



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/high-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

## RÉSUMÉ

**Contexte :** La valeur pronostique du volume plasmatique (VP) dans l'insuffisance cardiaque aiguë (ICA) a récemment été évaluée. On ne sait toutefois pas si le volume plasmatique à lui seul peut suffire.

**Méthodologie :** Sur les 675 patients présentant une ICA diagnostiquée, 601 ont été retenus. Le VP, l'indice nutritionnel pronostique (PNI; plus l'indice est faible, plus l'état nutritionnel est mauvais) et le score CONUT (*Controlling Nutritional Status*, contrôle de l'état nutritionnel; plus le score est élevé, plus l'état nutritionnel est mauvais) ont été évalués. Les patients ont été répartis en deux groupes en fonction du VP (VP faible et VP élevé), puis de nouveau en quatre sous-groupes (VP/CONUT faible ou élevé et VP/PNI faible ou élevé).

**Résultats :** La courbe de Kaplan-Meier montre que le taux de survie est significativement inférieur dans le groupe VP élevé par rapport au

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.<sup>1–3</sup> Therefore, volume status varies among individuals.<sup>4</sup> Volume expansion, that is,

systemic venous congestion, sometimes leads to adverse outcomes in patients with HF.<sup>5</sup> In the 2010s, the noninvasive evaluation of plasma volume (PV) was explored in patients with chronic HF or AHF, and the clinical implications of the calculated or estimated plasma volume status (PVS) were described.<sup>6–9</sup>

The importance of evaluating nutritional status also has been suggested in patients with HF.<sup>10</sup> Because malnutrition is a major problem in an aging society,<sup>11</sup> HF guidelines recommend the evaluation of nutritional status.<sup>2,3</sup> 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.<sup>12–16</sup> We also previously reported the importance of malnutrition in patients with severely decompensated AHF.<sup>17</sup> However, the association between the nutritional status and the degree of general congestion/PV has not been adequately explored.

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**Ethics Statement:** 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. Research Ethics Committee information; Reference number; 543-1.

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See page 314 for disclosure information.

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 medical 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,<sup>18</sup> 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.<sup>2,3</sup> 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.

**Conclusions :** L'évaluation du VP a permis de prédire une issue défavorable; en outre, les données montrent qu'un état de malnutrition conjugué à un VP élevé est un facteur de mauvais pronostic. Il est essentiel d'évaluer simultanément l'état nutritionnel et le VP pour prédire l'ICA.

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,<sup>18</sup> 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.

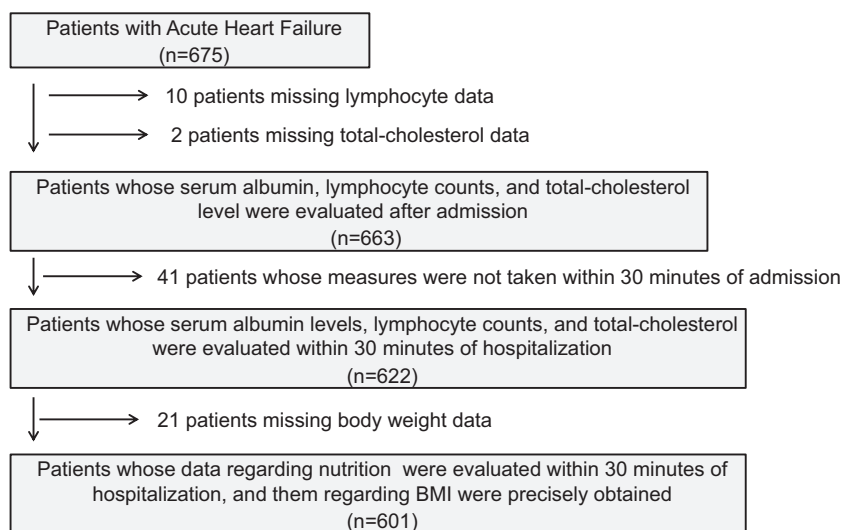
The LVEF was calculated using the Teichholz method or Simpson's method at admission (Sonos 5500; Hewlett Packard, Palo Alto, CA; or Vivid I; GE Yokogawa Medical, Tokyo, Japan). Because the LVEF was measured during the acute phase, it was not adequately evaluated because of severe orthopnea. The methodology 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:  $([\text{actual PV} - \text{ideal PV}]/\text{ideal PV}) \times 100(\%)$ . The actual and ideal PV were defined as follows: actual PV =  $(1 - \text{hematocrit}) \times (a + [b \times \text{body weight}])$  ( $a = 1530$  in male and  $864$  in female patients;  $b = 41.0$  in male and  $47.9$  in female patients), ideal PV =  $c \times \text{body weight}$  ( $c = 39$  in male and  $40$  in female patients).<sup>9</sup>

The PNI was calculated using the following formula:  $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{lymphocyte } (/\mu\text{L})$  (lower = worse).<sup>19</sup> The CONUT score was calculated using a scoring system consisting of serum albumin, lymphocytes, and total cholesterol (range, 0-12; higher = worse).<sup>20</sup>

The patients who were admitted to intensive care unit between May 2011 and March 2018 were enrolled in present study



**Figure 1.** Patient selection process. Between May 2011 and March 2018, 1412 patients who were admitted to the intensive care unit (ICU) at Nippon Medical School Chiba Hokusoh Hospital were screened. Of these, 12 patients who lacked serum albumin, lymphocyte counts, or total cholesterol measures were excluded. A further 41 for whom these measures were not obtained within 30 minutes of admission and 21 for whom the data of body weight were missed were also excluded, leaving 601 patients with acute heart failure (AHF) who were enrolled in the study. BMI, body mass index.

Patients were divided into 4 groups (severe, moderate, mild, and normal) based on their serum albumin, lymphocyte, and total cholesterol levels: serum albumin  $\geq 3.5$  g/dL (normal), 3 to 3.49 (mild), 2.5 to 2.99 (moderate), and  $< 2.5$  (severe); lymphocytes  $\geq 1600/\mu\text{L}$  (normal), 1200 to 1599 (mild), 800 to 1199 (moderate), and  $< 800$  (severe); and total cholesterol  $\geq 180$  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  $\geq 42.30$ ) and 3 for the CONUT score (low: CONUT score  $\leq 3$ ; high: CONUT score  $\geq 4.0$ ).

Patients were divided into 2 groups according to the PVS value (low PVS: PVS  $\leq 12.0\%$ ,  $n = 300$ ; 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-PVS 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  $W$ -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.

**Table 1. Characteristics of patients by the difference in PVS**

	Total (n = 601)	PVS		P value
		Low (n = 300)	High (n = 301)	
<b>Status and vital signs</b>				
Age (y)	76 (67-82)	71 (62-78)	80 (72-85)	< 0.001
Gender (male, %)	393 (65.4%)	242 (80.7%)	157 (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 (94-130)	102 (84-119)	< 0.001
<b>Etiology</b>				
Ischemia (yes, %)	240 (39.9%)	124 (41.3%)	116 (38.5%)	0.506
<b>Medical history</b>				
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
<b>Arterial blood gas</b>				
pH	7.36 (7.24-7.43)	7.36 (7.22-7.43)	7.36 (7.26-7.43)	0.176
PCO <sub>2</sub> (mm Hg)	38.8 (32.7-52.6)	40.1 (33.7-54.3)	37.8 (32.3-49.8)	0.060
PO <sub>2</sub> (mm Hg)	98.7 (71.2-145.0)	92.4 (71.1-136.0)	105.8 (71.5-155.0)	0.076
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	21.8 (19.2-24.3)	22.1 (19.5-24.5)	21.3 (18.4-24.1)	0.065
SaO <sub>2</sub> (%)	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
<b>Laboratory data</b>				
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
BUN (µmol/L)	9.4 (6.5-15.2)	8.9 (6.0-12.1)	11.6 (7.3-17.6)	< 0.001
Creatinine (µmol/L)	107 (78-185)	100 (76-147)	120 (79-229)	< 0.001
CRP (µg/L)	8200 (2300-3680)	7250 (2475-30,200)	8700 (2100-47,500)	0.437
BNP (pmol/L)	34.5 (15.7-159.4)	26.9 (12.6-468.4)	41.2 (20.1-134.8)	< 0.001
<b>Nutritional status</b>				
PNI	42.3 (37.2-48.8)	44.8 (39.1-50.9)	40.2 (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
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
<b>Medication (cases) during ICU</b>				
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
Spirolactone (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
<b>Outcome</b>				
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).

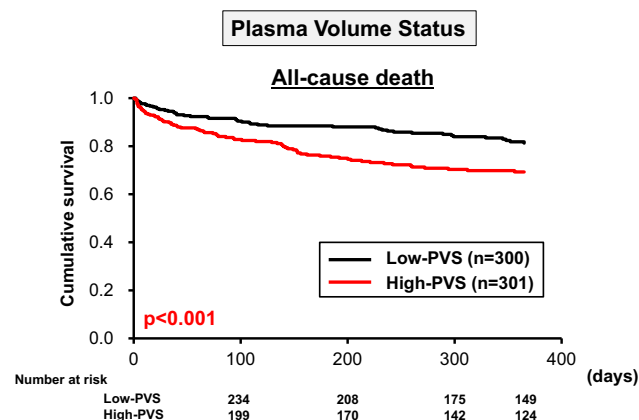
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PNI, prognostic nutritional index; PVS, plasma volume status.

## 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],



**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.

drug-induced cardiomyopathy [n = 1] and sarcoidosis [n = 1]), hypertensive heart disease (n = 92), valvular disease (n = 144), and other heart diseases (n = 57). Most patients were NYHA class IV (n = 468, 77.9%), and the median LVEF on admission was 39.0%.

The high-PVS group included fewer men and more readmitted patients. Patients in this group were significantly older, had significantly more LVEF preservation, and had heart rates that were significantly lower than those reported in the low-PVS group. Furthermore, the levels of serum total bilirubin and hemoglobin were significantly lower in the high-PVS group vs the low-PVS group. In contrast, the levels of blood urea nitrogen, creatinine, CRP, and brain natriuretic peptide were significantly higher in the high-PVS group vs the low-PVS group (Table 1).

The Kaplan–Meier survival curves, including all-cause death within 365 days, for the 4 PVS groups are shown in Figure 2. The survival rates in the high-PVS group were significantly lower than those in the low-PVS group. The multivariate Cox proportional hazards regression model showed that high PVS was an independent predictor of 365-day mortality in patients with AHF (HR, 1.642; 95% confidence interval [CI], 1.049-2.570;  $P = 0.030$ ) (Table 2).

### PVS and nutrition status

Both the low- and high-PVS cohorts in the high-CONUT group had significantly lower systolic blood pressures and heart rates and significantly higher levels of serum blood urea nitrogen and CRP than those in the low-CONUT group. Furthermore, the administration of nitroglycerine was significantly less frequent in patients in the high-CONUT group vs the low-CONUT group. In contrast, the administration of dobutamine was significantly more frequent in the high-CONUT group. Indeed, the duration of ICU stay in patients in the high-CONUT group was significantly longer than in the low-CONUT group (Table 3). This tendency was also observed when using the PNI to assess the nutritional status of patients (Table 4).

The Kaplan–Meier curves for the low- or high-PVS/CONUT and low- or high-PVS/PNI groups are shown in Figure 3. The prognosis in both the high- and low-PVS

groups, including all-cause death within 365 days, was significantly poorer in patients with a high CONUT score than in those with a low CONUT score (Fig. 3A). Similar prognostic results were observed for patients with a low PNI vs those with a high PNI (Fig. 3B). The multivariate Cox proportional hazards regression model showed that high PVS/high CONUT was an independent predictor of 365-day mortality (HR, 2.076; 95% CI, 1.147-3.757;  $P = 0.016$ ) (Table 2). A similar result was obtained for the PNI; only high PVS/low PNI was an independent predictor of 365-day mortality (HR, 2.094; 95% CI, 1.166-3.761;  $P = 0.013$ ) (Table 2). These results suggest that the evaluation of PVS alone is insufficient to predict mortality caused by AHF. Evaluation of both the nutritional status and PVS is required for the accurate prediction of mortality in patients with severely decompensated AHF.

### 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.<sup>6-9,12-16</sup> 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.<sup>9,21</sup> Duarte et al.<sup>21</sup> 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.<sup>21</sup> Kobayashi et al.<sup>8</sup> also determined the prognostic impact of PVS during the discharge of patients with AHF using the Strauss formula.<sup>22</sup> Yoshihisa et al.<sup>6</sup> 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.<sup>7</sup> 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,<sup>23</sup> echocardiography,<sup>24</sup> and volume biomarkers<sup>25</sup> is traditionally reported, an immediate,

**Table 2. Multivariate analyses of the associations with 365-day all-cause death**

All-cause death	Univariate			Multivariate									
	HR	95% CI	<i>P</i> value	Model 1			Model 2			Model 3			
				HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> 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	0.567-1.173	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)	1.151	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	0.995-2.104	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	2.122-4.317	<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.

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

	Low PVS		<i>P</i> value	High PVS		<i>P</i> value
	Low CONUT	High CONUT		Low CONUT	High CONUT	
	(n = 189)	(n = 111)		(n = 141)	(n = 160)	
<b>Status and vital signs</b>						
Age (y)	70 (61-78)	72 (64-79)	0.204	79 (72-86)	80 (72-84)	0.406
Gender (male, %)	148 (78.3%)	94 (84.7%)	0.226	61 (43.3%)	90 (56.3%)	0.028
Type (readmission, %)	59 (31.2%)	33 (29.7%)	0.897	62 (44.0%)	65 (40.6%)	0.561
LVEF (%)	33 (25-47)	35 (24-51)	0.939	41 (30-52)	42 (30-57)	0.584
LVEF ≤ 40% (yes, %)	119 (63.0%)	71 (64.0%)	0.902	65 (46.1%)	77 (48.1%)	0.729
NYHA (IV, %)	155 (82.0%)	84 (75.7%)	0.234	114 (80.9%)	115 (71.9%)	0.079
Systolic blood pressure (mm Hg)	172 (141-199)	139 (108-166)	< 0.001	165 (140-190)	143 (110-161)	< 0.001
Pulse (beats/min)	117 (99-136)	100 (91-120)	< 0.001	108 (93-126)	94 (79-111)	< 0.001
<b>Etiology</b>						
Ischemia (yes, %)	82 (43.4%)	42 (37.8%)	0.396	61 (43.3%)	55 (34.4%)	0.124
<b>Medical history</b>						
Hypertension (yes, %)	142 (75.1%)	74 (66.7%)	0.143	107 (75.9%)	129 (80.6%)	0.329
Diabetes mellitus (yes, %)	86 (45.5%)	53 (47.7%)	0.721	77 (54.6%)	76 (47.5%)	0.248
Dyslipidemia (yes, %)	103 (54.5%)	53 (47.7%)	0.282	72 (51.1%)	80 (50.0%)	0.908
<b>Arterial blood gas</b>						
pH	7.31 (7.19-7.41)	7.40 (7.29-7.45)	< 0.001	7.32 (7.20-7.42)	7.39 (7.32-7.44)	< 0.001
PCO <sub>2</sub> (mm Hg)	45.3 (35.9-57.2)	35.3 (29.0-46.7)	< 0.001	42.8 (34.4-55.6)	36.4 (32.0-41.8)	< 0.001
PO <sub>2</sub> (mm Hg)	92.6 (69.2-134.0)	91.1 (75.7-160.0)	0.233	109.0 (74.0-169.0)	103.0 (69.8-144.0)	0.065
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	22.3 (19.8-24.5)	22.0 (19.4-24.4)	0.550	21.3 (18.7-23.7)	21.3 (18.3-24.2)	0.758
SaO <sub>2</sub> (%)	96 (92-98)	97 (94-99)	0.041	97 (92-99)	97 (94-99)	0.119
Lactate (mmol/L)	1.8 (1.2-3.6)	1.8 (1.2-3.8)	0.651	2.0 (1.2-3.7)	1.7 (1.0-2.9)	0.010
<b>Laboratory data</b>						
Total bilirubin (μmol/L)	10.3 (6.8-17.1)	13.7 (8.6-23.1)	0.003	8.6 (5.1-12.0)	10.3 (6.8-15.4)	0.004
Uric acid (μmol/L)	416 (333-482)	405 (330-538)	0.515	363 (297-446)	422 (327-495)	0.003
Sodium (mmol/L)	140 (138-142)	138 (135-141)	< 0.001	140 (137-142)	139 (136-143)	0.588
Potassium (mmol/L)	4.2 (4.0-4.6)	4.3 (3.9-5.0)	0.227	4.3 (3.8-4.8)	4.3 (3.8-4.7)	0.708
Hemoglobin (g/L)	140 (130-153)	133 (121-142)	< 0.001	109 (97-122)	99 (88-110)	< 0.001
BUN (μmol/L)	7.5 (5.9-10.3)	9.8 (6.6-15.0)	0.001	9.8 (6.5-14.9)	13.8 (8.6-19.2)	< 0.001
Creatinine (μmol/L)	95.5 (73.4-126.4)	118.5 (3.1-169.3)	0.003	106.1 (73.4-188.3)	148.1 (89.1-256.4)	0.008
CRP (μg/L)	5200 (1800-16,800)	17,800 (4550-59,850)	< 0.001	3700 (1100-12,100)	24,800 (5050-77,700)	< 0.001
BNP (pmol/L)	21.5 (10.4-100.9)	36.3 (16.6-979.3)	0.008	41.2 (20.2-121.1)	40.8 (19.6-136.2)	0.684
<b>Nutritional status</b>						
PNI	48.3 (44.8-57.5)	37.8 (34.7-40.2)	< 0.001	46.1 (42.6-53.1)	35.5 (31.3-39.0)	< 0.001
CONUT score	1 (0-2)	5 (4-6)	< 0.001	2 (1-3)	6 (5-7)	< 0.001
Albumin (g/L)	38 (35-40)	33 (30-35)	< 0.001	36 (35-38)	31 (28-33)	< 0.001
Lymphocyte count (/μL)	2194 (1524-3880)	765 (542-1211)	< 0.001	1843 (1400-3136)	714 (487-1036)	< 0.001
Total cholesterol (mmol/L)	4.73 (4.03-5.61)	3.65 (3.30-4.32)	< 0.001	4.65 (4.03-5.20)	3.61 (3.10-4.39)	< 0.001
<b>Medication (cases) during ICU</b>						
Furosemide (yes, %)	171 (90.5%)	98 (88.3%)	0.560	127 (90.1%)	145 (90.6%)	1.000
Nitroglycerin (yes, %)	94 (49.7%)	28 (25.2%)	< 0.001	76 (53.9%)	52 (32.5%)	< 0.001
Nicorandil (yes, %)	29 (15.4%)	14 (12.6%)	0.610	20 (14.2%)	32 (20.0%)	0.222
Carperitide (yes, %)	69 (36.5%)	43 (38.7%)	0.712	49 (34.8%)	60 (37.5%)	0.633
Dopamine (yes, %)	10 (5.3%)	9 (8.1%)	0.337	5 (3.5%)	14 (8.8%)	0.095
Dobutamine (yes, %)	32 (16.9%)	36 (32.4%)	0.003	17 (12.1%)	47 (29.4%)	< 0.001
ACE-I/ARB (yes, %)	76 (40.2%)	32 (28.8%)	0.061	41 (29.1%)	33 (20.6%)	0.107
β-Blocker (yes, %)	69 (36.5%)	32 (28.8%)	0.206	38 (27.0%)	32 (20.0%)	0.173
Spirololactone (yes, %)	85 (45.0%)	46 (41.4%)	0.630	42 (29.8%)	42 (26.3%)	0.521
Statin (yes, %)	63 (33.3%)	33 (29.7%)	0.608	45 (31.9%)	41 (25.6%)	0.251
<b>Outcome</b>						
ICU hospitalization (d)	3 (3-5)	5 (3-10)	< 0.001	3 (2-4)	4 (3-7)	< 0.001
Total hospitalization (d)	19 (14-31)	32 (20-47)	< 0.001	23 (16-38)	28 (18-47)	0.151
In-hospital mortality (yes, %)	9 (4.8%)	19 (17.1%)	0.001	13 (9.2%)	30 (18.8%)	0.021

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.

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.<sup>26,27</sup> 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.<sup>28</sup> Patients develop enteral protein loss, and

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

	Low PVS		P value	High PVS		P value
	High PNI	Low PNI		High PNI	Low PNI	
	(n = 180)	(n = 120)		(n = 121)	(n = 180)	
<b>Status and vital signs</b>						
Age (y)	70 (61-78)	72 (64-79)	0.166	79 (71-85)	80 (72-84)	0.127
Gender (male, %)	140 (77.8%)	102 (85.0%)	0.137	54 (44.6%)	97 (53.9%)	0.751
Type (readmission, %)	61 (33.9%)	31 (25.8%)	0.160	57 (47.1%)	70 (38.9%)	0.190
LVEF (%)	33 (25-47)	36 (22-50)	0.986	41 (30-57)	42 (30-53)	0.550
LVEF ≤ 40% (yes, %)	114 (63.3%)	76 (63.3%)	1.000	58 (47.9%)	84 (46.7%)	0.906
NYHA (IV, %)	146 (81.1%)	93 (77.5%)	0.467	99 (81.8%)	130 (72.2%)	0.073
Systolic blood pressure (mm Hg)	172 (146-200)	140 (108-168)	< 0.001	162 (139-190)	146 (113-167)	< 0.001
Pulse (beats/min)	119 (100-138)	100 (86-120)	< 0.001	108 (90-126)	98 (81-112)	0.002
<b>Etiology</b>						
Ischemia (yes, %)	77 (42.8%)	47 (39.2%)	0.552	49 (40.5%)	67 (37.2%)	0.629
<b>Medical history</b>						
Hypertension (yes, %)	134 (74.4%)	82 (68.3%)	0.294	98 (81.0%)	133 (76.7%)	0.395
Diabetes mellitus (yes, %)	82 (45.6%)	57 (47.5%)	0.813	67 (55.4%)	86 (47.8%)	0.240
Dyslipidemia (yes, %)	103 (57.2%)	53 (44.2%)	0.034	60 (49.6%)	92 (51.1%)	0.815
<b>Arterial blood gas</b>						
pH	7.30 (7.19-7.40)	7.40 (7.30-7.45)	< 0.001	7.30 (7.18-7.40)	7.39 (7.31-7.44)	< 0.001
PCO <sub>2</sub> (mm Hg)	46.7 (36.7-57.7)	35.0 (29.1-43.7)	< 0.001	46.3 (35.7-60.2)	35.5 (31.1-41.6)	< 0.001
PO <sub>2</sub> (mm Hg)	90.3 (68.2-134.0)	94.7 (75.4-145.0)	0.140	109.5 (76.8-156.0)	103.0 (69.4-147.5)	0.091
HCO <sub>3</sub> <sup>-</sup> (mmol/L)	22.4 (20.0-24.6)	21.8 (18.9-24.2)	0.112	21.3 (19.3-23.6)	21.3 (18.1-24.3)	0.897
SaO <sub>2</sub> (%)	96 (92-98)	97 (94-99)	0.008	96 (92-98)	98 (93-99)	0.085
Lactate (mmol/L)	1.8 (1.2-3.7)	1.9 (1.2-3.6)	0.682	2.1 (1.2-4.2)	1.7 (1.0-2.9)	0.006
<b>Laboratory data</b>						
Total bilirubin (mg/dL)	10.3 (6.8-17.4)	12.0 (8.6-21.0)	0.007	8.6 (5.1-12.0)	10.3 (6.8-15.4)	0.014
Uric acid (mg/dL)	413 (333-470)	416 (332-537)	0.117	357 (297-446)	416 (326-494)	0.005
Sodium (mmol/L)	140 (138-142)	139 (135-141)	< 0.001	140 (138-142)	139 (136-143)	0.530
Potassium (mmol/L)	4.2 (4.0-4.6)	4.3 (3.9-5.0)	0.176	4.3 (3.9-4.7)	4.3 (3.8-4.9)	0.932
Hemoglobin (g/dL)	140 (129-153)	133 (123-142)	< 0.001	111 (100-122)	98 (88-111)	< 0.001
BUN (mmol/L)	7.4 (5.8-10.1)	9.7 (6.9-14.6)	< 0.001	9.0 (6.3-14.1)	13.7 (9.1-19.5)	< 0.001
Creatinine (g/dL)	95.0 (73.4-126.4)	115.4 (86.0-163.5)	0.001	100.8 (72.5-168.0)	152.1 (89.3-256.4)	0.001
CRP (mg/dL)	4500 (1775-14,425)	21,000 (5375-61,725)	< 0.001	2600 (1000-8500)	24,400 (5325-68,625)	< 0.001
BNP (pg/mL)	21.7 (10.6-84.1)	37.5 (14.8-1140.7)	0.017	35.6 (17.9-75.1)	47.0 (21.0-147.5)	0.072
<b>Nutritional status</b>						
PNI	49.2 (45.7-58.6)	38.0 (35.0-39.8)	< 0.001	48.6 (45.1-55.2)	36.3 (32.0-39.3)	< 0.001
CONUT score	1 (0-2)	5 (4-6)	< 0.001	2 (0-3)	6 (4-7)	< 0.001
Albumin (g/L)	38 (36-40)	33 (30-35)	< 0.001	37 (35-39)	32 (29-34)	< 0.001
Lymphocyte count (μL)	2339 (1613-4130)	814 (542-1248)	< 0.001	2309 (1658-3832)	741 (490-1117)	< 0.001
Total cholesterol (mmol/L)	4.59 (3.88-5.54)	3.84 (3.36-4.69)	< 0.001	4.55 (3.78-5.12)	3.98 (3.31-4.73)	< 0.001
<b>Medication (cases) during ICU</b>						
Flurosemide (yes, %)	162 (90.0%)	107 (89.2%)	0.848	111 (91.7%)	161 (89.4%)	0.556
Nitroglycerin (yes, %)	90 (50.0%)	32 (26.7%)	< 0.001	66 (54.5%)	62 (34.4%)	0.001
Nicorandil (yes, %)	27 (15.0%)	16 (13.3%)	0.739	18 (14.9%)	34 (18.9%)	0.438
Carperitide (yes, %)	63 (35.0%)	49 (40.8%)	0.331	42 (34.7%)	67 (37.2%)	0.714
Dopamine (yes, %)	10 (5.6%)	9 (7.5%)	0.629	4 (3.3%)	15 (8.3%)	0.093
Dobutamine (yes, %)	29 (16.1%)	39 (32.5%)	0.001	17 (14.0%)	47 (26.1%)	0.014
ACE-I/ARB (yes, %)	72 (40.0%)	36 (30.0%)	0.086	34 (28.1%)	40 (22.2%)	0.276
β-Blocker (yes, %)	68 (37.8%)	33 (27.5%)	0.081	30 (24.8%)	40 (22.2%)	0.677
Spirolactone (yes, %)	75 (41.7%)	56 (46.7%)	0.408	39 (32.2%)	45 (25.0%)	0.191
Statin (yes, %)	62 (34.4%)	34 (28.3%)	0.312	38 (31.4%)	48 (26.7%)	0.435
<b>Outcome</b>						
ICU hospitalization (d)	3 (3-5)	5 (3-10)	< 0.001	3 (2-4)	4 (3-6)	0.001
Total hospitalization (d)	19 (15-30)	32 (19-47)	< 0.001	22 (16-37)	29 (17-47)	0.060
In-hospital mortality (yes, %)	8 (4.4%)	20 (16.7%)	< 0.001	12 (9.9%)	31 (17.2%)	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).

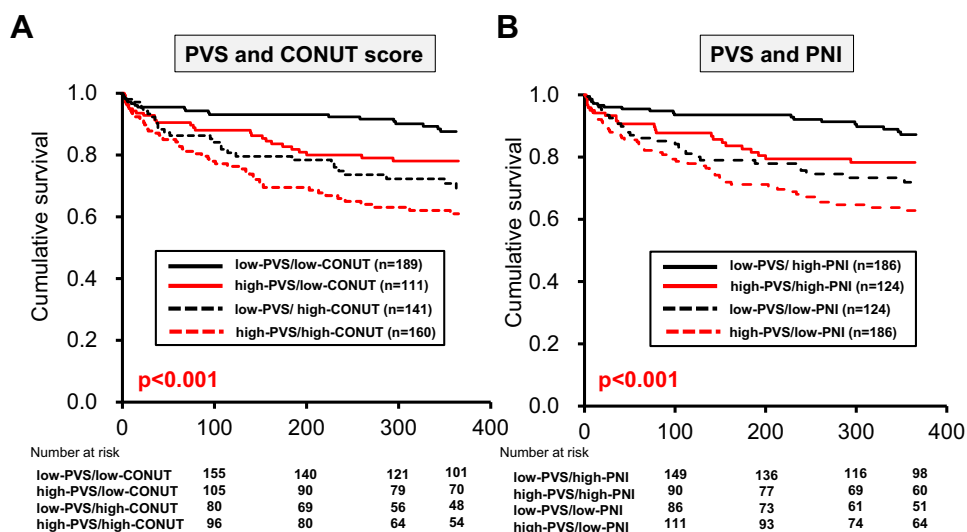
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ICU, intensive care unit; NYHA, New York Heart Association; PNI, prognostic nutritional index; LVEF, left ventricular ejection fraction; PVS, plasma volume status.

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,<sup>16</sup> and cachexia is associated with an adverse outcome.<sup>13</sup> Under these circumstances, weight loss develops, leading to marked worsening of

prognosis.<sup>29</sup> 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.



**Nutrition and Plasma Volume Status**



**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.

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.<sup>2</sup> 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.<sup>30</sup> 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 treatments for myocardial protection (eg, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers,  $\beta$ -blockers, and spironolactone) in intensive care because of the remaining congestion from the acute phase. Complete decongestion is a priority for 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.<sup>31,32</sup> 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.<sup>33</sup> 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.<sup>31</sup> 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.<sup>34–36</sup> The 1-month mortality rate among patients who received albumin was similar to that reported for patients who received saline.<sup>34</sup> 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.<sup>37</sup> 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. Valentova et al.<sup>38</sup> reported that patients

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.<sup>39</sup> This positive intervention may lead to a better outcome in patients with AHF with high PVS complicated by malnutrition via improvement of 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.<sup>40,41</sup> 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 decompensated 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 (ie, 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

The authors have no conflicts of interest to disclose.

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