The controlling nutritional status score predicts outcomes of cardiovascular events in patients with heart failure with preserved ejection fraction

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1. Introduction

For the purpose of treating heart failure (HF), it is important to (1) suppress the progression of cardiac dysfunction, (2) improve symptoms, exercise skills and quality of life (QOL), and (3) prevent readmission and improve the life prognosis [1]. In the progressive stage of HF, physical function and nutritional status change in parallel, and the nutritional status of patients with HF worsens toward the end of life. Serum albumin and cholesterol levels, commonly used as indicators of nutritional status, are predictors of prognosis independent of age and severity of HF [2,3]. It has been reported that hypoalbuminemia progression after hospitalization is associated with a worse prognosis in patients with acute HF [4].

Serum albumin has a long half-life of approximately 20 days, is susceptible to invasion and is not suitable for individuals evaluation. For this reason, the Controlling Nutritional Status (CONUT) method was developed as a tool to evaluate nutritional status using three biomarkers: protein metabolism, immunocompetence, and lipid metabolism [5]. The serum albumin level reflects protein metabolism, the total lymphocyte count reflects immunity, and the total cholesterol level reflects lipid metabolism; these items are scored, and the nutritional status is comprehensively and pleiotropically evaluated according to the three biological indices. The CONUT index has been reported as a useful index for the early screening of malnutrition in patients with HF [5]. It has been reported that undernutrition in chronic HF patients could be

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https://doi.org/10.1016/j.ijcha.2020.100563
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evaluated with the CONUT index and was correlated with subsequent cardiovascular events [6], and a correlation was found between the CONUT score and mortality in patients with HF [7,8].

Accumulating clinical studies have demonstrated that HF with reduced left ventricular (LV) ejection fraction (EF) (HFrEF) and HF with preserved LVEF (HFpEF) are separate pathological conditions because of differences in survival rates [9,10] and effective drug therapies; thus, we have proposed that HFrEF and HFpEF patients should be managed differently [11].

In the present study, we sought to evaluate the relationship between the CONUT score and cardiovascular outcomes in patients with HFpEF.

2. Methods

This study was a prospective, single-center, observational study.

2.1. Ethics statement

All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the institutional review board of Kumamoto University (approval number, Senshin 2225). This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000036884). Opt-out materials are available at http://www.kumadai-junnai.com/home/wp-content/uploads/houkatsu.pdf.

2.2. Study design and patients

We prospectively investigated 948 consecutive patients with HF who were hospitalized in Kumamoto University Hospital between January 2007 and September 2013. We recorded each patient’s medical history and relevant clinical characteristics. We excluded 440 patients for the following reasons: severe valvular disease (n = 118), chronic renal failure requiring hemodialysis (n = 65), systemic inflammatory disease (n = 5), acute renal failure (n = 1), and not meeting the diagnostic criteria for HFpEF as subsequently described (including HF with a reduced LVEF [HFrEF]; n = 251). Finally, 506 patients of the remaining 508 HFpEF patients, excluding those with insufficient data, were enrolled in this study. We subsequently calculated the CONUT score in these HFpEF patients, and the subjects were subdivided into normal- (0–1), light- (2–4), moderate- (5–8), and severe-score (9–12) groups according to the original concepts of CONUT score [5], with the occurrence of cardiovascular events followed for up to 1500 days. The study flow chart is shown in Fig. 1.

2.3. Definition of HFpEF

HFpEF was clinically defined according to the European Society of Cardiology task force as follows:

1. symptoms or signs of HF;
2. normal or mildly reduced LVEF (LVEF > 50% and LV end-diastolic volume index < 97 mL/m2);
3. evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness.

We excluded HFpEF patients who had shown even a transient reduction in ejection fraction. Hence, HFpEF patients whose LVEF was <50% and was improved by optimal medical therapy were not included in the present study. In our study, we stratified patients by the E/e’ ratio, grouped by either a ≥15 ratio or >8 but <15 ratio, and by plasma B-type natriuretic peptide (BNP) levels, with a cut-off of 100 pg/mL. Physicians further confirmed that patients had HF by determining the New York Heart Association (NYHA) functional class [12], which was assessed by the standard questionnaire while the patient was in a stable condition after optimal therapy.

2.4. Calculation of the CONUT score

The CONUT score was calculated as described previously [5]. In brief, 3 parameters were used to calculate the score: (i) serum albumin level (g/dL); (ii) total cholesterol level (mg/dL); and (iii) total lymphocyte count (count/mL) (Supplemental Table 1). Thus, the CONUT score enables assessment of protein reserves, caloric depletion, and immune defenses in each patient.

2.5. Clinical parameters

The clinical parameters were described previously [11,13–17]. In brief, the baseline demographic data, cardiovascular risk factors, and medications on discharge were documented. Hypertension was defined as a recorded blood pressure >140/90 mmHg or the use of any antihypertensive medications as described previously. Diabetes mellitus (DM) was defined as the presence of symptoms of diabetes and a random plasma glucose concentration ≥200 mg/dL, fasting plasma glucose concentration ≥126 mg/dL, or a 2-hr plasma glucose concentration ≥200 mg/dL according to a 75 g oral glucose tolerance test or the use of any medications for DM. Dyslipidemia was defined as low-density lipoprotein levels ≥140 mg/dL (≥3.63 mmol/L), high-density lipoprotein levels <40 mg/dL (1.04 mmol/L), triglycerides ≥150 mg/dL (≥1.7 mmol/L) or the use of medications for dyslipidemia.

2.6. Echocardiographic examinations

Echocardiography was performed while the patient was in a stable condition on admission by experienced cardiac
sonographers who had no knowledge of the study data. Left ventricular ejection fraction (LVEF) was measured using a modified Simpson’s method. The LVEF and the ratio of early transmitral flow velocity to early diastolic mitral annular velocity (E/e₀), which was assessed by tissue Doppler, were measured by echocardiography (Vivid 7®; GE-Vingmed Ultrasound, Horton, Norway; Aplio XG®; Toshiba, Tokyo, Japan) as previously reported [11,14,16].

2.7. Biomarker measurement

Blood samples were obtained in stable and fasting conditions in the early morning. The patient’s BNP levels were analyzed using a commercially available assay (Abbott Japan, Matsudo, Japan) in the hospital clinical laboratory on admission. The BNP levels were transformed into natural logarithmic levels (ln-BNP) to achieve a normal distribution. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese Society of Nephrology formula [18].

2.8. Follow-up and outcomes

Patients were followed up prospectively at our outpatient clinics or by the primary care physician every month until July 2017 or until the occurrence of a cardiovascular event, including the following: cardiovascular death, hospitalization for HF decompensation, non-fatal myocardial infarction (MI), unstable angina pectoris, coronary revascularization for a new diagnosis of angina or in-stent restenosis after percutaneous coronary intervention, and nonfatal ischemic stroke. Cardiovascular death was defined as death within 30 days of documented sudden death without apparent noncardiovascular causes, MI, death from HF, or death from stroke. Hospitalization for HF decompensation was defined if the patient was admitted for at least an overnight stay in the hospital because of HF with typical symptoms and had objective signs of worsening HF requiring intravenous drug administration. MI was diagnosed by an increase or decrease in cardiac biomarkers (plasma creatine kinase-MB or cardiac troponin) above the 99th percentile of the upper limit of the normal range together with evidence of myocardial ischemia and at least 1 of the following symptoms: electrocardiographic changes (new ST-T changes, left bundle branch block, or pathological Q wave) or imaging evidence of new viable myocardial loss, or a new regional wall motion abnormality [19]. Unstable angina pectoris was diagnosed according to new or accelerating symptoms of myocardial ischemia accompanied by new ischemic ST-T-wave changes. Ischemic stroke was diagnosed according to the documented focal neurological deficit with radiological evidence of brain infarction excluding intracranial hemorrhage. Cardiovascular events were ascertained by reviewing medical records and were confirmed by direct contact with the patients, their families, and physicians or by annual telephone interview with each patient. An Events Committee comprising at least 3 independent physicians reviewed all events to avoid intraobserver biases.

2.9. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation for normally distributed variables according to the Shapiro–Wilk test. Variables with a non-normal distribution are expressed as the median value with the interquartile range. Categorical variables are presented as frequencies and percentages. Differences

![Fig. 2. Distribution of the CONUT score. Blue indicates a CONUT score of 0–1 point (normal degree of undernutrition). Green indicates a CONUT score of 2–5 points (light degree of undernutrition). Red indicates a CONUT score of 6–8 points (moderate degree of undernutrition). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image-url)
between groups were determined using Fisher’s exact test for categorical variables. Differences in continuous variables were analyzed by the unpaired t test or the Mann–Whitney U test, as appropriate. Missing data were excluded from the analyses. A Kaplan–Meier curve was used to determine the cumulative incidence of composite cardiovascular events. The Cox proportional hazards model was used to estimate composite cardiovascular events using the net reclassification index (NRI) and IDI were performed by R package of "dictABEL" [26]. The software Statistical Package for Social Sciences (SPSS) ver. 26.0 (IBM Japan, Tokyo, Japan) was used for other statistical analyses.

### 3. Results

#### 3.1. Clinical characteristics of enrolled patients with HFpEF

A total of 506 patients with HFpEF were enrolled in this study. The numbers of patients (percentage) with normal, light, moderate, and severe CONUT groups were 231, 226, and 49, respectively. The basal characteristics of enrolled patients are shown in Table 1. The numbers of patients with normal, light, and moderate CONUT groups for each study were included in Table 2. These results indicate that the patients in the CONUT moderate group were older than those in the other groups. In addition, the numbers of patients with previous hospitalization for HF, diabetes mellitus, and hypertension were significantly higher in the CONUT moderate group compared to those in the other groups. Furthermore, the numbers of patients with atrial fibrillation and dyslipidemia were significantly lower in the CONUT moderate group compared to those in the other groups.

### Table 1

Baseline characteristics of HFpEF patients according to group determined by CONUT (controlling nutritional status) scores.

|                | All HFpEF patients | Normal group | Light group | Moderate group | P value |
|----------------|---------------------|--------------|-------------|----------------|---------|
| Age, years     | 71.6 ± 9.4          | 71.7 ± 9.4    | 71.0 ± 9.5  | 74.1 ± 8.6     | 0.114   |
| Male, n (%)    | 277 (54.7)          | 133 (57.5)    | 117 (51.7)  | 27 (55.1)      | 0.461   |
| BMI (kg/m²)    | 24.1 ± 3.6          | 24.5 ± 3.5    | 23.8 ± 3.8  | 23.4 ± 2.9     | 0.061   |
| NYHA III or IV, n (%) | 86 (16.9)       | 35 (15.1)     | 39 (17.2)   | 12 (24.4)      | 0.363   |
| Diabetes mellitus, n (%) | 156 (30.8)      | 92 (39.8)     | 52 (23.0)   | 12 (24.4)      | <0.001  |
| Hypertension, n (%) | 396 (78.2)       | 198 (85.7)    | 163 (72.1)  | 35 (71.4)      | 0.001   |
| Dyslipidemia, n (%) | 393 (77.6)       | 192 (83.1)    | 163 (72.1)  | 38 (77.5)      | 0.013   |
| IHD, n (%)     | 266 (52.5)          | 143 (62.7)    | 100 (44.2)  | 21 (42.8)      | <0.001  |
| Atrial fibrillation, n (%) | 145 (28.6)  | 54 (23.3)     | 74 (32.7)   | 17 (34.6)      | 0.054   |
| SBP (mmHg)     | 130.1 ± 21.2        | 129.6 ± 20.1  | 130.2 ± 22.4| 132.7 ± 20.7   | 0.646   |
| DBP (mmHg)     | 71.0 ± 13.1         | 70.2 ± 12.3   | 71.9 ± 13.4 | 70.3 ± 12.8    | 0.328   |
| Hemoglobin (g/dL) | 12.7 ± 1.8         | 12.8 ± 1.8    | 12.7 ± 1.9  | 12.5 ± 1.7     | 0.508   |
| hs-CRP (mg/L)  | 0.44 ± 1.9          | 0.27 ± 0.8    | 0.39 ± 2.0  | 1.5 ± 3.9      | 0.073   |
| eGFR (ml/min/1.73 m²) | 62.2 ± 19.5 | 62.0 ± 18.6   | 63.6 ± 20.6 | 56.9 ± 17.4    | 0.095   |
| LVEF (%)       | 62.7 ± 5.8          | 63.1 ± 5.3    | 62.1 ± 6.0  | 63.1 ± 6.8     | 0.120   |
| SVI            | 40.2 ± 9.9          | 40.9 ± 9.7    | 39.8 ± 9.5  | 39.3 ± 12.5    | 0.410   |
| LAD (mm)       | 39.5 ± 7.0          | 39.5 ± 7.3    | 39.2 ± 6.9  | 40.8 ± 6.6     | 0.391   |
| E/e'           | 17.5 ± 5.0          | 17.0 ± 4.0    | 17.9 ± 5.7  | 18.3 ± 5.7     | 0.054   |
| TR-PG (mmHg)   | 25.3 ± 8.0          | 24.6 ± 8.1    | 25.3 ± 7.4  | 28.6 ± 9.7     | 0.017   |
| PAP (mmHg)     | 31.6 ± 9.1          | 30.5 ± 9.2    | 31.9 ± 8.6  | 35.5 ± 10.2    | 0.006   |
| Diuretics, n (%)| 124 (24.5)          | 48 (20.7)     | 58 (25.6)   | 18 (36.7)      | 0.082   |
| ACE-I or ARB, n (%) | 317 (62.6)    | 159 (68.8)    | 124 (54.8)  | 34 (69.3)      | 0.006   |
| CCB, n (%)     | 294 (58.1)          | 139 (60.1)    | 122 (53.9)  | 33 (67.3)      | 0.154   |
| Beta-blocker, n (%) | 225 (44.4)   | 121 (52.3)    | 86 (38.1)   | 18 (36.7)      | 0.006   |
| Statin, n (%)  | 303 (59.8)          | 145 (62.7)    | 161 (71.2)  | 29 (59.1)      | <0.001  |
| CONUT score    | 4.3 ± 1.2           | 0.5 ± 0.4     | 2.6 ± 0.7   | 5.8 ± 0.8      | <0.001  |

Data are presented as the mean ± SD, median (interquartile range), or number (percentage).

#### Table 2

Cardiovascular events according to CONUT score.

|                          | Total (n = 506) | Normal group (n = 231) | Light group (n = 226) | Moderate group (n = 49) | P value |
|--------------------------|----------------|----------------------|----------------------|------------------------|---------|
| Total cardiovascular events, n (%) | 238 (47.0) | 95 (41.1)             | 110 (48.6)           | 32 (65.3)               | 0.005   |
| Cardiovascular death, n (%) | 31 (6.1)  | 7 (3.0)               | 10 (4.4)             | 14 (28.5)               | <0.001  |
| Hospitalization for HF decompensation, n (%) | 110 (21.7) | 36 (15.5)            | 62 (27.4)            | 12 (24.4)               | 0.003   |
| Non-fatal myocardial infarction, n (%) | 6 (1.1)   | 2 (0.8)               | 2 (0.8)              | 2 (4.0)                 | 0.544   |
| Unstable angina pectoris, n (%) | 15 (2.9)  | 8 (3.4)               | 5 (2.2)              | 1 (2.0)                 | 0.811   |
| Coronary revascularization, n (%) | 61 (12.0) | 32 (13.8)            | 27 (11.9)            | 2 (4.0)                 | 0.023   |
| Nonfatal ischemic stroke, n (%) | 15 (2.9)  | 10 (4.3)              | 4 (1.7)              | 1 (2.0)                 | 0.278   |

1 P < 0.01 vs. light group.

2 P < 0.05.

3 P < 0.01 vs. normal group.

BNP; 4 prognostic factors [PF4] [20]. We also assessed the incremental benefits of adding a higher CONUT score to the PF4 to predict composite cardiovascular events using the net reclassification index (NRI). A P value <0.05 was considered statistically significant. The Harrell’s C-statistic, NRI and IDI were performed by R package of PredictABEL. The software Statistical Package for Social Sciences (SPSS) ver. 26.0 (IBM Japan, Tokyo, Japan) was used for other statistical analyses.
moderate, and severe scores were 231 (45.6%), 226 (44.6%), 49 (9.4%), and 0 (0%), respectively. Fig. 2 shows the distribution of CONUT scores among HFpEF patients. The baseline characteristics of the HFpEF patients are shown in Table 1. Overall, the patients had a mean age of 71.6 ± 9.4 years, and 54.7% were male. The prevalence of ischemic heart disease (IHD) was significantly lower in both the light group and moderate group than in the normal group. Plasma BNP levels were significantly higher, and the prevalence of DM, hypertension, and dyslipidemia and the use of beta-blockers were significantly lower in the light group than in the normal group. While the tricuspid regurgitation pressure gradient (TR-PG) and pulmonary artery systolic pressure (PAP) were significantly higher in the moderate group than in the normal group, NYHA class III or IV and transthoracic echocardiographic parameters, including LVEF, E/e₀, stroke volume index (SVI), and left atrial diameter (LAD), were not significantly different between these groups.

3.2. Cardiovascular events at follow-up

Overall, 238 cardiovascular events were recorded during the follow-up period (median: 1159 days). Table 2 shows the details of cardiovascular events during follow-up. We found significantly higher rates of composite cardiovascular events in the patients in the moderate group than in the patients in the normal group (P = 0.005) and light groups (P < 0.001) and significantly higher rates of cardiovascular death in the patients in the moderate group than in the patients in the normal and light groups (P < 0.001). Moreover, the rate of hospitalization for HF decompensation was significantly higher in the moderate group than in the normal group (P = 0.003).

3.3. Kaplan–Meier curves

We performed a Kaplan–Meier analysis and observed that the moderate group was at higher risk of composite cardiovascular events than the normal group (P < 0.001; Fig. 3) and the light group (P = 0.031; Fig. 3). It also showed that the light group was at higher risk of composite cardiovascular events than the normal group (P = 0.038; Fig. 3).

3.4. Cox proportional hazards analyses

Table 3 shows the results of univariate and multivariable Cox proportional hazards analyses for cardiovascular events. Univariate Cox proportional hazards analysis identified age (HR: 1.01, 95% CI: 1.00–1.03, P = 0.031), previous hospitalization for HF (HR: 1.62, 95% CI: 1.19–2.21, P = 0.002), NYHA III or IV (HR: 1.80, 95% CI: 1.33–2.43, P < 0.001), hemoglobin (HR: 0.87, 95% CI: 0.81–0.93, P < 0.001), ln-BNP (HR: 1.16, 95% CI: 1.05–1.28, P = 0.003), LAD (HR: 1.01, 95% CI: 1.00–1.03, P = 0.047), PAP (HR: 1.01, 95% CI: 1.00–1.03, P = 0.018), diuretic usage (HR: 1.48, 95% CI: 1.12–1.95, P = 0.005) and CONUT score (HR: 1.14, 95% CI: 1.08–1.24, P < 0.001) as significant factors associated with cardiovascular events. In a multivariate Cox proportional hazard analysis including PF4 by forced entry methods (model 1), previous hospitalization for HF (HR: 1.42, 95% CI: 1.02–1.99, P = 0.036) and CONUT score (HR: 1.14, 95% CI: 1.06–1.22, P < 0.001) were independently and significantly associated with cardiovascular events. Multivariable Cox proportional hazards analysis using the abovementioned 5 significant factors from the univariate analysis (model 2) identified hemoglobin (HR: 0.90, 95% CI: 0.83–0.99, P = 0.033) and CONUT score (HR: 1.12, 95% CI: 1.03–1.21, P = 0.005) as independent predictors of cardiovascular events in patients with HFpEF.

3.5. Receiver operating characteristic (ROC) analysis for composite cardiovascular events and CONUT score

ROC curves were constructed to assess the ability of the CONUT score to predict composite cardiovascular events (Fig. 4). The area under the curve of the CONUT score for the detection of composite cardiovascular events was 0.599 (95% CI 0.550–0.648; P < 0.001). Using the cutoff value for the CONUT score (2.5), the sensitivity and specificity were 38.2% and 76.9%, respectively, for the detection of composite cardiovascular events.

3.6. C-statistic for regression models, continuous NRI and integrated discrimination improvement (IDI)

The C-statistic value for PF4 was 0.608 (95% CI: 0.559–0.658); after adding a CONUT score >2.5 as a factor, the value was 0.643 (95% CI: 0.594–0.691; P = 0.039). We reclassified the risk of
cardiovascular events after adding a CONUT score >2.5 to PF4; the continuous NRI was 30.5% ($P < 0.001$), and the IDI was 2.2% ($P < 0.001$) (Table 4). The ROC curves for composite cardiovascular events are shown in Fig. 5.

Table 3
Cox proportional hazards regression analyses for cardiovascular outcome within 1500 days follow-up.

| Variable                        | Univariable Regression | Multivariable Regression |
|---------------------------------|------------------------|--------------------------|
|                                 | HR 95% CI P value      | Model 1 (I-PRESERVE) HR 95% CI P value | Model 2 HR 95% CI P value |
| Age (years)                     | 1.01 1.00–1.03 0.031   | 1.01 0.99–1.02 0.075      | 1.00 0.99–1.02 0.433      |
| Male sex (yes)                  | 0.90 0.73–1.17 0.453   |                          |                          |
| BMI (kg/m²)                     | 0.96 0.93–1.00 0.091   |                          |                          |
| Previous hospitalization for HF (yes) | 1.62 1.19–2.21 0.002  | 1.42 1.02–1.99 0.036     | 1.47 0.97–2.24 0.068     |
| NYHA III or IV (yes)            | 1.80 1.33–2.43 <0.001  |                          | 1.16 0.78–1.73 0.453     |
| Diabetes mellitus (yes)         | 1.14 0.87–1.49 0.137   |                          |                          |
| Hypertension (yes)              | 0.77 0.57–1.03 0.083   |                          |                          |
| Dyslipidemia (yes)              | 0.99 0.72–1.36 0.977   |                          |                          |
| IHD (yes)                       | 1.04 0.80–1.34 0.740   |                          |                          |
| Atrial fibrillation (yes)       | 1.18 0.89–1.59 0.237   |                          |                          |
| SBP (mm Hg)                     | 1.00 0.99–1.00 0.877   |                          |                          |
| DBP (mm Hg)                     | 0.99 0.98–1.00 0.126   |                          |                          |
| Hemoglobin (g/dl)               | 0.87 0.81–0.93 <0.001  |                          |                          |
| eGFR (mL/min/1.73 m²)           | 1.02 0.97–1.07 0.422   |                          |                          |
| ln-BNP                          | 1.16 1.05–1.28 0.003   | 1.08 0.96–1.20 0.160     | 1.01 0.88–1.16 0.823     |
| LVEF (%)                        | 0.99 0.97–1.01 0.552   |                          |                          |
| SVI (L/min)                     | 0.99 0.98–1.00 0.555   |                          |                          |
| LAD (mm)                        | 1.01 1.00–1.03 0.047   |                          |                          |
| E/e                             | 1.02 0.99–1.04 0.082   |                          |                          |
| TR-PC (mm Hg)                   | 1.01 0.99–1.03 0.124   |                          |                          |
| PAP (mm Hg)                     | 1.01 1.00–1.03 0.018   |                          |                          |
| Diuretics (yes)                 | 0.98 0.96–1.00 0.175   |                          |                          |
| ACE-I or ARB (yes)              | 1.01 1.00–1.03 0.018   |                          |                          |
| CCB (yes)                       | 0.98 0.96–1.00 0.175   |                          |                          |
| Beta-blocker (yes)              | 0.98 0.96–1.00 0.175   |                          |                          |
| Statin (yes)                    | 1.05 0.98–1.12 0.038   |                          |                          |
| CONUT score                     | 1.16 1.08–1.24 <0.001  | 1.14 1.06–1.22 <0.001    | 1.12 1.03–1.21 0.005     |

Model 1: age, previous hospitalization for HF, diabetes mellitus, ln-BNP and CONUT score.
Model 2: variables of statistical significance in the univariable analyses ($P < 0.05$).
Abbreviations as shown in this table. HR: hazard ratio CI: confidence interval ln-BNP: natural logarithmic transformed B-type natriuretic peptide level.

Fig. 4. Receiver operating characteristic (ROC) curves of CONUT scores for the prediction of cardiovascular events.

4. Discussions

The main feature of this study is that the prognosis of HfPEF patients was classified by CONUT score, and the main findings of this study were as follows:

(i) The Kaplan-Meier curve revealed that the higher the CONUT score, the higher the incidence of composite cardiovascular events.

(ii) Multivariate Cox proportional hazards analysis revealed that the CONUT score was an independent and significant predictor of clinical outcome in HfPEF patients.

(iii) The cutoff level of the CONUT score for composite cardiovascular events was 2.5.

(iv) The NRI and IDI were significant when a CONUT score >2.5 was added to the PF4.

Obesity has been shown to be an independent risk factor for the future development of cardiovascular disease and a risk factor for the development of HF in the general population [21]. Therefore, conventional nutritional guidance for patients with HF has mainly focused on suppressing energy intake. However, Anker et al. reported that weight loss of 7.5% or more in HF patients followed for at least 6 months is a worse prognostic factor independent of HF prognosis factors such as age, NYHA functional classification, and LVEF and that preserved body weight is a better prognostic factor [22]. The concept of better prognosis when BMI is preserved was introduced. Similar large-scale multicenter trials revealed that low BMI was associated with poor prognosis, and some guidelines warn about underweight [23,24]. Similar phenomena were reported in Japanese patients [25–27].
C-statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for the Cox hazard model to predict cardiovascular events in patients with HFpEF by the addition of CONUT score >2.5 to the PF4.

|               | C-statistic | NRI | IDI |
|---------------|-------------|-----|-----|
|               | Value       | 95% CI | P value | Value       | 95% CI | P value | Value       | 95% CI | P value |
| PF4           | 0.608       | 0.559–0.658 | <0.001 | 0.594–0.691 | 0.039 | 0.146–0.456 | <0.001 |
| PF4 + CONUT score >2.5 | 0.643       | 0.594–0.691 | 0.039 | 0.146–0.456 | <0.001 | 0.022 | 0.010–0.035 | <0.001 |

Table 4: C-statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for the Cox hazard model to predict cardiovascular events in patients with HFpEF by the addition of CONUT score >2.5 to the PF4.

The CONUT score is simple, and the calculation is not only easy in clinical practice but is also well validated and has a low cost, which indicates that the score can be widely applied. If this score further predicts subsequent cardiovascular events in HFpEF patients, it can also represent a useful indicator for general clinicians, as well as cardiologists in clinical practice. Although the CONUT score is strongly expected to have clinical value, large-scale clinical studies are required to confirm its value. Therefore, additional detailed, prospective, multicenter studies are warranted to verify this precise usefulness.

5. Study limitations

The present study has some limitations. First, it was a single-center study with a relatively small population. Therefore, a larger multiracial and multicenter study is required. Second, there were small numbers with only 49 with a "moderate" CONUT score and none with a severe score. Third, it is unclear which factors contribute—and the extent of their contribution—to the worse HF prognosis and malnutrition. Thus, further pathophysiological and molecular physiological studies, including animal experiments, are warranted. Additional detailed, large-scale clinical studies may be required to verify our results. Finally, the study population discussed in this study had the relatively non-obese nature which is less typical than what is seen in the West where the obese phenotype of HFpEF is more prevalent. This might decrease the generalizability of the results of the Western world.

6. Conclusion

Despite the limitations mentioned above, the results of the present study demonstrate the following: the CONUT score may be useful for predicting cardiovascular events in HFpEF patients. The CONUT score provides important prognostic information regarding HFpEF patients, and the optimal CONUT score might be a promising therapeutic target for HFpEF.

Acknowledgments

We thank all paramedical staff and clinical secretaries for their kind support during this work.
This study was supported in part by Grants-in-Aid for Scientific Research (18K07720) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Declaration of Competing Interest

Dr. Sakamoto has received significant research grant support from Daiichi Sankyo Co., Ltd. Dr. Kaikita has received significant research grant support from Bayer Yakuhi, Ltd.; Daiichi Sankyo Co., Ltd.; Novartis Pharma A.G.; and SBI Pharma Co., Ltd. and has received Honoraria from Bayer Yakuhi, Ltd. and Daiichi Sankyo Co., Ltd. Dr. Tsujita has received Honoraria from Asten Angstel BioPharm K.K.; Bayer Yakuhi, Ltd.; Daiichi Sankyo Co. Ltd.; MSD K.K.; and Sanofi K.K. and has received grants from AstraZeneca K.K.; Astellas Pharma Inc.; Bayer Yakuhi, Ltd.; Boehringer Ingelheim Japan; Boston Scientific Japan K.K.; Chugai Pharmaceutical Co., Ltd.; Daiichi Sankyo Co., Ltd.; Eisai Co., Ltd.; Kowa Pharmaceutical Co. Ltd.; Mitsubishi Tanabe Pharma; MSD K.K.; Pfizer Japan, Inc.; Sanofi K.K.; Shionogi & Co., Ltd.; and Takeda Pharmaceutical Co., Ltd. The remaining authors have nothing to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jchd.2020.100563.

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