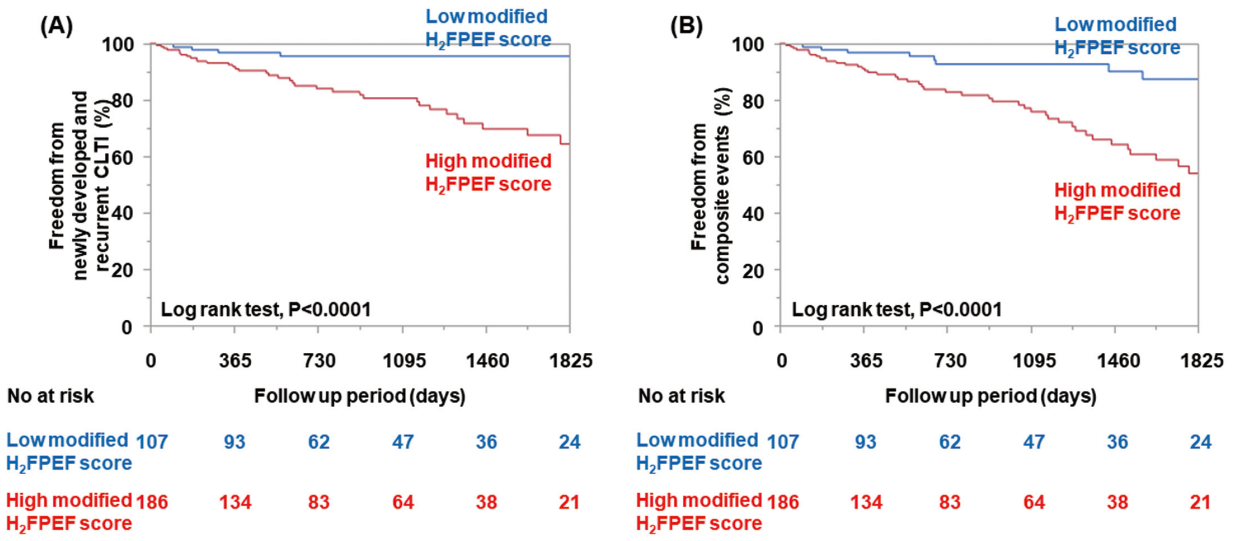


**Figure 3.** Kaplan-Meier analysis for (**A**) newly developed and recurrent chronic limb-threatening ischemia in patients and (**B**) composite events in patients with high and low modified H2FPEF scores.

**Table 2. Univariate Cox Proportional Hazard Analysis for the Prediction of Clinical Outcomes in Patients With Lower Extremity Artery Disease**

| | Newly developed and recurrent CLTI | | | Composite event | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Age (per 1-year increase) | 1.03 | 0.99–1.07 | 0.1216 | 1.04 | 1.01–1.07 | 0.0224 |
| Sex (male vs. female) | 0.49 | 0.26–0.95 | 0.0352 | 0.48 | 0.28–0.82 | 0.0069 |
| BMI (per 1-SD increase) | 1.07 | 0.80–1.46 | 0.5770 | 1.04 | 0.97–1.12 | 0.2286 |
| Hypertension | 0.74 | 0.33–1.68 | 0.4779 | 1.27 | 0.58–2.79 | 0.5566 |
| Diabetes | 1.37 | 0.74–2.53 | 0.3177 | 1.84 | 1.10–3.09 | 0.0207 |
| Hyperlipidemia | 0.80 | 0.42–1.51 | 0.4933 | 1.10 | 0.63–1.91 | 0.7332 |
| Smoking | 2.68 | 1.41–5.10 | 0.0026 | 3.33 | 2.00–5.55 | <0.0001 |
| Hemodialysis | 4.67 | 2.49–8.74 | <0.0001 | 3.66 | 2.19–6.12 | <0.0001 |
| Previous ischemic heart disease | 0.95 | 0.50–1.82 | 0.8883 | 1.36 | 0.81–2.27 | 0.2428 |
| Previous cerebrovascular disease | 1.85 | 0.99–3.43 | 0.0523 | 1.50 | 0.89–2.51 | 0.1281 |
| CTLI at baseline | 5.80 | 2.99–11.3 | <0.0001 | 4.26 | 2.53–7.15 | <0.0001 |
| Pre ABI (per 1-SD increase) | 0.87 | 0.63–1.21 | 0.3839 | 0.91 | 0.70–1.21 | 0.4935 |
| BNP (per 1-SD increase) | 1.25 | 1.06–1.39 | 0.0009 | 1.22 | 1.07–1.34 | 0.0003 |
| CRP (per 1-SD increase) | 1.35 | 1.09–1.62 | 0.0020 | 1.27 | 1.02–1.51 | 0.0131 |
| eGFR (per 1-SD increase) | 0.44 | 0.29–0.66 | <0.0001 | 0.41 | 0.29–0.57 | <0.0001 |
| CONUT score (per 1-point increase) | 1.26 | 1.12–1.40 | <0.0001 | 1.20 | 1.09–1.32 | 0.0001 |
| Malnutrition | 3.10 | 1.59–6.03 | 0.0009 | 2.61 | 1.48–4.59 | 0.0009 |
| H2FPEF score (per 1-point increase) | 1.35 | 1.14–1.59 | 0.0004 | 1.37 | 1.19–1.56 | <0.0001 |
| Modified H2FPEF score (per 1-point increase) | 1.37 | 1.17–1.60 | <0.0001 | 1.35 | 1.18–1.53 | <0.0001 |

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

patients with LEAD. Moreover, there was a significant relationship between composite events and age, sex, diabetes, smoking, hemodialysis, baseline CLTI, BNP, CRP, eGFR, CONUT score, and malnutrition (**Table 2**). Multivariate Cox proportional hazard regression analyses demonstrated that the modified H2FPEF score was an independent predictor of composite events, after adjusting for confounding risk factors (**Table 3**).

### Improved Reclassification by the Addition of the H2FPEF Score to Predict Newly Developed and Recurrent CLTI

We evaluated improvements in the NRI and IDI to examine whether the prediction capacity improved upon the addition of the H2FPEF score and modified H2FPEF score to the basic predictors, such as hemodialysis, smoking, CLTI at baseline, malnutrition, and BNP. Both NRI and IDI improved significantly after the addition of the

**Table 3. Multivariate Cox Proportional Hazard Regression Analysis for the Prediction of Clinical Outcomes in Patients With Lower Extremity Artery Disease**

| | Newly developed and recurrent CLTI | | | Composite event | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Model 1 | | | | | | |
| $H_2$FPEF score (per-1 score increase) | 1.28 | 1.06–1.54 | 0.0098 | 1.32 | 1.12–1.54 | 0.0008 |
| Modified $H_2$FPEF score (per-1 score increase) | 1.35 | 1.13–1.61 | 0.0013 | 1.33 | 1.14–1.54 | 0.0002 |
| Model 2 | | | | | | |
| $H_2$FPEF score (per-1 score increase) | 1.26 | 1.03–1.54 | 0.0237 | 1.31 | 1.10–1.55 | 0.0018 |
| Modified $H_2$FPEF score (per-1 score increase) | 1.31 | 1.10–1.57 | 0.0031 | 1.30 | 1.12–1.52 | 0.0006 |

Model 1 includes hemodialysis, chronic limb-threatening ischemia (CTLI) at baseline, malnutrition, and smoking. Model 2 includes hemodialysis, CTLI at baseline, malnutrition, and B-type natriuretic peptide. CI, confidence interval; HR, hazard ratio.

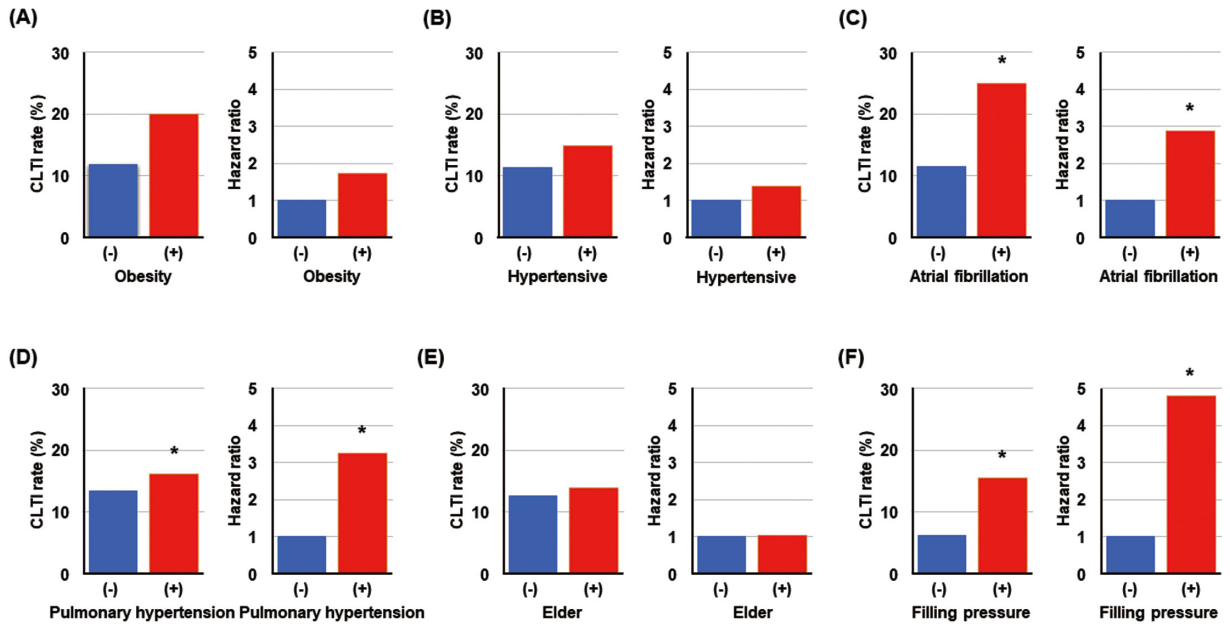


**Figure 4.** Hazard ratios and the rate of newly developed and recurrent chronic limb-threatening ischemia (CTLI) according to the presence of (**A**) obesity, (**B**) hypertension, (**C**) atrial fibrillation, (**D**) pulmonary hypertension, (**E**) elder, and (**F**) filling pressure. *P<0.05 compared with the control group (i.e., without the corresponding component of the modified $H_2$FPEF score).

**Table 4. Statistics for Model Fit and Improvement With the Addition of $H_2$FPEF Score on the Prediction of Newly Developed and Recurrent CTLI**

| | NRI (95% CI) | P value | IDI (95% CI) | P value |
|---|---|---|---|---|
| Baseline model | Reference | | Reference | |
| +$H_2$FPEF score | 0.3306 (0.004–0.6620) | 0.0505 | 0.0064 (0.0045–0.0172) | 0.2481 |
| +Modified $H_2$FPEF score | 0.4439 (0.1145–0.7732) | 0.0083 | 0.0214 (0.0012–0.0416) | 0.0378 |

The baseline model includes hemodialysis, CTLI, malnutrition, smoking, and B-type natriuretic peptide. IDI, integrated discrimination index; NRI, net reclassification index. Other abbreviations as in Table 3.

modified $H_2$FPEF score, but not $H_2$FPEF score, to the basic predictors (**Table 4**).

## Discussion

The main findings of the present study are that: (1) the modified $H_2$FPEF score was normally distributed, with a mean modified $H_2$FPEF score of 3.4 in patients with LEAD; (2) the modified $H_2$FPEF score was significantly increased with Fontaine class; (3) patients with highly modified $H_2$FPEF scores had higher rates of newly developed and recurrent CLTI and composite events compared

with those with low H2FPEF scores (Kaplan-Meier analysis); (4) modified H2FPEF scores were significantly associated with newly developed and recurrent CLTI and composite events after adjusting for confounding risk factors in multivariate analysis; (5) among the components of the modified H2FPEF score, atrial fibrillation, pulmonary hypertension, and filling pressure were significantly related to both CTLI at baseline and newly developed and recurrent CLTI in patients with LEAD; and (6) the NRI and IDI were significantly improved by adding modified H2FPEF scores to the established risk factors.

There are 2 important goals of LEAD treatment: limb salvage and prevention of cardiovascular disease. In this study we demonstrated, for the first time, the prognostic usefulness of the modified H2FPEF score for newly developed and recurrent CLTI in patients with LEAD. It is well known that the H2FPEF score serves as a diagnostic and prognostic marker for HFpEF. Therefore, we also indicated the prognostic importance of the modified H2FPEF score in predicting composite events, including newly developed and recurrent CLTI and HF in patients with LEAD.

### LEAD and H2FPEF Score Components

Obesity is a common risk factor for HFpEF and LEAD.[28,29] Because Asians tend to be lean or heavy, the "heavy" component of the H2FPEF score was only identified in 4% of patients with LEAD. This called for modification of the definition of "heavy" for the Asian population. Therefore, we calculated a modified H2FPEF score using the Asian definition of obesity (BMI >25 kg/m$^2$).

Hypertension is a well-established risk factor for cardiovascular diseases, including LEAD.[26] Most of the guidelines for LEAD and CLTI consider the effectiveness of angiotensin converting enzyme (ACE) inhibitors to reduce cardiovascular events and mortality.[30] In addition, the prescription of ACE inhibitors and angiotensin receptor blockers has been shown to improve limb salvage in patients with CLTI.[31] Conversely, the Examining Use of Ticagrelor In Peripheral Artery Disease (EUCLID) trial demonstrated a lower prevalence of hypertension in patients with than without CLTI.[32] Thus, it is plausible that hypertension was not related to CLTI at baseline and newly developed and recurrent CLTI because of the potential benefits of the prescription of antihypertensive medications.

The ARIC study showed that patients with an ABI ≤0.90 had an increased risk of developing atrial fibrillation.[33] The prevalence of atrial fibrillation in patients with CLTI was double that in patients with intermittent claudication.[34] Atrial fibrillation is a strong predictor of clinical outcome in patients with CLTI.[35,36] These findings support our results that atrial fibrillation is indeed closely associated with CLTI at baseline and newly developed and recurrent CLTI.

Epidemiologically, LEAD is uncommon in people aged <50 years, but its prevalence in people aged >70 and >80 years reaches 15–20% and 20%, respectively.[37,38] A Swedish cohort study demonstrated that the prevalence of CLTI was 0.4% in patients aged between 60 and 90 years, and 3.3% in those aged 80–84 years.[39] Several studies have reported the relationship between age and severity of LEAD.[7,40] However, in the present study, "elder" was not related to CLTI at baseline or newly developed and recurrent CLTI due to its high prevalence.

The clinical significance of echocardiographic parameters in diastolic function has not yet been examined in patients with LEAD. Yamasaki et al indicated the presence of diastolic dysfunction in relation to BNP elevation in patients with LEAD.[41] Yanaka et al demonstrated that septal E/e' and tricuspid regurgitation velocity were higher in patients with than without LEAD.[13] In the present study we showed that the prevalence of pulmonary hypertension and elevated filling pressure was significantly higher in patients with than without CLTI. These findings indicate that echocardiographic parameters of diastolic function worsened with increasing LEAD severity.

Collectively, there was a good relationship between the components of the H2FPEF score and LEAD development and prognosis, although not all components were equally associated with CLTI. These findings support our hypothesis that the modified H2FPEF score could provide useful clinical information for the treatment and management of LEAD.

### CLTI and Modified H2FPEF Score

Notably, the components of the modified H2FPEF score relating to cardiac function were significantly related to CLTI at baseline and newly developed and recurrent CLTI. Because the present study was a prospective observational study, we could not determine a causal relationship between the modified H2FPEF score and both LEAD severity and newly developed and recurrent CLTI. Arterial stiffness is a potential link between HFpEF and LEAD because it is a common risk factor for the development of both HFpEF and LEAD. Arterial stiffness amplifies pulse pressure by increasing the systolic load on the ventricles and decreasing aortic pressure during diastole, leading to augmented myocardial oxygen demand during systole and reduced coronary perfusion during diastole. Therefore, progression of arterial stiffness exacerbates diastolic function in the heart.[42] A meta-analysis indicated that several parameters of arterial stiffness were related to diastolic dysfunction, such as the cardio-ankle vascular index, brachial-ankle pulse wave velocity, and augmentation index.[43] LEAD increases pulse wave velocity through systemic atherosclerosis and the augmentation index through premature pulse wave reflection due to peripheral artery obstruction.[44,45] Therefore, it is plausible that pulmonary hypertension and elevated filling pressure were derived from arterial stiffness caused by atherosclerosis in LEAD. In addition, diastolic dysfunction is considered a risk factor for the development of atrial fibrillation.[46] Atrial fibrillation generally disturbs atrial kick, which accounts for 10–15% of the normal cardiac output.[47] In contrast, low blood supply to the lower limb artery, secondary to cardiac diastolic dysfunction, potentially exacerbates limb ischemia and leads to the development of CLTI. Importantly, we showed that NRI and IDI were improved by adding the modified H2FPEF score, indicating that this score can provide additional information to existing confounding risk factors. Therefore, the modified H2FPEF score is a feasible marker of newly developed and recurrent CLTI in patients with LEAD.

### Clinical Perspective

The modified H2FPEF score, which reflects diastolic dysfunction, can be used for the early identification of patients at high risk of future HF, as well as LEAD patients at high risk of CLTI events. It is possible that patients with high modified H2FPEF scores require management and

treatment for diastolic dysfunction. Although EVT has been reported to reduce central blood pressure and the augmentation index,[48] further research considering optimal medical treatment is required to improve diastolic dysfunction in patients with LEAD.

### Study Limitations

This study has some limitations. First, the precise mechanism by which the clinical conditions related to the modified H2FPEF score accelerate atherosclerosis could not be revealed given that this study was a prospective observational study. Second, echocardiography was performed only once. Third, due to the small number of HF rehospitalizations during the study period, we could not determine the prognostic usefulness of the H2FPEF score for worsening HF in patients with LEAD. Fourth, CLTI patients who underwent bypass surgery were not included in the study. Finally, the study population was small; thus, further studies with larger populations are needed to determine the abnormal cut-off value for the modified H2FPEF score in patients with LEAD.

## Conclusions

We have demonstrated, for the first time, that the modified H2FPEF score, a diagnostic marker for HFpEF, is associated with clinical outcomes, notably newly developed and recurrent CLTI, in patients with LEAD. The modified H2FPEF score could potentially be a useful marker for clinical outcomes, specifically for tracking limb ischemia in patients with LEAD.

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### Disclosures

The authors have no conflicts of interest to declare.

### IRB Information

This study was approved by the Institutional Ethics Committee of Yamagata University School of Medicine (No. 2020-344).

### Data Availability

The datasets generated and/or analyzed during the present study are available from the corresponding author upon reasonable request.

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## Supplementary Files

Please find supplementary file(s);
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