Utility of Nutritional Screening in Predicting Short-Term Prognosis of Heart Failure Patients

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Summary
Controlling nutritional status (CONUT) uses 2 biochemical parameters (serum albumin and cholesterol level), and 1 immune parameter (total lymphocyte count) to assess nutritional status. This study examined if CONUT could predict the short-term prognosis of heart failure (HF) patients.

A total of 482 (57.5%) HF patients from the Ibaraki Cardiovascular Assessment Study-HF (n = 838) were enrolled (298 men, 71.7 ± 13.6 years). Blood samples were collected at admission, and nutritional status was assessed using CONUT. CONUT scores were defined as follows: 0-1, normal; 2-4, light; 5-8, moderate; and 9-12, severe degree of undernutrition. Accordingly, 352 (73%) patients had light-to-severe nutritional disturbances. The logarithmically transformed plasma brain natriuretic peptide (log BNP) concentration was significantly higher in the moderate-severe nutritional disturbance group (2.92 ± 0.42) compared to the normal group (2.72 ± 0.45, \( P < 0.01 \)). CONUT scores were significantly higher in the in-hospital death patients [4 (3-8), \( n = 14 \)] compared with patients who were discharged following symptom alleviation [3 (1-5), \( n = 446, P < 0.05 \)]. With the exception of transferred HF patients (\( n = 22 \)), logistic regression analysis that incorporated the CONUT score and the log BNP, showed that a higher CONUT score (\( P = 0.019 \)) and higher log BNP (\( P = 0.009 \)) were predictors of in-hospital death, and the median duration of hospital stay was 20 days.

Our results demonstrate the usefulness of CONUT scores as predictors of short-term prognosis in hospitalized HF patients.

Key words: Aging society, Brain natriuretic peptide, CONUT score, Nutritional status, Undernutrition

The prevalence of cardiovascular disorders in Japan has increased markedly due to a rapidly aging society and the westernization of lifestyle, as both increase the risk of developing coronary artery disease and other diseases. In an epidemiological study conducted in Japan, the number of heart failure (HF) patients was predicted to reach 1,300,000 by the year 2030.17 Angiotensin-converting enzyme inhibitors and \( \beta \)-blockers are essential components of the treatment regimen for patients with chronic HF. Recently, non-pharmacological therapies, such as cardiac resynchronization therapy (CRT),2 exercise therapy,3 and Waon therapy4 have also been used for the treatment of HF patients. Similarly, various other HF therapy regimens have been developed, and the field is dynamic and progressive. However, although therapies have significantly improved, or may improve, patient survival, HF is still associated with high morbidity and mortality.

According to some registry studies conducted in Japan, the 1-year HF mortality rate is 7-9%, while the rate of hospital readmission due to an HF exacerbation within 1-year of hospital discharge is 15-40%.5 These reports indicate that the currently employed HF treatment regimen is insufficient.

Undernutrition is one of the most important determinants of worse clinical outcomes in HF patients. Intestinal edema or anorexia-induced low nutritional intake, liver dysfunction, cytokine-induced hypercatabolism, insulin resistance, and other mechanisms may all result in HF-related undernutrition.6,7 HF patients with undernutrition...
enter a vicious cycle of inflammation, catabolic drive, and undernutrition, that further exacerbate HF. Thus, HF therapy and cardiac rehabilitation cannot advance smoothly in patients with undernutrition, and undernutrition further increases the rate of HF-related mortality and readmission. A substantial number of studies have examined the relationship between undernutrition and HF prognosis, and on the basis of their results, it is apparent, that undernutrition is an independent disease prognosticator in HF patients. Therefore, nutritional screening to differentiate between malnourished and non-malnourished patients is the first step in the successful nutritional management of HF patients. Controlling nutritional status (CONUT) uses 2 biochemical parameters (serum albumin and cholesterol level), and 1 immune parameter (total lymphocyte count) to assess the nutritional status. CONUT is a simple, well-defined tool to identify patients at risk of developing nutrition-related complications. Hospitalized patients with advanced HF are at a high risk of undernutrition and death. Although Suzuki, et al. have reported slightly longer hospital stays among HF patients with higher CONUT scores, the relationship between a higher CONUT score and in-hospital death has not been elucidated. The aim of this study was to assess the usefulness of CONUT in predicting the short-term prognosis of hospitalized patients with HF symptoms.

Methods

Study population: A total of 838 patients with HF symptoms were hospitalized between June 2012 and March 2015 and were enrolled in the Ibaraki Cardiovascular Assessment Study-HF (ICAS-HF) registry. The ICAS-HF is a multicenter registry study involving 11 hospitals in Ibaraki Prefecture, Japan. The ICAS-HF registry inclusion criteria were patient age ≥ 20 years and fulfillment of the Framingham criteria for HF. The registry exclusion criteria were patient age < 20 years, patients who did not provide informed consent to the attending physician, patients with a limited life expectancy due to a malignant neoplasm, patients in whom a two-year observation was deemed to be impossible, and patients who were medically judged as inappropriate by the attending physician. Written informed consent was obtained from all patients, and data collection for this study was approved by the institutional review boards of the 11 participating hospitals. Additionally, the ICAS-HF registry study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Data from the ICAS-HF registry were retrospectively analyzed. Three parameters are used to calculate the CONUT score: serum albumin level, total cholesterol level, and total lymphocyte count (Table I). Among the 838 patients enrolled in the registry, serum albumin level was unavailable for 25 patients, total cholesterol level was unavailable for 146 patients, and total lymphocyte count was unavailable for 267 patients. Registry patients for whom CONUT scores could not be estimated were excluded (n = 356), thus, a total of 482 patients with CONUT scores were ultimately enrolled in this study. Table II summarizes the clinical characteristics of the excluded patients. The patient characteristics of the excluded patients were comparable to those of the enrolled patients, and most study variables were similar, with the exception of the serum albumin level and therapeutic agents prescribed (Table II).

Data collection: Baseline clinical data were collected for each patient. All patient-related information collected at enrollment, including medical history, laboratory test results, and echocardiographic findings, was recorded in a computer database. Essentially, blood sampling and echocardiographic examinations were performed within 72 hours of admission. Blood tests were performed to determine total lymphocyte counts, hemoglobin, albumin, total cholesterol, serum creatinine, C-reactive protein, and plasma brain natriuretic peptide (BNP) levels. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR = 194 × serum creatinine^{-1.094} × age in years^{-0.287} for male patients. The adjusted eGFR value for female patients was calculated using the following formula: eGFR female = eGFR × 0.739. As edema is known to significantly affect patient body weight at admission, we measured body weight after the condition of the patient had stabilized. The body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters. In the present study, we defined a reduced left ventricular ejection fraction (LVEF) as a visual LVEF < 40% at admission.

Assessment of nutritional status using CONUT scores: The CONUT was developed by Ignacio de Ulibarri, et al. as a screening tool for undernutrition utilizing a hospital population. The CONUT score is a sum of 3 parameters: the serum albumin level (g/dL), total cholesterol level (mg/dL), and the total lymphocyte count (count/μL) (Table I). The serum albumin level serves as an indicator of the protein reserves, while the total cholesterol level is an indicator of caloric depletion. The total lymphocyte count is used as an indicator of undernutrition-mediated impaired immune defense. Patients with CONUT scores of 0-1 have a normal nutritional status, those with CONUT scores of 2-4 have a light degree of undernutrition, those with CONUT scores of 5-8 have a moderate degree of undernutrition, and those with CONUT scores of 9-12 have a severe degree of undernutrition (Table I).

Correlation between BNP level and nutritional status: Since the number of patients with severe nutritional disturbance was only 15, the logarithmically transformed plasma BNP (log BNP) level was compared between the normal group (n = 130), the light nutritional disturbance

Table I. Assessment of Undernutrition Degree by CONUT Score

| Parameter          | Normal | Light | Moderate | Severe |
|--------------------|--------|-------|----------|--------|
| Serum albumin (g/dL) | ≥ 3.5  | 3.0-3.49 | 2.5-2.9  | < 2.5  |
| Score              | 0      | 2     | 4        | 6      |
| Total lymphocytes (μL) | ≥ 1600 | 1200-1599 | 800-1199 | < 800  |
| Score              | 0      | 1     | 2        | 3      |
| Total cholesterol (mg/dL) | ≥ 180  | 140-180 | 100-139  | < 100  |
| Score              | 0      | 1     | 2        | 3      |
| Total CONUT Score  | 0-1    | 2-4   | 5-8      | 9-12   |

CONUT indicates controlling nutritional status
group (n = 222), and the moderate-severe nutritional disturbance group (n = 130), after combining the moderate and severe nutritional groups.

**Assessment of short-term prognosis by CONUT score:**
We segregated the study patients into 3 groups: HF patients with in-hospital death, HF patients who were discharged after alleviation of symptoms, and HF patients who were transferred elsewhere for continued medical care.

We examined whether the nutritional status of the patients, as assessed by the CONUT scores, was associated with in-hospital death. Cardiovascular death was defined as a death attributable to cardiovascular origin, and a non-cardiovascular death was defined as a death attributable to reasons of non-cardiovascular origin (e.g., respiratory, gastrointestinal, renal, cancer-related, or infectious).

With the exception of transferred HF patients, the median duration of hospital stay was 20 days (25th percentile, 14.5 days; 75th percentile, 30 days) for all other patients. The criterion of longer hospital stays was defined as more than or equal to 30 days (75th percentile duration of hospital stay). We compared the CONUT scores of HF patients with longer (≥ 30 days) and shorter hospital stays (< 30 days).

**Statistical analysis:** Continuous variables are expressed as the mean ± standard deviation if normally distributed and as the median (inter-quartile range) if non-normally distributed. Differences between 2 groups were compared using the unpaired Student’s t-test or Mann-Whitney U-test, as appropriate. The chi-square test was used to compare categorical variables. Continuous variables were compared between the 3 study groups using a one-factor ANOVA test. The Games-Howell test was used to identify variables that differed significantly between the study groups. The Kruskal-Wallis test was used for non-normally distributed data. Logistic regression analysis was performed to determine the significant predictors of in-hospital death in all HF patients except those transferred for continued medical care.

A P value < 0.05 was considered statistically signifi-

### Table II. Baseline Characteristics of the Patients without Information for CONUT Score Calculation

| Variable | Group of patients without CONUT scores (n = 356) | Group of patients with CONUT scores (n = 482) | P |
|----------|-----------------------------------------------|-----------------------------------------------|---|
| Age (years) | 73.4 ± 12.4 | 71.7 ± 13.6 | 0.07 |
| Male, n (%) | 215 (60.4%) | 298 (61.8%) | 0.72 |
| NYHA (III or IV), n (%) | 295 (86.0%) | 427 (89.5%) | 0.98 |
| Clinical scenarios (1/2/3/4/5) | 167/149/21/36/6 | 223/205/31/17/6 | 0.98 |
| BMI (kg/m²) at stable state | 22.6 ± 4.2 | 22.2 ± 3.9 | 0.18 |
| Systolic blood pressure (mmHg) | 148 ± 37 | 146 ± 38 | 0.59 |
| Heart rate (beats/minute) | 98 ± 31 | 99 ± 29 | 0.69 |
| Current or past smoker, n (%) | 187 (52.5%) | 248 (51.5%) | 0.78 |
| Number of HF-related readmissions (0/1/2/3) | 249/32/35/40 | 351/47/32/52 | 0.39 |
| HF etiology, ischemic, n (%) | 138 (38.8%) | 163 (33.8%) | 0.15 |
| Population of patients with reduced LVEF, n (%) | 149 (47.5%) | 225 (49.1%) | 0.66 |
| Hypertension, n (%) | 207 (58.1%) | 269 (55.8%) | 0.53 |
| Dyslipidemia, n (%) | 122 (34.3%) | 148 (30.7%) | 0.3 |
| Cerebrovascular disease, n (%) | 28 (7.9%) | 27 (5.6%) | 0.21 |
| Laboratory measurements | | | |
| Hemoglobin (g/dL) | 12.5 ± 2.4 | 12.3 ± 2.6 | 0.42 |
| Estimated GFR (mL-minute⁻¹·1.73m⁻²) | 47.2 (33.0-63.0) | 47.8 (31.5-66.9) | 0.73 |
| BNP (pg/mL) | 716.0 (408.4-1264.8) | 741.5 (387.0-1257.8) | 0.63 |
| log BNP | 2.81 ± 0.45 | 2.83 ± 0.44 | 0.62 |
| Albumin (g/dL) | 3.67 ± 0.51 | 3.58 ± 0.55 | 0.01 |
| C-reactive protein (mg/dL) | 0.50 (0.17-1.76) | 0.57 (0.20-1.94) | 0.71 |
| Visual LVEF (%) | 41.3 ± 14.1 | 40.5 ± 15.2 | 0.48 |
| Medication administered at admission | | | |
| Positively inotropic agents or phosphodiesterase inhibitors, n (%) | 108 (30.3%) | 190 (39.4%) | 0.01 |
| Carperitide, n (%) | 223 (62.6%) | 283 (58.7%) | 0.25 |
| Tolvaptan, n (%) | 42 (11.8%) | 60 (12.4%) | 0.83 |
| β-Blocker, n (%) | 121 (34.0%) | 156 (32.4%) | 0.66 |
| Statin, n (%) | 90 (25.3%) | 115 (23.9%) | 0.69 |

Results are expressed as mean ± standard deviation or as median (inter-quartile range). BMI indicates body mass index; BNP, brain natriuretic peptide; CONUT, controlling nutritional status; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; n, number of patients; and NYHA, New York Heart Association. Data were missing for the following characteristics: BMI for 19 patients in the with CONUT score group, and 15 in the with CONUT score group; Hemoglobin for 1 patient in the without CONUT score group; BNP for 59 patients in the without CONUT score group, and 62 in the with CONUT score group; Albumin for 25 patients in the without CONUT score group; C-reactive protein for 7 patients in the without CONUT score group, and 1 in the with CONUT score group; and LVEF for 42 patients in the without CONUT score group, and 24 in the with CONUT score group.
Figure. Comparisons of CONUT scores among the 3 groups. Box-and-whisker plots show the distributions of the CONUT scores for the in-hospital death group (dark gray box plot, n = 14), the discharged group (white box plot, n = 446), and the transferred group (light gray box plot, n = 22). The CONUT score is significantly higher in the in-hospital death group (3.19 ± 0.50, P < 0.05) compared to the discharged group (2.92 ± 0.45, P < 0.05). Furthermore, the CONUT score was significantly higher in the in-hospital death group [4 (3-8)] compared to the discharged group [3 (1-5); P < 0.05] (Figure).

Results

Baseline characteristics of study patients: Table II shows the baseline characteristics of the patients with the CONUT scores. The mean age was 71.7 ± 13.6 years, and male patients accounted for 61.8% (n = 298) of the study population. At the time of admission, based on the New York Heart Association functional classification, 50 patients were classified as class II, 174 patients as class III, and 253 patients were classified as class IV. The median plasma BNP level of the study population was 741.5 (387.0-1257.8) pg/mL, and as the distribution of the BNP level was highly skewed, we normalized the data through a logarithmic transformation (log BNP). The mean visual LVEF, as measured by echocardiography, was 40.5 ± 15.2%. The median CONUT score of the study population was 3 (1-5). Of the 482 enrolled HF patients for whom CONUT scores could be calculated, 352 (73%) had nutritional disturbances (light, 46.1%; moderate, 23.9%; severe, 3.1%). The log BNP level was significantly higher in the moderate-severe nutritional disturbance group (2.92 ± 0.42) than in the normal group (2.72 ± 0.45, P < 0.01).

In-hospital death occurred in 14 patients, of which 10 deaths (71.4%) were due to a cardiovascular origin (8 HF, 1 ventricular fibrillation due to myocardial ischemic attack, and 1 septic shock due to infective endocarditis), and 4 deaths (28.6%) were non-cardiovascular in origin (1 gastrointestinal bleeding, 1 sepsis due to gastrointestinal perforation, 1 pneumonia, and 1 bladder cancer).

Evaluation of short-term prognosis by CONUT assessment: The 482 patients in the study population were categorized as follows: patients who suffered in-hospital death (n = 14), patients who were discharged after alleviation of HF symptoms (n = 446), and patients who were transferred elsewhere for continued medical care (n = 22). The clinical characteristics of the enrolled patients are shown in Table III. BMI, systolic blood pressure, hypertension history, plasma BNP level, serum albumin level, C-reactive protein, CONUT score, and the use of positively inotropic agents or phosphodiesterase inhibitors differed significantly between the 3 groups.

Plasma BNP level was significantly higher in the in-hospital death group [2392.4 (697.8-3726.7) pg/mL] compared to the discharged group [732.5 (383.6-1206.4) pg/mL, P < 0.05]. The log BNP level was also significantly higher in the in-hospital death group (3.19 ± 0.50) compared to the discharged group (2.81 ± 0.43, P < 0.05). Furthermore, the CONUT score was significantly higher in the in-hospital death group [4 (3-8)] compared to the discharged group [3 (1-5); P < 0.05] (Figure).

However, age, sex, heart rate, smoking status, HF-related admission history, population of HF patients with ischemic etiology, population of patients with reduced LVEF, dyslipidemia, hemoglobin, percentages of lymphocytes, eGFR, total cholesterol, and visual LVEF and the use of carperitide, β-blockers, and statins did not differ significantly between the 3 groups.

Impact of nutritional screening using CONUT scores on in-hospital death events: With the exception of the transferred HF patients, logistic regression analysis was performed on data from all other patients to identify the significant predictors of in-hospital death. The CONUT score was associated with increased risk of in-hospital death in the unadjusted model (model 1) and in the age, sex, and log BNP adjusted model, respectively (model 2) (Table IV). In model 2, a higher CONUT score (P = 0.019) and higher log BNP (P = 0.009) were identified as significant predictors of in-hospital death.

Association between hospitalization duration and CONUT scores: With the exception of the transferred HF patients, the CONUT scores were higher in patients with longer hospital stays (≥ 30 days, n = 122) than in those with shorter hospital stays (< 30 days, n = 338) [4 (2-5) versus 2 (1-4), P < 0.001]. The median hospitalization duration in the in-hospital death group was 29.5 (17-55) days.

Discussion

In the present study, we examined whether patient nutritional status, assessed using CONUT scores, was associated with in-hospital death. Our results showed that a higher CONUT score was a significant predictor of in-hospital death in hospitalized HF patients. Evidence for this association was that a higher CONUT score was associated with increased risk of in-hospital death in the unadjusted model (model 1) and in the age, sex, and log BNP
CONUT SCORE TO PREDICT SHORT-TERM PROGNOSIS

Table III. Clinical Characteristics of the Enrolled Patients

| Variable                        | HF patients with in-hospital death (n = 14) | HF patients discharged from hospital after alleviation of symptoms (n = 446) | HF patients transferred for continued medical care (n = 22) | P   |
|--------------------------------|--------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------|-----|
| Age (years)                    | 74.0 ± 16.7                                | 71.7 ± 13.4                                                                 | 71.1 ± 15.7                                              | 0.8 |
| Male, n (%)                    | 6 (42.9%)                                  | 281 (63.0%)                                                                | 11 (50.0%)                                               | 0.16|
| NYHA (III/IV/Unknown)          | 1/4/0                                      | 46/164/232/4                                                               | 3/6/12/12                                               |     |
| NYHA (III or IV), n (%)        | 13 (92.9%)                                 | 396 (89.6%)                                                                | 18 (85.7%)                                              |     |
| Clinical scenarios (1/2/3/4/5)  | 2/830/1                                    | 216/187/23/16/4                                                            | 5/105/1/1                                               |     |
| BMI (kg/m²)                    | 21.5 ± 3.8                                 | 22.3 ± 3.9                                                                 | 19.7 ± 3.1                                              | 0.01|
| Systolic blood pressure (mmHg) | 119 ± 29*                                  | 148 ± 38                                                                  | 125 ± 32                                                | <0.01|
| Heart rate (beats/minute)      | 94 ± 28                                    | 99 ± 29                                                                   | 97 ± 26                                                  | 0.76|
| Medical history                |                                            |                                                                            |                                                         |     |
| Current or past smoker, n (%)  | 3 (21.4%)                                  | 235 (52.7%)                                                                | 10 (45.5%)                                              | 0.06|
| Number of HF-related readmissions (0/1/2/3) | 7/12/4/20                                 | 326/64/20/46                                                              | 18/0/1/3                                                 |     |
| Number of HF-related readmissions (0/1) | 7/7                                        | 326/120                                                                    | 18/4                                                     | 0.1 |
| HF etiology, ischemic, n (%)   | 2 (14.3%)                                  | 155 (34.8%)                                                                | 6 (27.3%)                                               | 0.23|
| Population of patients with reduced LVEF, n (%) | 8 (61.5%)                                  | 207 (48.7%)                                                                | 10 (50%)                                                | 0.66|
| Hypertension, n (%)            | 2 (14.3%)                                  | 257 (57.6%)                                                                | 10 (45%)                                                | <0.01|
| Dyslipidemia, n (%)            | 1 (7.1%)                                   | 143 (32.1%)                                                                | 4 (18.2%)                                               | 0.06|
| Cerebrovascular disease, n (%) | 0 (0%)                                     | 25 (5.6%)                                                                  | 2 (9.1%)                                                |     |
| Laboratory measurements        |                                            |                                                                            |                                                         |     |
| Hemoglobin (g/dL)              | 11.6 ± 2.7                                 | 12.3 ± 2.6                                                                 | 12.8 ± 2.5                                              | 0.37|
| Percentages of lymphocytes (%) | 17.65 (7.5-29.0)                           | 20.2 (12.9-29.4)                                                           | 12.85 (8.4-27.7)                                         | 0.13|
| Estimated GFR (ml·minute⁻¹·1.73m²) | 35.2 (21.5-67.8)                          | 47.8 (32.3-66.0)                                                           | 60.4 (34.7-78.1)                                         | 0.18|
| BNP (pg/mL)                    | 2392.4 (697.8-3726.7)‡                     | 732.5 (383.6-1206.4)                                                       | 752.8 (437.8-2126.0)                                     | 0.01|
| log BNP                        | 3.19 ± 0.50†                               | 2.81 ± 0.43                                                                | 2.92 ± 0.52                                             | <0.01|
| Albumin (g/dL)                 | 3.24 ± 0.70                                | 3.60 ± 0.55                                                                | 3.44 ± 0.50                                             | 0.03|
| Total cholesterol (mg/dL)      | 157.8 ± 38.2                               | 165.1 ± 40.9                                                               | 155.9 ± 25.1                                            | 0.47|
| C-reactive protein (mg/dL)     | 1.58 (0.72-3.35)†                          | 0.51 (0.19-1.71)                                                           | 1.35 (0.35-5.15)                                         | <0.01|
| CONUT score as a continuous variable | 4 [3-8]‡                                   | 3 [1-5]                                                                    | 4 [3-6]                                                 | <0.01|
| CONUT score as a categorical variable |                                            |                                                                             |                                                         |     |
| CONUT score 0-1, n (%)         | 1 (7.1%)                                   | 125 (28.0%)                                                                | 4 (18.2%)                                               |     |
| CONUT score 2, n (%)           | 1 (7.1%)                                   | 79 (17.7%)                                                                 | 1 (4.5%)                                                |     |
| CONUT score 3-12, n (%)        | 12 (85.7%)                                 | 242 (54.3%)                                                                | 17 (77.3%)                                              |     |
| Visual LVEF (%)                | 32.5 (17.5-62.5)                           | 42.5 (27.5-52.5)                                                           | 37.5 (22.5-50.0)                                         | 0.73|
| Medication administered at admission |                                            |                                                                            |                                                         |     |
| Positively inotropic agents or phosphodiesterase inhibitors, n (%) | 10 (71.4%)                                 | 167 (37.4%)                                                                | 13 (59.1%)                                              | <0.01|
| Carperitide, n (%)             | 6 (42.9%)                                  | 266 (59.6%)                                                                | 11 (50%)                                                | 0.32|
| Tolvaptan, n (%)               | 5 (35.7%)                                  | 53 (11.9%)                                                                 | 2 (9.1%)                                                |     |
| β-Blocker, n (%)               | 6 (42.9%)                                  | 143 (32.1%)                                                                | 7 (31.8%)                                               | 0.7 |
| Statin, n (%)                  | 4 (28.6%)                                  | 107 (24.0%)                                                                | 4 (18.2%)                                               | 0.75|

Results are expressed as mean ± standard deviation or as median (inter-quartile range). *P < 0.01; †P < 0.05 versus patients discharged following symptom alleviation. ‡P < 0.01 versus patients transferred for continued medical care. Data are missing for the following characteristics: BMI for 1 patient in the in-hospital death group, 12 patients in the discharged group, and 2 in the transferred group; BNP for 1 patient in the in-hospital death group, 60 patients in the discharged group, and 1 patient in the transferred group; C-reactive protein for 1 patient in the discharged group; LVEF for 1 patient in the in-hospital death group, 21 patients in the discharged group, and 2 patients in the transferred group. Abbreviations as in Table II.

Table IV. Impact of Nutritional Screening Using CONUT Scores on In-Hospital Death Events

| No. of events/ at risk (%) | Model 1: unadjusted OR (95% CI) | P     | Model 2: age adjusted OR (95% CI) | P     | Model 2: sex adjusted OR (95% CI) | P     | Model 2: log BNP adjusted OR (95% CI) | P     |
|---------------------------|---------------------------------|-------|----------------------------------|-------|----------------------------------|-------|--------------------------------------|-------|
| CONUT score as continuous variable | 14/460 (3.0)                   | 1.37 (1.12-1.66) | 0.002 | 1.36 (1.12-1.66) | 0.002 | 1.37 (1.13-1.67) | 0.002 | 1.32 (1.05-1.66) | 0.019 |

OR indicates odds ratio; CI, and confidence interval. Other abbreviations as in Table II. BNP data are missing for 61 patients.

Suzuki, et al. observed that HF patients with higher CONUT scores tended to have longer hospital stays. Nochioka, et al. reported that poor nutritional status was associated with increased incidence of death in HF patients classified as stage B in the AHA/ACC guidelines. Furthermore, Narumi, et al. reported that the CONUT score was independently associated with the occurrence of
cardiovascular events in chronic HF patients. These studies support our observation that a higher CONUT score was a significant predictor of in-hospital death in hospitalized HF patients.

In addition, we noted that undernutrition occurred frequently in hospitalized HF patients, and that 73% of HF patients in our study population had nutritional disturbances. Suzuki, et al. identified nutritional disturbances in 95% of their HF-affected study population. Narumi, et al. noted a malnutrition prevalence of 60-69% in chronic HF patients. Additionally, according to a recent review by Lin, et al., the prevalence of malnutrition is higher in advanced HF, and in acute decompensated HF (75-90%). The undernutrition prevalence in our study population is comparable to those reported in the above-mentioned studies. Therefore, supportive therapies should be promptly administered on the assumption that hospitalized HF patients often have undernutrition. Furthermore, as HF and undernutrition can each influence the other, once patients develop severe HF, their nutritional status deteriorates further. HF patients with undernutrition thus enter a vicious cycle of inflammation, catabolic drive, undernutrition, and HF exacerbation. Strategies to improve nutritional status in the early stages of HF are thus a crucial component of HF management and are important in preventing HF exacerbation and improving patient prognosis. Nutritional screening should thus be performed at the earliest possible time to identify malnourished and non-malnourished patients.

In a recently published review by Lin, et al., the use of various nutritional assessment and screening tools was compared in studies conducted on HF patients. The study compared the usage frequency of 2 nutritional assessment tools [Mini Nutritional Assessment (MNA), and SCORE], 7 nutritional screening tools [MNA-short-form (SF), Nutritional Risk Screening, Nutritional Risk Index (NRI), Geriatric Nutritional Risk Index (GNRI), Prognostic Nutritional Index, CONUT, and the Nutritional Screening Initiative], and 2 other tools. The review noted that the most commonly used tool was the MNA (used in 5 studies), followed by GNRI (4 studies), NRI (3 studies), and the MNA-SF (2 studies). The meta-analysis based review also noted that compared with the scores obtained from other nutritional assessment and screening tools, MNA scores were the strongest predictors of mortality in HF patients. However, as only 1 study on the CONUT score was included in the review by Lin, et al., its value as a predictor of HF-related mortality may have been underestimated.

As the MNA includes subjective data evaluated by medical staff, this index cannot be used conveniently in a routine clinical setting. Moreover, in HF patients who experience progressive loss of body weight due to incremental doses of diuretics, or in HF patients who experience weight gain due to fluid retention, the changes in body weight cannot be used reliably for nutritional assessment.

Hypoalbuminemia results in pulmonary congestion and pleural effusion and is an aggravating factor for HF. A patient’s albumin level can thus serve as a useful prognostic indicator. Bonilla-Palomas, et al. have demonstrated an association between hypoalbuminemia (albumin ≤ 3.4 g/dL) and poor outcomes in patients with acute HF. However, hypoalbuminemia in HF patients often does not resolve despite sufficient energy and protein supplementation. In such patients, the albumin levels may not correctly assess the appropriateness of the ongoing nutritional therapy. The levels of total cholesterol, hemoglobin, and lymphocyte counts are used to assess nutritional status. However, these indices alone cannot provide a comprehensive and accurate indication of a patient’s nutritional status.

The CONUT score is a unique index that focuses on protein metabolism, lipid metabolism, and immune parameters. As the CONUT score utilizes albumin levels, the score may represent not only the nutritional status but also the severity of HF. Our study shows that a higher CONUT score and a higher BNP level are significant predictors of in-hospital death. Therefore, we recommend an initial nutritional screening of HF patients using a simple CONUT screening. A more detailed examination using for example computerized tomography (CT) images, bioelectrical impedance analysis (BIA), or dual-energy X-ray absorption (DXA) may be performed for patients in whom the CONUT scores indicate undernutrition.

Despite an abundance of evidence on the relation between undernutrition and immunologic dysfunction, the exact mechanism of interaction remains unclear. In general, severe undernutrition causes atrophy of all lymphoid tissues, including the thymus, tonsils, and lymph nodes. Cell-mediated immunity is diminished more than antibody production. Normal humoral immunity requires adequate function of B-lymphocytes under proper regulation of T-helper lymphocytes. Law, et al. have reported that both the T and B systems were impaired in adults with moderate protein calorie malnutrition, and it was restored by nutritional repletion.

**Study limitations:** The total number of patients enrolled in the ICAS-HF registry and the number of in-hospital death events were not large. Therefore, the number of indices that could be incorporated into the logistic analysis models was small. Additionally, as the CONUT score is a relatively new index of nutritional status measurement, further validation and the establishment of reference scores are required. Ignacio de Ulíbarri, et al. demonstrated an agreement between the CONUT score and 2 other classical nutritional assessment methods, the Subjective Global Assessment and the Full Nutritional Assessment. In our study, however, we did not examine the extent of agreement between the CONUT scores and other screening tools such as CT, BIA, and DXA. Moreover, we did not exclude comorbid diseases such as nephrotic syndrome, statin use, the presence of infectious diseases, and blood disorders, which can affect the levels of albumin and cholesterol, and also the lymphocyte count.

**Conclusions**

Our results demonstrate the usefulness of the CONUT score as a predictor of short-term prognosis in hospitalized HF patients. Nutritional screening should thus be performed at the earliest possible time to identify mal-
nourished and non-malnourished HF patients.

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Disclosures

Conflicts of interest: The authors declare that they have no conflicts of interest or financial relationships relevant to this study.

Appendix

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