Original Article

Prognostic Value of Both Plasma Volume Status and Nutritional Status in Patients With Severely Decompensated Acute Heart Failure

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ABSTRACT

Background: Plasma volume status (PVS) has been evaluated recently as a prognostic marker of acute heart failure (AHF). However, whether evaluating PVS alone is sufficient remains unclear.

Methods: Of 675 patients with AHF screened, 601 were enrolled. The PVS, prognostic nutritional index (PNI) (lower = worse), and Controlling Nutritional Status (CONUT) score (higher = worse) were evaluated. Patients were divided into 2 groups according to PVS value (low- or high-PVS group) and were further subdivided into 4 groups (low- or high-PVS/CONUT group and low- or high-PVS/PNI group).

Results: A Kaplan-Meier curve showed a significantly lower survival rate in the high-PVS group than in the low-PVS group, the high-PVS/CONUT group than in the high-PVS/low-CONUT group, and the high-PVS/low-PNI group than in the high-PVS/high-PNI group. A Kaplan-Meier curve showed a significant survival difference between high-PVS/low-PNI and low-PVS/high-PNI groups. The high-PVS group had a significantly higher mortality rate than the low-PVS group. The high-PVS/low-CONUT group had a significantly higher mortality rate than the high-PVS/high-CONUT group.

The features of acute heart failure (AHF) may differ. Sudden-onset pulmonary edema with high systolic blood pressure is categorized as “vascular” failure or “hypertensive” heart failure (HF), whereas HF with the gradual development of symptoms over days is characterized as “cardiac” failure or “normotensive—hypotensive” HF. Therefore, volume status varies among individuals.

The importance of evaluating nutritional status also has been suggested in patients with HF. Because malnutrition is a major problem in an aging society, HF guidelines recommend the evaluation of nutritional status. Previous research evaluating nutrition status in patients with AHF using various tools (ie, albumin, total cholesterol, controlling nutritional status [CONUT] score, and prognostic nutritional index [PNI]) has indicated that malnutrition is an independent predictor of mortality, HF progression, HF events, and adverse outcomes. The association between the nutritional status and the degree of general congestion/PV has not been adequately explored.

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multivariate Cox regression model showed that high PVS (hazard ratio [HR], 1.642; 95% confidence interval [CI], 1.049-2.570) and high PVS/high CONUT (HR, 2.076; 95% CI, 1.147-3.757) and high PVS/low PNI (HR, 2.094; 95% CI, 1.166-3.761) were independent predictors of 365-day mortality.

Conclusions: An adverse outcome was predicted by the evaluation of PVS; furthermore, a malnutrition status with a high PVS leads to an adverse outcome. The simultaneous evaluation of nutrition status and PVS is essential to predict an AHF outcome.

Volume overload/expansion due to malnutrition was hypothesized to have a prognostic impact in patients with AHF. However, patients with volume overload may not have a poor prognosis if their nutrition status is good. Therefore, the prognostic efficacy of PVS alone and PVS with the PNI and the CONUT score was examined in patients with AHF.

Methods

Patients

A total of 675 patients with AHF admitted to the intensive care unit (ICU) of Nippon Medical School Chiba Hokusoh Hospital (Chiba, Japan) between May 2011 and March 2018 were screened. Of these, 12 patients who lacked serum albumin, lymphocyte count, or total cholesterol data were excluded from this study. An additional 41 patients for whom these examinations were not performed within 30 minutes of hospitalization were excluded. Finally, 21 patients missing body weight data in their hospital records were also excluded. Ultimately, 601 patients with AHF were enrolled in this study (Fig. 1).

AHF is defined as a gradual or rapid change in HF signs and symptoms requiring urgent therapy. HF was diagnosed on the basis of clinical history (ie, symptoms, functional limitation, prior cardiac disease, risk factors, exacerbating factors, comorbidities, and drugs), physical examination (ie, of vital signs, weight and volume status of the heart, lungs, abdomen, and peripheral vascular regions), and initial investigations (ie, chest radiography, 12-lead electrocardiography, laboratory measurements of troponins, blood urea nitrogen, creatinine, sodium, potassium, glucose, liver function, and complete blood count). Furthermore, evaluations of plasma natriuretic peptide and echocardiography were performed to support the diagnosis of HF. The treating physician in the emergency department diagnosed AHF according to the aforementioned procedure within 30 minutes of admission. All patients had a New York Heart Association (NYHA) functional class of III or IV.

Furthermore, all included patients received treatment with diuretics or vasodilators for AHF. The patients who needed 1 of the following 3 treatments required intensive care: (1) high-flow oxygen therapy (including mechanical support) to treat orthopnea; (2) inotropes or mechanical support due to low blood pressure; or (3) various types of diuretics to improve general or lung edema. Patients with HF caused by ST-T segment elevation acute coronary syndrome were excluded from the study. The physician selected the treatment strategy.

Blood sample measurements and data collection

Blood samples from the included patients were collected within 30 minutes of admission. The samples were centrifuged within 5 minutes of collection at 4°C, immediately frozen, and stored at −80°C until analysis. The data were retrospectively retrieved from the hospital medical records.

Patient characteristics, including age, sex, presence of de novo or recurrent HF, etiology of HF, risk factors for atherosclerosis (diabetes mellitus, hypertension, and dyslipidemia), vital signs (systolic blood pressure and heart rate), left ventricular ejection fraction (LVEF) on echocardiograms, arterial blood gas data, laboratory data (eg, blood urea nitrogen, total bilirubin, hemoglobin, brain natriuretic peptide, C-reactive protein [CRP]), medications administered during admission to the ICU, and duration of admission (duration of ICU stay and hospital stay) were compared.

The LVEF was calculated using the Teichholz method or Simpson’s method at admission (Sonos 5500; Hewlett Packard, Palo Alto, CA; or Vivid I; GE Yokogawa Medical, Tokyo, Japan). Because the LVEF was measured during the acute phase, it was not adequately evaluated because of severe orthopnea. The methodology for the LVEF measurement (Teichholz method or Simpson’s method) was decided on a case-by-case basis.

Procedures and prognosis

PVS was calculated using the following formula: (actual PV – ideal PV)/ideal PV × 100()]. The actual and ideal PV were defined as follows: actual PV = (1 – hematocrit) × (a + [b × body weight]) (a = 1530 in male and 864 in female patients; b = 41.0 in male and 47.9 in female patients), ideal PV = c × body weight (c = 39 in male and 40 in female patients). The PNI was calculated using the following formula: 10 × serum albumin (g/dL) + 0.005 × lymphocyte (×10^3/L) [lower = worse]. The CONUT score was calculated using a scoring system consisting of serum albumin, lymphocytes, and total cholesterol (range, 0-12; higher = worse).
Patients were divided into 4 groups (severe, moderate, mild, and normal) based on their serum albumin, lymphocyte, and total cholesterol levels: serum albumin ≥ 3.5 g/dL (normal), 3 to 3.49 (mild), 2.5 to 2.99 (moderate), and < 2.5 (severe); lymphocytes ≥ 1600/µL (normal), 1200 to 1599 (mild), 800 to 1199 (moderate), and < 800 (severe); and total cholesterol ≥ 180 mg/dL (normal), 140 to 179 (mild), 100 to 139 (moderate), and < 100 (severe). The median PNI and CONUT scores established the cutoff values for the low and high groups: 42.33 for the PNI (low PNI: PNI < 42.30; high PNI: PNI ≥ 42.30) and 3 for the CONUT score (low: CONUT score ≤ 3; high: CONUT score ≥ 4.0).

Patients were divided into 2 groups according to the PVS value (low PVS: PVS ≤ 12.0%, n = 300; high PVS: PVS > 12.0%, n = 301). The median PVS established the cutoff value for the low and high groups. Subsequently, patients were further subdivided into 4 groups according to nutritional status and PVS. By using the CONUT score, patients were divided as follows: low-PVS/low-CONUT group (n = 189), low-PVS/high-CONUT group (n = 111), high-PVS/low CONUT group (n = 141), and high-PVS/high-CONUT group (n = 160). By using the PNI, patients were divided as follows: low-PVS/high-PNI group (n = 180), low-PVS/low-PNI group (n = 120), high-PVS/high-PNI group (n = 121), and high-PVS/low-PNI group (n = 180).

Long-term prognosis, including all-cause death within 365 days, was evaluated. Patients had clinical follow-ups at routine outpatient visits. The prognoses of patients being followed up at other institutes were determined through telephone interviews. The prognosis of 365-day mortality and HF events was evaluated using the Cox proportional hazards regression model and Kaplan–Meier curve analysis.

**Statistical analyses**

All data were analyzed using the SPSS 22.0 software program (SPSS Japan Institute, Tokyo, Japan). All numerical data were expressed as the median and range or interquartile range, according to normality. We used the Shapiro–Wilk test to assess normality. The Mann–Whitney U test was used for comparisons between the 2 groups. The chi-square test was used to compare proportions. P values < 0.05 indicated statistical significance.

The prognostic value of PVS (high vs low PVS) and nutrition status and PVS (by low or high PVS/PNI or low or high PVS/CONUT) vs a reference group of normal patients (low PVS/low CONUT and low PVS/high PNI) was assessed using a multivariate Cox proportional hazards regression model. A multivariate Cox regression analysis was performed to determine the hazard ratio (HR) for 365-day mortality. The cumulative survival rates in the 4 groups were analyzed using Kaplan–Meier curves, and a log-rank test was used to calculate the statistical significance of the differences.

**Ethical review**

The Research Ethics Committee of Nippon Medical School Chiba Hokusoh Hospital approved the study protocol. Because of the retrospective design of the study, written informed consent was waived, in accordance with the guidance provided by the Ethics Committee.
Results

Patient characteristics and differences between PVS groups

The study population had a median age of 76 years; 65.4% were male with a median age of 76 years. During the initial evaluation, it was determined that 219 patients (36.4%) had been previously hospitalized for HF. Within the total cohort, 240 patients (39.9%) had ischemic heart disease, and 361 patients (60.1%) had nonischemic heart disease, including cardiomyopathy (hypertrophic cardiomyopathy [n = 16], dilated cardiomyopathy [n = 50],

Table 1. Characteristics of patients by the difference in PVS

| Status and vital signs | PVS | P value |
|------------------------|-----|---------|
| **Low** (n = 300) | **High** (n = 301) |
| Status and vital signs | | |
| Age (y) | 76 (67-82) | 71 (62-78) | 80 (72-85) | < 0.001 |
| Gender (male, %) | 393 (65.4%) | 242 (80.7%) | 151 (50.2%) | < 0.001 |
| Type (readmission, %) | 219 (36.4%) | 92 (30.7%) | 127 (42.2%) | 0.004 |
| LVEF (%) | 39 (27-51) | 34 (25-50) | 42 (30-55) | < 0.001 |
| LVEF ≤ 40% (yes, %) | 332 (55.2%) | 190 (63.3%) | 142 (47.2%) | < 0.001 |
| NYHA (IV, %) | 468 (77.9%) | 239 (79.7%) | 229 (76.1%) | 0.326 |
| Systolic blood pressure (mm Hg) | 158 (122-183) | 162 (122-189) | 152 (123-180) | 0.048 |
| Pulse (beats/min) | 107 (88-125) | 110 (94-120) | 102 (84-119) | < 0.001 |

Etiology

| Ischemia (yes, %) | 240 (39.9%) | 124 (41.3%) | 116 (38.5%) | 0.506 |
| Hypertension (yes, %) | 452 (75.2%) | 216 (72.0%) | 236 (78.4%) | 0.073 |
| Diabetes mellitus (yes, %) | 292 (48.6%) | 139 (46.3%) | 153 (50.8%) | 0.289 |
| Dyslipidemia (yes, %) | 308 (51.2%) | 156 (52.0%) | 152 (50.5%) | 0.744 |

Arterial blood gas

| pH | 7.36 (7.24-7.43) | 7.36 (7.22-7.43) | 7.36 (7.26-7.43) | 0.176 |
| PCO2 (mm Hg) | 38.8 (32.7-52.6) | 40.1 (33.7-54.3) | 37.8 (32.3-49.8) | 0.060 |
| PO2 (mm Hg) | 98.7 (71.2-145.0) | 92.4 (71.1-136.0) | 105.8 (71.5-155.0) | 0.076 |
| HCO3- (mmol/L) | 21.8 (19.2-24.3) | 22.1 (19.5-24.5) | 21.3 (18.4-24.1) | 0.065 |
| SaO2 (%) | 97 (93-99) | 96 (93-98) | 97 (93-99) | 0.046 |
| Lactate (mmol/L) | 1.8 (1.2-3.5) | 1.8 (1.2-3.7) | 1.8 (1.1-3.2) | 0.081 |

Laboratory data

| Total bilirubin (µmol/L) | 10.3 (6.8-17.1) | 12.0 (8.6-18.8) | 8.6 (6.8-13.7) | < 0.001 |
| Uric acid (µmol/L) | 410 (321-482) | 416 (333-494) | 399 (309-476) | 0.029 |
| Sodium (mmol/L) | 140 (137-142) | 140 (137-142) | 140 (137-142) | 0.705 |
| Potassium (mmol/L) | 4.3 (3.9-4.8) | 4.3 (4.0-4.8) | 4.3 (3.8-4.7) | 0.296 |
| Hemoglobin (g/L) | 122 (103-137) | 137 (126-149) | 105 (92-118) | < 0.001 |
| Albumin (g/L) | 35 (32-38) | 36 (33-39) | 34 (31-37) | < 0.001 |
| Lymphocyte count (/µL) | 1400 (721-2358) | 1570 (879-2694) | 1159 (621-1952) | < 0.001 |
| Total cholesterol (mmol/L) | 4.24 (3.57-5.04) | 4.34 (3.65-5.26) | 4.16 (3.47-4.89) | 0.007 |

Nutritional status

| PNI | 42.3 (37.2-48.8) | 44.8 (39.1-50.9) | 40.3 (35.2-46.2) | < 0.001 |
| CONUT score | 3 (1-5) | 3 (1-4) | 4 (2-6) | < 0.001 |
| Albumin (g/L) | 35 (32-38) | 36 (33-39) | 34 (31-37) | < 0.001 |
| Total hospitalization (d) | 24 (16-41) | 23 (15-38) | 27 (16-45) | 0.122 |

Medication (cases) during ICU

| Furosemide (yes, %) | 541 (90.0%) | 269 (89.7%) | 272 (90.4%) | 0.787 |
| Nitroglycerin (yes, %) | 250 (41.6%) | 122 (40.7%) | 128 (42.5%) | 0.679 |
| Nicorandil (yes, %) | 95 (15.8%) | 43 (14.3%) | 52 (17.3%) | 0.371 |
| Carperitide (yes, %) | 221 (36.8%) | 112 (37.3%) | 109 (36.2%) | 0.800 |
| Dopamine (yes, %) | 38 (6.3%) | 19 (6.3%) | 19 (6.3%) | 1.000 |
| Dobutamine (yes, %) | 132 (22.0%) | 68 (22.7%) | 64 (21.3%) | 0.694 |
| ACE-I/ARB (yes, %) | 182 (30.3%) | 108 (36.0%) | 74 (24.6%) | 0.030 |
| β-Blocker (yes, %) | 171 (28.5%) | 101 (33.7%) | 70 (23.3%) | 0.003 |
| Spironolactone (yes, %) | 215 (35.8%) | 131 (43.7%) | 84 (27.9%) | < 0.001 |
| Statin (yes, %) | 182 (30.3%) | 96 (32.0%) | 86 (28.6%) | 0.376 |

Outcome

| ICU hospitalization (d) | 4 (3-6) | 4 (3-6) | 4 (3-6) | 0.217 |
| Total hospitalization (d) | 24 (16-41) | 23 (15-38) | 27 (16-45) | 0.122 |
| In-hospital mortality (yes, %) | 71 (11.8%) | 28 (9.3%) | 43 (14.3%) | 0.076 |

P values between the low-PVS and high-PVS groups were determined using the Mann–Whitney U test or chi-square test. All numerical data are expressed as the median (25%-75% interquartile range).

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PNI, prognostic nutritional index; PVS, plasma volume status.
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Figure 2. Kaplan–Meier survival curves for PVS. Kaplan–Meier survival curves showed that the prognosis, including all-cause death, was significantly poorer in the high-PVS group than in the low-PVS group. PVS, plasma volume status.

Discussion

The present study revealed that a high PVS was clearly associated with an adverse outcome. Furthermore, a high PVS combined with malnutrition led to an adverse outcome. Therefore, a high PVS and malnutrition were essential factors in the AHF cohort. The prognostic impact of each factor has been demonstrated in previous studies.9,12,16 Therefore, the novelty of the present study vs previous investigations lies in the simultaneous evaluation of these factors. These findings underscore the importance of a prompt evaluation to determine both the general congestion and the nutritional status of patients with AHF, as well as the need for early intervention in these patients.

Tools for evaluating PV and AHF

In 2015, the importance of a noninvasive and simple estimation of PV in patients with HF was recognized, and formulae for predicting future cardiovascular events and mortality have been proposed.11,12 Duarte et al.21 used the Strauss formula (ie, changes in the concentrations of hemoglobin and hematocrit) to estimate the PV. They concluded that a higher instantaneous estimated PVS was significantly associated with a poorer outcome in patients with left ventricular systolic dysfunction after acute myocardial infarction.21 Kobayashi et al. also determined the diagnostic impact of PVS during the discharge of patients with AHF using the Strauss formula.27 Yoshihisa et al. showed that high PVS estimated using the Hakim formula (ie, using hematocrit and weight, with the same formula as that used in the present study) at admission was associated with a poor outcome in patients with AHF. Furthermore, estimating PVS in dyspneic patients in the emergency department using the Strauss formula has been shown to have diagnostic value for AHF.27 Thus, immediate evaluation of the PV in patients with AHF is required to predict prognosis. The optimal methodology for evaluating the PV remains debatable; in the present study, the formula incorporating weight was used. Weight is an essential factor when evaluating the general volume status. The results of the present study are consistent with those reported in previous studies.

The strategy for estimating the PV has differed among studies. Although the measurement of congestion using pulmonary artery catheterization,22 echocardiography,25 and volume biomarkers25 is traditionally reported, an immediate,
Table 2. Multivariate analyses of the associations with 365-day all-cause death

| All-cause death                                      | Univariate | Multivariate |
|-----------------------------------------------------|------------|--------------|
|                                                     |            | Model 1      | Model 2      | Model 3      |
|                                                     | HR  95% CI | P value      | HR  95% CI   | P value      | HR  95% CI   | P value      |
| PVS                                                 |            |              |              |              |              |              |
| Low                                                 | 1.000      |              | 1.000        |              |              |              |
| High                                                | 1.857 1.293-2.667 0.001 |              | 1.642 1.049-2.570 0.030 |              |              |              |
| PVS and CONUT score                                 |            |              |              |              |              |              |
| Low-PVS/low-CONUT                                   | 1.000      |              |              | 1.000        |              |              |
| High-PVS/low-CONUT                                  | 2.058 1.144-3.702 0.016 |              | 1.785 0.929-3.340 0.082 |              |              |              |
| Low-PVS/high-CONUT                                  | 2.784 1.554-4.986 0.001 |              | 1.422 0.767-2.637 0.264 |              |              |              |
| High-PVS/high-CONUT                                  | 3.982 2.349-6.750 < 0.001 |              | 2.076 1.147-3.757 0.016 |              |              |              |
| PVS and PNI                                          |            |              |              |              |              |              |
| Low-PVS/high-PNI                                     | 1.000      |              |              | 1.000        |              |              |
| High-PVS/high-PNI                                    | 2.076 1.120-3.846 0.020 |              | 1.705 0.873-3.332 0.118 |              |              |              |
| Low-PVS/low-PNI                                      | 2.742 1.522-4.938 0.001 |              | 1.438 0.774-2.674 0.251 |              |              |              |
| High-PVS/low-PNI                                     | 3.814 2.238-6.498 < 0.001 |              | 2.094 1.166-3.761 0.013 |              |              |              |
| Adjusting factors                                    |            |              |              |              |              |              |
| Status                                               |            |              |              |              |              |              |
| Age (per 10-y old)                                   | 1.269 1.072-1.501 0.006 |              | 1.454 1.182-1.790 < 0.001 |              | 1.443 1.173-1.776 0.001 |              | 1.450 1.177-1.787 < 0.001 |              |
| Gender (male)                                        | 0.983 0.680-1.422 0.929 |              | 1.209 0.806-1.814 0.359 |              | 1.185 0.787-1.783 0.417 |              | 1.159 0.768-1.748 0.483 |              |
| Etiology (ischemia, yes)                             | 0.816 0.567-1.713 0.272 |              | 0.691 0.462-1.032 0.071 |              | 0.701 0.47-1.047 0.083 |              | 0.706 0.471-1.058 0.092 |              |
| Type (readmission, yes)                              | 1.511 0.804-1.646 0.442 |              | 0.717 0.481-1.069 0.102 |              | 0.719 0.482-1.071 0.105 |              | 0.757 0.504-1.137 0.179 |              |
| NYHA (IV, yes)                                       | 1.984 1.174-3.353 0.011 |              | 2.201 1.276-3.797 0.005 |              | 2.219 1.287-3.827 0.004 |              | 2.187 1.269-3.769 0.005 |              |
| Medical history (diabetes mellitus, yes)             | 1.260 0.886-1.792 0.198 |              | 1.465 1.008-2.128 0.045 |              | 1.542 0.999-2.111 0.051 |              | 1.447 0.999-2.104 0.053 |              |
| LVEF (per 10% increase)                              | 0.953 0.860-1.056 0.360 |              | 0.974 0.874-1.085 0.631 |              | 0.970 0.870-1.081 0.58 |              | 0.974 0.874-1.085 0.627 |              |
| Vital signs                                          |            |              |              |              |              |              |
| SBP (per 10 mm Hg increase)                          | 0.848 0.815-0.882 < 0.001 |              | 0.855 0.815-0.897 < 0.001 |              | 0.859 0.817-0.902 < 0.001 |              | 0.858 0.817-0.902 < 0.001 |              |
| Heart rate (per 10 beats/min increase)               | 1.004 0.961-1.048 0.863 |              | 1.021 0.998-1.044 0.069 |              | 1.020 0.999-1.042 0.068 |              | 1.020 0.999-1.042 0.062 |              |
| Laboratory data                                      |            |              |              |              |              |              |
| Total bilirubin (per 1 mg/dL increase)               | 1.008 1.000-1.016 0.039 |              | 1.001 0.991-1.010 0.914 |              | 1.000 0.990-1.009 0.951 |              | 1.000 0.990-1.009 0.926 |              |
| Creatinine (per 0.1 mg/dL increase)                  | 1.011 1.004-1.019 0.002 |              | 1.010 1.001-1.019 0.032 |              | 1.010 1.001-1.019 0.035 |              | 1.010 1.001-1.019 0.038 |              |
| Sodium (per 1.0 mmol/L increase)                     | 0.946 0.919-0.975 < 0.001 |              | 0.993 0.960-1.026 0.661 |              | 0.996 0.963-1.029 0.792 |              | 0.994 0.961-1.027 0.705 |              |
| Potassium (per 1.0 mmol/L increase)                  | 1.537 1.265-1.866 0.001 |              | 1.379 1.097-1.734 0.006 |              | 1.365 1.087-1.715 0.007 |              | 1.363 1.087-1.787 0.007 |              |
| Medication                                           |            |              |              |              |              |              |
| Dobutamine (yes)                                     | 3.027 2.122-3.317 <0.001 |              | 1.710 1.119-2.614 0.013 |              | 1.657 1.079-2.543 0.021 |              | 1.657 1.080-2.543 0.021 |              |
| ACE-I/ARB (yes)                                      | 0.302 0.179-0.510 <0.001 |              | 0.594 0.343-1.028 0.063 |              | 0.600 0.346-1.041 0.069 |              | 0.598 0.345-1.037 0.067 |              |
| β-Blocker (yes)                                      | 0.813 0.544-1.215 0.312 |              | 0.941 0.620-1.429 0.775 |              | 0.944 0.622-1.431 0.785 |              | 0.942 0.621-1.428 0.777 |              |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; HR, hazard ratio; LVEF, left ventricular ejection fraction; PNI, prognostic nutritional index; PVS, plasma volume status; SBP, systolic blood pressure.
simple, and noninvasive methodology may be required for an early intervention of volume expansion. The Strauss formula, which uses the levels of hemoglobin and hematocrit, may be affected by the anemia status. Anemia at admission or within 3 days after admission is an independent risk factor for future adverse events in patients with AHF.\textsuperscript{25,26} Therefore, the Hakim formula was selected to estimate the PV.

### Malnutrition and PVS in AHF

Malnutrition is a common complication in patients with chronic HF. Previous reports have attributed malnutrition to a low nutritional intake or malabsorption due to intestinal edema, anorexia, liver dysfunction, or cytokine-induced hypercatabolism.\textsuperscript{28} Patients develop enteral protein loss, and

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**Table 3. Characteristics of patients by the difference in PVS and CONUT**

|                      | Low PVS | High PVS |
|----------------------|---------|----------|
|                      | Low CONUT | High CONUT | P value |
| Status and vital signs | (n = 189) | (n = 111) |         |
| Age (y) | 70 (61-78) | 72 (64-79) | 0.204 |
| Gender (male, %) | 148 (78.3%) | 94 (84.7%) | 0.220 |
| Type (readmission, %) | 59 (31.2%) | 33 (29.7%) | 0.897 |
| LVEF (%) | 33 (25-47) | 35 (24-51) | 0.939 |
| LVEF ≤ 40% (yes, %) | 119 (63.0%) | 71 (64.0%) | 0.902 |
| NYHA (IV, %) | 155 (82.0%) | 84 (75.7%) | 0.234 |
| Systolic blood pressure (mm Hg) | 172 (141-199) | 139 (108-166) | < 0.001 |
| Pulse (beats/min) | 117 (99-136) | 100 (91-120) | < 0.001 |
| Etiology | Ischemia (yes, %) | 82 (43.4%) | 42 (37.8%) | 0.396 |
|                  | Medical history | 142 (75.1%) | 74 (66.7%) | 0.143 |
|                  | Diabetes mellitus (yes, %) | 86 (45.5%) | 53 (47.7%) | 0.721 |
|                  | Dyslipidemia (yes, %) | 103 (54.5%) | 53 (47.7%) | 0.282 |
| Laboratory data | pH | 7.31 (7.19-7.41) | 7.40 (7.29-7.45) | < 0.001 |
|                  | PO2 (mm Hg) | 45.3 (35.9-57.2) | 35.3 (29.0-46.7) | < 0.001 |
|                  | PCO2 (mm Hg) | 92.6 (69.2-134.0) | 91.1 (75.7-160.0) | 0.233 |
|                  | HCO3 (mmol/L) | 22.3 (19.8-24.5) | 22.0 (19.4-24.4) | 0.550 |
|                  | Total bilirubin (mg/L) | 9.6 (92-98) | 97 (94-99) | 0.041 |
|                  | Total cholesterol (mmol/L) | 1.8 (1.2-3.6) | 1.8 (1.2-3.8) | 0.651 |
|                  | BUN (mg/dL) | 10.3 (6.8-17.1) | 3.7 (8.6-23.1) | 0.003 |
|                  | Albumin (g/L) | 416 (333-482) | 405 (330-538) | 0.515 |
|                  | Creatinine (mg/dL) | 140 (130-153) | 133 (121-142) | 0.001 |
|                  | Uric acid (mg/dL) | 7.5 (5.9-10.3) | 9.8 (6.6-15.0) | < 0.001 |
|                  | Serum creatinine (mg/dL) | 95.5 (73.4-126.4) | 118.5 (3.1-169.3) | < 0.001 |
|                  | Potassium (mmol/L) | 4.2 (4.0-4.6) | 4.3 (3.9-5.0) | < 0.001 |
|                  | Sodium (mmol/L) | 1.40 (1.30-1.53) | 133 (121-142) | < 0.001 |
|                  | Total cholesterol (mmol/L) | 1.5 (10.4-100.9) | 36.3 (16.6-979.3) | < 0.001 |
|                  | Proteinuria (mg/dL) | 48.3 (44.8-57.5) | 37.8 (34.7-40.2) | < 0.001 |
|                  | Total proteinuria (mg/dL) | 51 (40.2-60.2) | 45 (38.2-52.2) | 0.002 |
|                  | Total proteinuria (mg/dL) | 7.5 (5.9-10.3) | 9.8 (6.6-15.0) | < 0.001 |
|                  | Total proteinuria (mg/dL) | 95.5 (73.4-126.4) | 118.5 (3.1-169.3) | < 0.001 |
|                  | CRP (mg/dL) | 5200 (1800-16,800) | 17,800 (4550-59,850) | < 0.001 |
|                  | Creatinine (mg/dL) | 21.5 (10.4-100.9) | 36.3 (16.6-979.3) | 0.008 |
|                  | Total proteinuria (mg/dL) | 48.3 (44.8-57.5) | 37.8 (34.7-40.2) | < 0.001 |
|                  | Total proteinuria (mg/dL) | 51 (40.2-60.2) | 45 (38.2-52.2) | 0.002 |
|                  | Total proteinuria (mg/dL) | 7.5 (5.9-10.3) | 9.8 (6.6-15.0) | < 0.001 |
|                  | Total proteinuria (mg/dL) | 95.5 (73.4-126.4) | 118.5 (3.1-169.3) | < 0.001 |
|                  | Lactate (mg/dL) | 2.0 (1.2-3.7) | 1.7 (1.0-2.9) | 0.010 |
|                  | ECMO (yes, %) | 171 (90.5%) | 88 (98.8%) | 0.560 |
|                  | Nitroglycerin (yes, %) | 94 (49.7%) | 28 (25.2%) | < 0.001 |
|                  | Dobutamine (yes, %) | 29 (15.4%) | 14 (12.6%) | 0.610 |
|                  | Dobutamine (yes, %) | 69 (36.5%) | 43 (38.7%) | 0.712 |
|                  | Dobutamine (yes, %) | 10 (5.3%) | 9 (8.1%) | 0.337 |
|                  | Dobutamine (yes, %) | 32 (16.9%) | 15 (12.6%) | 0.003 |
|                  | Dobutamine (yes, %) | 76 (40.2%) | 32 (28.8%) | 0.061 |
|                  | Dobutamine (yes, %) | 69 (36.5%) | 32 (28.8%) | 0.020 |
|                  | Dobutamine (yes, %) | 85 (45.0%) | 46 (41.4%) | 0.630 |
|                  | Dobutamine (yes, %) | 63 (33.3%) | 33 (29.7%) | 0.605 |
|                  | Dobutamine (yes, %) | 3 (3-5) | 5 (3-10) | < 0.001 |
|                  | Dobutamine (yes, %) | 19 (14-31) | 32 (20-47) | < 0.001 |
|                  | Dobutamine (yes, %) | 9 (4.8%) | 19 (17.1%) | 0.001 |

All numerical data are expressed as the median (25%-75% interquartile range). P values between the low-CONUT and high-CONUT groups were determined using the Mann—Whitney U test or chi-square test.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ICU, intensive care unit; NYHA, New York Heart Association; PNI, prognostic nutritional index; PVS, plasma volume status; LVEF, left ventricular ejection fraction.
the total daily energy expenditure shifts to a catabolic state. Therefore, malnutrition leads to cachexia and is occasionally complicated by inflammation. Inflammation itself is an independent risk factor for AHF, and cachexia is associated with an adverse outcome. Under these circumstances, weight loss develops, leading to marked worsening of prognosis. Both malnutrition and inflammation are major factors affecting volume expansion in patients with AHF. Indeed, the degree of volume expansion is exacerbated in patients with an extremely poor nutritional status. Because these patients tend to develop adverse outcomes, an immediate procedural intervention must be considered.

Table 4. Characteristics of the patients by the difference in PVS and PNI

|                          | Low PNI (n = 120) | P value | High PNI (n = 180) | P value |
|--------------------------|-------------------|---------|--------------------|---------|
| Status and vital signs   |                   |         |                    |         |
| Age (y)                  | 70 (61-78)        | 0.166   | 79 (71-85)         | 0.127   |
| Gender (male, %)         | 140 (77.8%)       | 0.137   | 54 (44.6%)         | 0.971   |
| Type (readmission, %)    | 61 (33.9%)        | 0.160   | 57 (47.1%)         | 0.190   |
| LVEF (%)                 | 33 (25-47)        | 0.986   | 41 (30-57)         | 0.550   |
| LVEF ≤ 40% (yes, %)      | 114 (63.3%)       | 1.000   | 58 (47.9%)         | 0.906   |
| NYHA (IV, %)             | 146 (81.1%)       | 0.467   | 99 (81.8%)         | 0.073   |
| Systolic blood pressure (mm Hg) | 172 (146-200) | <0.001 | 162 (139-190) | <0.001 |
| Pulse (beats/min)        | 119 (100-138)     | <0.001 | 108 (99-126)       | 0.002   |
| Etiology                 |                   |         |                    |         |
| Ischemia (yes, %)        | 77 (42.8%)        | 0.552   | 49 (40.5%)         | 0.629   |
| Medical history          |                   |         |                    |         |
| Hypertension (yes, %)    | 134 (74.4%)       | 0.294   | 98 (81.0%)         | 0.395   |
| Diabetes mellitus (yes, %)| 82 (45.6%)        | 0.813   | 67 (55.4%)         | 0.240   |
| Dyslipidemia (yes, %)    | 103 (57.2%)       | 0.034   | 60 (49.6%)         | 0.815   |
| Arterial blood gas       |                   |         |                    |         |
| pH                       | 7.30 (7.19-7.40)  | <0.001  | 7.30 (7.18-7.40)   | <0.001  |
| PO2 (mm Hg)              | 46.7 (36.7-57.7)  | <0.001  | 46.3 (35.7-60.2)   | <0.001  |
| PO2 (mm Hg)              | 90.3 (68.2-134.0)<0.140  | 109.5 (76.8-156.0) | 0.091   |
| HCO3 (mmol/L)            | 22.4 (20.0-24.6)  | 0.112   | 21.3 (19.3-23.6)   | 0.897   |
| SaO2 (%)                 | 96 (92-98)        | 0.008   | 96 (92-98)         | 0.085   |
| Lactate (mmol/L)         | 1.8 (1.2-3.7)     | 0.682   | 2.1 (1.2-4.2)      | 0.006   |
| Laboratory data          |                   |         |                    |         |
| Total bilirubin (mg/dL)  | 10.3 (6.8-17.4)   | 0.007   | 8.6 (5.1-12.0)     | 0.014   |
| Uric acid (mg/dL)        | 413 (333-470)     | 0.117   | 357 (297-440)      | 0.005   |
| Sodium (mmol/L)          | 140 (138-142)     | <0.001  | 140 (138-142)      | 0.530   |
| Potassium (mmol/L)       | 4.2 (4.0-4.6)     | 0.176   | 4.3 (3.9-4.7)      | 0.952   |
| Hemoglobin (g/dL)        | 140 (129-153)     | <0.001  | 111 (100-122)      | <0.001  |
| BUN (mmol/L)             | 7.4 (5.8-10.1)    | <0.001  | 9.0 (6.3-14.1)     | <0.001  |
| Creatinine (g/dL)        | 95.0 (73.4-126.4)| <0.001  | 100.8 (72.5-168.0)| 0.001   |
| CRP (mg/dL)              | 4500 (1775-14,452)| <0.001  | 2600 (1800-8500)   | <0.001  |
| BNP (pg/mL)              | 21.7 (10.6-84.1)  | 0.017   | 35.6 (17.9-75.1)   | 0.072   |
| Nutritional status       |                   |         |                    |         |
| PNI                       | 49.2 (45.7-58.6)  | <0.001  | 48.6 (45.1-55.2)   | <0.001  |
| CONUT score              | 1 (0-2)           | <0.001  | 2 (0-3)            | <0.001  |
| Albumin (g/L)            | 38 (36-40)        | <0.001  | 37 (35-39)         | <0.001  |
| Total cholesterol (mmol/L)| 4.59 (3.88-5.54) | <0.001  | 4.55 (3.78-5.12)   | <0.001  |
| Medication (cases) during ICU |                     |         |                    |         |
| Flurosemide (yes, %)     | 162 (90.0%)       | 0.848   | 111 (91.7%)        | 0.556   |
| Nitroglycerin (yes, %)   | 90 (50.0%)        | <0.001  | 66 (54.5%)         | 0.001   |
| Nicorandil (yes, %)      | 27 (15.0%)        | 0.739   | 18 (14.9%)         | 0.438   |
| Carperitide (yes, %)     | 63 (35.0%)        | 0.331   | 42 (34.7%)         | 0.714   |
| Dopamine (yes, %)        | 10 (5.6%)         | 0.629   | 4 (3.3%)           | 0.093   |
| Dobutamine (yes, %)      | 29 (16.1%)        | 0.001   | 17 (14.0%)         | 0.014   |
| ACE-I/ARB (yes, %)       | 72 (40.0%)        | 0.086   | 34 (28.1%)         | 0.276   |
| β-Blocker (yes, %)       | 68 (37.8%)        | 0.081   | 30 (24.8%)         | 0.677   |
| Spiironolactone (yes, %) | 75 (41.7%)        | 0.408   | 39 (32.2%)         | 0.191   |
| Statin (yes, %)          | 62 (34.4%)        | 0.312   | 38 (31.4%)         | 0.455   |
| Outcome                  |                   |         |                    |         |
| ICU hospitalization (d)  | 3 (3-5)           | <0.001  | 3 (2-4)            | 0.001   |
| Total hospitalization (d)| 19 (15-30)        | <0.001  | 22 (16-37)         | 0.060   |
| In-hospital mortality (yes, %) | 8 (4.4%) | <0.001  | 12 (9.9%)          | 0.093   |

P values between the high-PNI and low-PNI groups were determined using the Mann–Whitney U test or chi-square test. All numerical data are expressed as the median (25%-75% interquartile range).

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ICU, intensive care unit; NYHA, New York Heart Association; PNI, prognostic nutritional index; LVEF, left ventricular ejection fraction; PVS, plasma volume status.
Decongestion is the mainstay for the treatment of patients with AHF requiring intensive care. Diuretics have been proposed as the gold standard for treating patients with volume overload, and this strategy must be immediately applied in the emergency department. Tolvaptan was suggested as a new therapeutic option in Japan in 2010, and the immediate administration of tolvaptan was recommended in the acute phase of AHF.30 Evidence also supports the use of other traditional diuretics (ie, loop diuretics, spironolactone, and thiazide diuretics) in the acute phase. Continuous renal replacement therapy or the extracorporeal ultrafiltration method may be used for patients with acute kidney injury or end-stage chronic kidney disease. Several days are required for the treatment of decongestion in patients with high PVS. Therefore, treating physicians may hesitate to initiate treatment for myocardial protection (eg, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, β-blockers, and spironolactone) in intensive care because of the remaining congestion from the acute phase. Complete decongestion is a priority treatment in intensive care. These medical differences may influence the prognosis in each group. Therefore, we added the medication as an adjusting factor in the multivariate model. As mentioned earlier, numerous procedures are available for managing decongestion. However, on the basis of the results of the present study, PV overload and malnutrition must be treated. Therefore, combination therapy may be required for such patients.

Medical intervention for malnutrition has been reported in patients with chronic HF with complications from inflammation, cachexia, and wasting.31,32 Malnutrition is related to deprivation of macronutrients (eg, protein and energy) and micronutrients (eg, amino acids, vitamins, and minerals). Supplementation of essential amino acid has been suggested to improve the nutritional and metabolic status in patients with HF-related wasting syndrome under optimal medical treatment and adequate protein-energy intake.33 However, thus far, immediate and aggressive intervention to manage malnutrition during the acute phase of AHF has not been reported. The nutritional status is mainly evaluated using the concentration of serum albumin during the acute phase of AHF, because this can be easily and inexpensively obtained through a routine laboratory test. Currently, it is unclear whether a single parameter, such as serum albumin, can be used to assess the nutritional status. However, the presence of hypoalbuminemia may be useful for identifying extremely sick patients in the AHF cohort. However, malnutrition is only one factor inducing hypoalbuminemia in patients with AHF. Furthermore, whether or not nutritional and anti-inflammatory interventions can be relied on, at least in part, to increase the concentration of serum albumin in patients with HF is unclear.31 There is no evidence to suggest that administration of human albumin increases the concentration of serum albumin in patients with HF. Although several randomized controlled trials and meta-analyses have been conducted in critically ill patients in the ICU, few provided positive data.34,35 The 1-month mortality rate among patients who received albumin was similar to that reported for patients who received saline.34 However, when limiting the discussion to those who achieved a serum albumin concentration >3 g/dL, the administration of human albumin was able to reduce the rate of adverse outcomes in critically ill patients.37 Further research is required to determine the benefits of targeted nutritional and anti-inflammatory interventions, as well as the administration of albumin, for the survival of select patients with HF and hypoalbuminemia. Valenotova et al.38 reported that patients

![Figure 3. Kaplan–Meier survival curves for PVS and nutrition status. (A) Kaplan–Meier survival curves showed that the prognosis, including all-cause death, was significantly poorer in the high-CONUT/high-PVS group than in the low-CONUT/high-PVS group. (B) Kaplan–Meier survival curves showed that the prognosis, including all-cause death, was significantly poorer in the low-PNI/high-PVS group than in the high-PNI/high-PVS group. CONUT, Controlling Nutritional Status; PNI, prognostic nutritional index; PVS, plasma volume status.](image)
with cardiac cachexia display a more pronounced degree of right ventricular failure and hypoalbuminemia compared with noncachectic patients of a similar LVEF and NYHA class. Patients with high PVS are occasionally categorized as having biventricular AHF; thus, a majority of these patients had complicated right HF. Therefore, a high PVS coupled with malnutrition may complicate right HF. In a right ventricular volume overload model, administration of S-nitroso human serum albumin improved right ventricular-arterial coupling and reduced oxidative stress. This positive intervention may improve right ventricular function. The benefits of early nutritional intervention by enteral tube feeding vs parenteral central venous catheter and the best methodology for enteral intervention are current topics in intensive care. Strategies for the amelioration of the nutritional status and volume status must be considered during the acute phase of AHF to improve the poor prognosis of patients with malnutrition and volume expansion.

Study limitations

The present study has several limitations. First, the study population was limited to patients admitted to the ICU. Thus, patients with AHF admitted to the general wards were excluded from this study. This exclusion may reduce the generalizability of the present results. In our institute, the patients were treated by cardiologists in a “closed ICU.” Thus, the majority of severely decompenated patients with AHF were admitted to the ICU. However, clear criteria regarding the dose of high-flow oxygen, inotropes, and diuretics were not proposed. Moreover, the admission criteria may have differed annually. The physician ultimately decided where each patient should be admitted in the hospital (i.e., ICU or general ward), and patient bias may have affected this decision. Second, the study was performed at a single center and was not a prospective, randomized, controlled trial. Therefore, it is possible that unmeasured variables affected the results. Furthermore, the difficulty in standardizing care for each patient may have influenced the major findings of this study. Third, body weight before admission was adopted as the compensated dry weight. However, this may not accurately represent the patient’s dry weight and may even be more unreliable than using weight at admission. However, the most important issue was to avoid using the weight during volume overload. Therefore, the historical weight was used to represent the compensated weight. Fourth, although the percentage of patients receiving statin therapy during the ICU stay was revealed, the accurate percentage on admission was not determined. It may be important to know the actual number of patients receiving lipid-lowering therapy and whether this number affects the calculations related to nutrition. Fifth, the majority of patients in the present study had de novo HF (n = 382, 63.6%), which renders it difficult to reconcile cardiac cachexia and other findings. Finally, the prognoses of patients being followed up at other institutes were determined through unstructured telephone interviews. Therefore, HF events may have been missed.

Conclusions

PV expansion on admission was shown to be associated with adverse outcomes in patients with AHF; however, this value alone was insufficient for an accurate prognosis. The simultaneous evaluation of nutrition status and PVS is essential to predict the outcome of patients with severely decompensated AHF.

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Disclosures

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