

ORIGINAL RESEARCH

New Classification for the Combined Assessment of the Fractional Excretion of Urea Nitrogen and Estimated Plasma Volume Status in Acute Heart Failure

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BACKGROUND: The fractional excretion of urea nitrogen (FEUN) has been used as a renal blood flow index related to cardiac output, and the estimated plasma volume status (ePVS) as a body fluid volume index. However, the usefulness of their combination in acute decompensated heart failure (HF) management is unclear. We investigated the effect of 4 hemodynamic categories according to the high and low FEUN and ePVS values at discharge on the long-term prognosis of patients with acute decompensated HF.

METHODS AND RESULTS: Between April 2011 and December 2018, we retrospectively identified 466 patients with acute decompensated HF with FEUN and ePVS values at discharge. Primary end point was postdischarge all-cause death. Secondary end points were (1) the composite of all-cause death and HF readmission, and (2) HF readmission in a time-to-event analysis. The patients were divided into 4 groups according to the high/low FEUN ($\geq 35\%$, $< 35\%$) and ePVS ($> 5.5\%$, $\leq 5.5\%$) values at discharge: high-FEUN/low-ePVS, high-FEUN/high-ePVS, low-FEUN/low-ePVS, and low-FEUN/high-ePVS groups. During a median follow-up period of 28.1 months, there were 173 all-cause deaths (37.1%), 83 cardiovascular deaths (17.8%), and 121 HF readmissions (26.0%). The Kaplan–Meier curve analysis showed that the high-FEUN/low-ePVS group had a better prognosis than the other groups (log-rank test, $P < 0.001$). In the multivariable Cox regression analysis, the low-FEUN/high-ePVS group had a higher mortality than the high-FEUN/low-ePVS group (hazard ratio, 2.92 [95% CIs, 1.73–4.92; $P < 0.001$]).

CONCLUSIONS: The new classification of the 4 hemodynamic profiles using the FEUN and ePVS values may play an important role in improving outcomes in patients with stable acute decompensated HF.

Key Words: ADHF ■ ePVS ■ FEUN ■ heart failure

See Editorial by Rao.

Knowledge of cardiac output and volume status is essential for the implementation of an effective treatment strategy in acute decompensated heart failure (ADHF), in which congestion is one of the main causes of hospitalization. Furthermore, insufficient decongestion at discharge has been associated with

higher rehospitalization rates and death in patients with ADHF.^{1,2} However, hypoperfusion is also recognized as a poor prognostic factor. During the treatment of heart failure (HF), overcorrections because of excess fluid removal arising from the use of diuretics have been associated with adverse events, including worsening renal

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CLINICAL PERSPECTIVE

What Is New?

- The fractional excretion of urea nitrogen (FEUN) has been used as renal blood flow index related to cardiac output, and the estimated plasma volume status (ePVS) as body fluid volume index; however, the usefulness of their combination in acute decompensated heart failure (ADHF) management is unclear.
- We provide new insights into the ADHF management based on imprecise cardiac output and volume status markers, including symptom improvement, physical and laboratory examination findings, urine output, and weight loss.
- Low-FEUN/high-ePVS was independently associated with poor prognosis and may play an important role in improving outcomes of patients with ADHF.

What Are the Clinical Implications?

- Our study presents a new classification of 4 hemodynamic profiles using the FEUN and ePVS values that is both cost-effective and non-invasive, to properly understand the condition of patients with ADHF.
- Using FEUN and ePVS as markers for long-term prognosis in patients with ADHF has not been researched enough, and we hope that further research is conducted to verify our findings and study the correlation between the 4 FEUN/ePVS hemodynamic profiles using the values at discharge and long-term prognosis.

Nonstandard Abbreviations and Acronyms

ADHF	acute decompensated heart failure
ePVS	estimated plasma volume status
FEUN	fractional excretion of urea nitrogen

function, increased activity of the renin angiotensin system and sympathetic nervous system, and death.^{3–5} Therefore, international guidelines have suggested the assessment of the “volume status” and “perfusion” required to maintain an euvoletic state, by controlling the diuretic doses appropriately.^{6,7} However, in some clinical cases, it can be difficult to relieve the congestion while avoiding hypovolemic conditions arising from excessive diuresis. Therefore, objective indicators are needed to guide the adjustments of HF medications.

As a diagnostic approach to acute kidney injury, the fractional excretion of urea nitrogen (FEUN) is frequently used to diagnose renal or prerenal failure, and is more useful than the fractional excretion of sodium, which is

affected strongly by diuretic use.^{8–10} A low FEUN indicates prerenal failure, which is because of the dehydration that occurs in general conditions and the dehydration and low cardiac output that occurs in HF. In other words, the FEUN may be a novel surrogate marker of perfusion in patients with ADHF. Recently, we identified a lower FEUN as a predictor of the prognosis in patients with ADHF, especially in those with estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m².¹¹ However, we were unable to determine whether the low FEUN was because of the low cardiac function or the decrease in the circulating plasma volume.

The estimated plasma volume status (ePVS), which was derived from the hemoglobin and hematocrit values, showed a good correlation with the measured plasma volume.¹² Previous studies have demonstrated that a high ePVS was associated with a poor prognosis, and proposed a threshold of >5.5 mL/g (high ePVS) to indicate excessive congestion in patients with ADHF.^{13,14}

We hypothesized that the combination of the FEUN and ePVS is useful clinically to determine the perfusion and volume status. Therefore, the present study aimed to investigate the effect of the 4 hemodynamic categories according to the high and low FEUN and ePVS values at discharge on the long-term prognosis of patients with ADHF, and whether the usefulness of the 4 hemodynamic categories in patients with ADHF depends on renal function.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patients

The NARA-HF Study 4 (Nara Registry and Analyses for Heart Failure Study 4) is a prospective cohort study that comprises 1012 consecutive patients admitted as emergency cases to our department or the coronary care unit of our hospital with documented ADHF (either acute new-onset or acute-on-chronic HF) between April 2011 and December 2018. The diagnosis of HF was based on the Framingham Criteria.¹⁵ Patients with acute myocardial infarction, acute myocarditis, or acute HF with acute pulmonary embolism were excluded. Of the patients enrolled in the NARA-HF Study 4, 466 (excluding patients who died during hospitalization, on dialysis, or without measured urine urea nitrogen at discharge) were included in the present study. We divided the 466 patients with ADHF into 4 groups according to the high/low FEUN ($\geq 35\%$, $< 35\%$) and ePVS ($> 5.5\%$, $\leq 5.5\%$) values at discharge: high-FEUN/low-ePVS, high-FEUN/high-ePVS, low-FEUN/low-ePVS, and low-FEUN/high-ePVS groups (Figure 1).

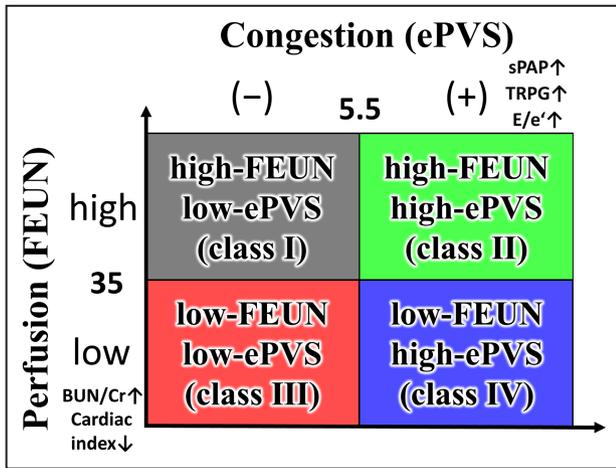


Figure 1. The 4 hemodynamic profiles based on the combined assessment of fractional excretion of urea nitrogen and estimated plasma volume status values at discharge. BUN/Cr indicates blood urea nitrogen/creatinine; E/e', early mitral inflow velocity to early diastolic mitral annular velocity; ePVS, estimated plasma volume status; FEUN, fractional excretion of urea nitrogen; sPAP, systolic pulmonary artery pressure; and TRPG, tricuspid regurgitation pressure gradient.

We investigated the impact of the combined assessment of the FEUN and ePVS values on the prognosis of ADHF. The study protocol was approved by the Ethics Committee of the Nara Medical University (approval number 624). Written informed consent was obtained from all the patients according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Data Collection and Definitions

The laboratory parameters including hemoglobin, hematocrit, albumin, blood urea nitrogen (BUN), creatinine, eGFR according to the diet modifications of the renal disease method, cystatin C, serum electrolytes (sodium and potassium), B-type natriuretic peptide (BNP), renin, aldosterone, urine electrolytes (sodium and potassium), and urine urea nitrogen (from the urine samples that were collected) were measured in all patients at discharge. The vital signs, including heart rate and blood pressure at discharge, were recorded.

The FEUN was calculated according to its well-defined formula^{8,16,17}:

$$FEUN = \frac{[\text{urinary urea} \times \text{plasma creatinine}]}{[\text{plasma urea} \times \text{urinary creatinine}] \times 100}$$

The ePVS was calculated using the Strauss-derived Duarte formula with the hematocrit and hemoglobin values^{12,18}:

$$ePVS = \frac{[100 - \text{hematocrit}]}{\text{hemoglobin}}$$

For loop diuretics other than furosemide, we converted the dose to furosemide equivalent doses: 4 mg of torasemide and 30 mg of azosemide were both considered to be equivalent to 20 mg of furosemide.^{19,20}

Outcomes

The primary end point was postdischarge all-cause death in a time-to-event analysis. The secondary end points were (1) the composite of all-cause death and HF readmission, and (2) HF readmission in a time-to-event analysis. The statuses of all the patients were surveyed, and the information on outcomes was obtained from the patients' medical records and the participating cardiologists. When this information was unavailable in the medical records, the clinicians sent letters to the patients' homes or telephoned the patients or their families to request the data.

Statistical Analysis

The data were expressed as means and SDs for the normally distributed data, and as medians with interquartile ranges for the non-normally distributed data. The Kolmogorov–Smirnov test was performed to assess for normality. The categorical data were expressed as numbers and percentages. The differences between the 4 groups were tested using the ANOVA for the normally distributed variables and the Kruskal–Wallis test for the non-normally distributed variables. The Chi-square test was used to compare categorical variables.

To evaluate the association between the combined assessment of the FEUN and ePVS values at discharge and outcomes, Kaplan–Meier analyses with log-rank tests, and univariate and multivariate Cox proportional hazard analyses were performed between groups. We selected the FEUN value (35%) that is used commonly as an indicator of prerenal failure in patients with acute kidney injury,⁸ and the ePVS value (5.5%) that is used commonly as an indicator of excessive congestion in patients with ADHF.¹² In the multivariate analysis, the following variables were selected as pre-existing and known prognostic factors for HF: age, sex, the New York Heart Association functional classification, diabetes, BNP, left ventricular ejection fraction at discharge, BUN, creatinine, serum sodium, systolic blood pressure at discharge, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and aldosterone antagonists.¹¹ In addition to the Cox proportional hazard analysis, a competing-risk analysis using the Fine and Gray model was used to analyze the risk of HF readmission. Finally, subgroup analyses in Kaplan–Meier analyses with log-rank tests for post-discharge all-cause death were conducted by eGFR (<60 mL/min per 1.73 m², ≥60 mL/min per 1.73 m²).

The results were reported as hazard ratios (HR), 95% CI, and *P* values. A value of *P*<0.05 was considered to be significant for the individual comparisons. All the statistical analyses were performed using the R software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

The median age was 76 (67–83) years, and 55.8% of patients were men. Among them, the high-FEUN/low-ePVS, high-FEUN/high-ePVS, low-FEUN/low-ePVS, and low-FEUN/high-ePVS groups comprised 134 (28.8%), 108 (23.2%), 99 (21.2%), and 125 (26.8%) patients, respectively (Figure 2).

There were no significant differences in the sex, systolic blood pressure, heart rate levels, and the grade of New York Heart Association, at discharge among the 4 groups (Table 1). Age in the high-FEUN/high-ePVS and low-FEUN/high-ePVS groups was significantly higher compared with that of the high-FEUN/low-ePVS and low-FEUN/low-ePVS groups. The proportion of diabetes in the low-FEUN/high-ePVS group was significantly higher compared with that of the high-FEUN/low-ePVS group (Table 1).

The proportion of patients treated with angiotensin-converting enzyme inhibitors or angiotensin receptor

blockers in the high-FEUN/low-ePVS and low-FEUN/low-ePVS groups was significantly higher compared with that of the high-FEUN/high-ePVS group. The proportion of patients treated with beta-blockers and aldosterone antagonist in the low-FEUN/low-ePVS group was significantly higher compared with that of the high-FEUN/high-ePVS group. The dose of loop diuretic in the low-FEUN/high-ePVS group was significantly higher compared with that of the other 3 groups (Table 1).

With regard to the laboratory parameters, hemoglobin, hematocrit, and albumin in the high-FEUN/low-ePVS and low-FEUN/low-ePVS groups were significantly higher compared with those of the high-FEUN/high-ePVS and low-FEUN/high-ePVS groups. BUN in the low-FEUN/high-ePVS group was significantly higher compared with that of the other 3 groups. Creatinine in the high-FEUN/high-ePVS and low-FEUN/high-ePVS groups were significantly higher compared with that of the high-FEUN/low-ePVS group. BUN/creatinine ratio in the low-FEUN/low-ePVS and low-FEUN/high-ePVS groups was significantly higher compared with that of the high-FEUN/low-ePVS and high-FEUN/high-ePVS groups. Cystatin C in the high-FEUN/low-ePVS and low-FEUN/low-ePVS groups were significantly lower compared with those of the high-FEUN/high-ePVS and low-FEUN/high-ePVS groups. BNP in the high-FEUN/high-ePVS group was significantly higher compared with that of the low-FEUN/low-ePVS group (Table 1).

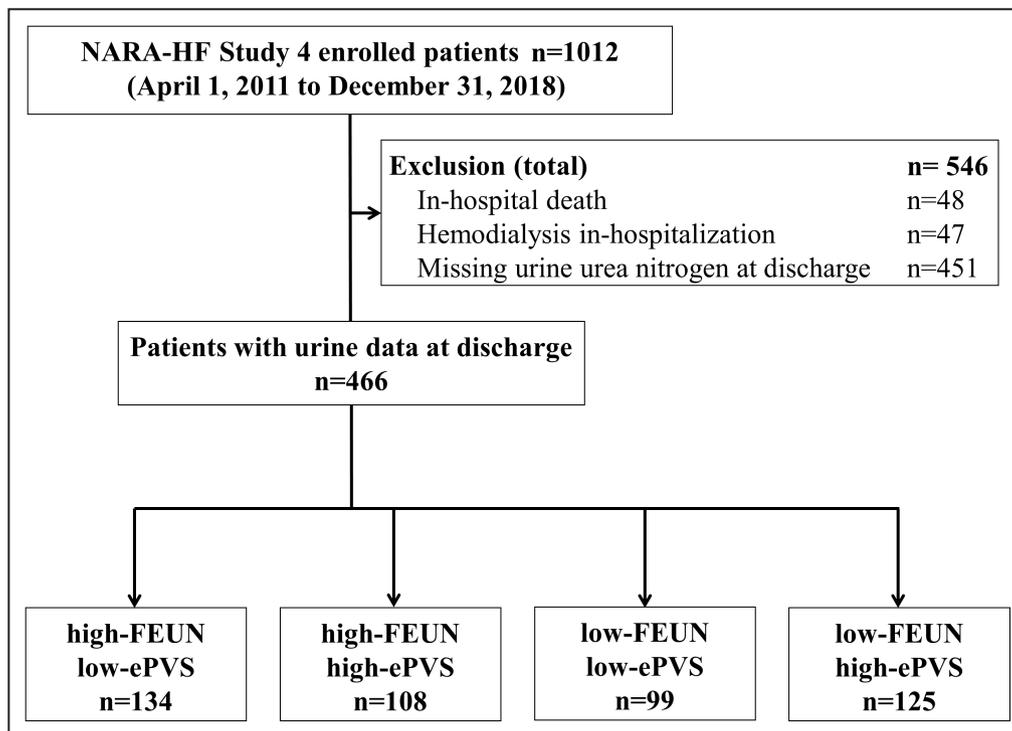


Figure 2. Flowchart of the study cohort.

ePVS indicates estimated plasma volume status; FEUN, fractional excretion of urea nitrogen; and NARA-HF Study 4, Nara Registry and Analyses for Heart Failure Study 4.

Table 1. Baseline Characteristics

	High-FEUN low-ePVS (n=134)	High-FEUN high-ePVS (n=108)	Low-FEUN low-ePVS (n=99)	Low-FEUN high-ePVS (n=125)	P value
Age, y	73 (61–81)	78 (71–84)	73 (64–80)	80 (71–85)	<0.001 [‡] ,# <0.05 [†]
Men, %	85 (63.4)	54 (50.0)	59 (59.6)	62 (49.6)	0.067
BMI, kg/m ²	21.8 (19.2–24.3)	20.1 (17.8–22.5)	21.6 (19.0–24.0)	20.4 (17.5–22.8)	<0.05 [‡]
SBP, mmHg	108 (99–120)	110 (99–126)	109 (100–120)	108 (96–119)	0.431
DBP, mmHg	63 (58–70)	60 (50–67)	61 (56–68)	58 (50–64)	<0.001 [‡] <0.05 [‡] ,#
HR, beats/min	70 (64–78)	71 (61–78)	70 (60–83)	71 (64–80)	0.856
NYHA at discharge, %					0.339
1	49 (36.6)	32 (29.6)	42 (54.5)	30 (24.0)	
2	83 (61.9)	72 (66.7)	54 (54.5)	88 (70.4)	
3	2 (1.5)	4 (3.7)	2 (2.0)	7 (5.6)	
4	0 (0)	0 (0)	1 (1.0)	0 (0)	
Medical history, %					
Hypertension	93 (69.4)	87 (80.6)	73 (73.7)	88 (70.4)	0.215
Dyslipidemia	55 (41.0)	52 (48.1)	33 (33.3)	60 (48.0)	0.093
Diabetes	37 (27.6)	47 (43.5)	38 (38.4)	62 (49.6)	<0.01 [‡]
Cerebrovascular disease	24 (17.9)	23 (21.3)	8 (8.1)	19 (15.2)	0.062
CKD	91 (67.9)	87 (80.6)	72 (72.7)	105 (84.0)	0.025 [‡]
COPD	22 (16.4)	19 (17.6)	6 (6.1)	14 (11.2)	0.048 [†]
Current or ex-smoker	90 (67.2)	55 (50.9)	63 (63.6)	69 (55.2)	0.042 [†]
Atrial fibrillation	60 (44.8)	40 (37.0)	45 (45.5)	59 (47.2)	0.431
Myocardial infarction	34 (25.4)	24 (22.2)	13 (13.1)	35 (28.0)	0.052
Medication at discharge, %					
ACE-I or ARB	124 (92.5)	87 (80.6)	92 (92.9)	110 (88.0)	0.012 ^{†,‡}
Beta blocker	111 (82.8)	75 (69.4)	86 (86.9)	94 (75.2)	0.009 [†]
Aldosterone antagonist	72 (53.7)	44 (40.7)	55 (55.6)	52 (41.6)	0.040 [†]
Statin	53 (39.6)	48 (44.4)	39 (39.4)	51 (40.8)	0.863
Diuretic	107 (79.9)	80 (74.1)	81 (81.8)	104 (83.2)	0.351
Loop diuretic	104 (77.6)	78 (72.2)	77 (77.8)	97 (77.6)	0.726
Loop diuretic dose, mg	22.5±17.8	22.7±18.1	24.0±18.1	32.0±27.8	<0.01 [‡] ,# <0.05 [‡] ,#
Tolvaptan	8 (6.0)	12 (11.1)	4 (4.0)	16 (12.8)	0.057
Nondrug therapy					
Pacemaker	7 (5.2)	10 (9.3)	3 (3.0)	8 (6.4)	0.302

(Continued)

Table 1. (Continued)

	High-FEUN low-ePVS (n=134)	High-FEUN high-ePVS (n=108)	Low-FEUN low-ePVS (n=99)	Low-FEUN high-ePVS (n=125)	P value
ICD	3 (2.2)	3 (2.8)	4 (4.0)	2 (1.6)	0.711
CRT	1 (0.7)	2 (1.9)	0 (0)	4 (3.2)	0.228
Laboratory data					
Hemoglobin, g/dL	13.3 (12.4–14.5)	10.3 (9.6–11.0)	13.3 (12.4–14.4)	10.3 (9.7–11.0)	<0.001 ^{§,¶}
Hematocrit, %	41.1 (38.0–44.5)	32.4 (30.1–34.0)	40.5 (38.3–44.5)	32.2 (29.6–33.9)	<0.001 ^{§,¶}
ePVS, mL/g	4.4 (3.8–5.0)	6.5 (6.0–7.3)	4.5 (3.9–4.9)	6.6 (6.0–7.3)	<0.001 ^{§,¶}
Albumin, g/dL	3.8 (3.7–4.0)	3.4 (3.2–3.8)	3.9 (3.6–4.2)	3.6 (3.3–3.8)	<0.001 ^{§,¶}
BUN, mg/dL	19.5 (15.0–25.0)	24.0 (16.0–35.0)	26.0 (20.5–36.5)	39.0 (24.0–52.0)	<0.001 ^{§,¶}
Creatinine, mg/dL	1.02 (0.82–1.30)	1.21 (0.86–1.80)	1.05 (0.82–1.36)	1.42 (1.01–1.93)	<0.001 ^{§,¶}
BUN/creatinine	18.4 (15.7–23.2)	17.6 (13.7–22.6)	26.0 (22.3–31.7)	25.5 (21.4–32.7)	<0.001 ^{§,¶}
eGFR, mL/min per 1.73m ²	51.3 (38.6–62.8)	38.9 (23.9–56.1)	48.9 (36.0–62.4)	34.5 (23.5–48.5)	<0.001 ^{§,¶}
Cystatin C, mg/L	1.33 (1.07–1.72)	1.80 (1.37–2.54)	1.47 (1.18–1.85)	2.08 (1.49–2.84)	<0.001 ^{§,¶}
Serum sodium, mEq/L	139 (137–141)	139 (136–141)	139 (136–141)	138 (135–140)	0.136
Serum potassium, mEq/L	4.2 (3.9–4.6)	4.3 (4.0–4.6)	4.2 (3.8–4.7)	4.3 (4.0–4.6)	0.702
BNP, pg/mL	259 (135–438)	328 (161–577)	203 (124–380)	242 (129–529)	<0.05 [†]
Renin, ng/ml per h	3.8 (1.4–9.5)	1.9 (0.9–6.7)	5.9 (2.4–15.5)	5.4 (1.5–13.8)	<0.001 [†]
Aldosterone, pg/mL	136.3 (88.9–200.3)	81.6 (61.6–133.8)	109.3 (84.3–162.5)	87.9 (63.2–123.9)	<0.001 [§]
AVP, pg/mL*	2.3 (1.4–3.2)	1.9 (1.1–3.6)	4.0 (2.3–5.8)	2.4 (1.4–4.1)	<0.001 [†]
Urine sodium, mEq/L	67 (50–81)	65 (44–83)	72 (54–90)	67 (49–81)	0.143
Urine potassium, mEq/L	23 (17–28)	15 (12–22)	24 (20–33)	18 (14–27)	<0.001 ^{†,§}
FENa, %	0.72 (0.53–1.10)	1.26 (0.85–1.92)	0.63 (0.42–1.20)	1.14 (0.67–2.07)	<0.01 [†]
FEUN, %	42.0 (37.8–46.9)	42.1 (38.4–45.9)	29.0 (25.7–32.6)	28.2 (23.9–31.6)	<0.001 ^{†,§,¶}

P value refers to comparisons of the means, median, or proportions among the groups by the 1-way ANOVA, Kruskal-Wallis, and Pearson Chi-square tests with Bonferroni post hoc analysis. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AVP, arginine vasopressin; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ePVS, estimated plasma volume status; FENa, fractional excretion of sodium; FEUN, fractional excretion of urea nitrogen; HR, heart rate; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; and SBP, systolic blood pressure.

Values are n (%) or median [interquartile range]. The body mass index is the weight in kilograms divided by the square of the height in meters.

*Data on arginine vasopressin were available for 246 patients (high-FEUN/low-ePVS: 116 patients, high-FEUN/high-ePVS: 75 patients, low-FEUN/low-ePVS: 71 patients, low-FEUN/high-ePVS: 81 patients).

[†]High-FEUN/low-ePVS vs high-FEUN/high-ePVS.

[‡]High-FEUN/low-ePVS vs low-FEUN/low-ePVS.

[§]High-FEUN/low-ePVS vs low-FEUN/high-ePVS.

[¶]High-FEUN/high-ePVS vs low-FEUN/low-ePVS.

^{||}High-FEUN/high-ePVS vs low-FEUN/high-ePVS.

^{|||}Low-FEUN/low-ePVS vs low-FEUN/high-ePVS.

Table 2. Echocardiographic Data at Discharge in the 4 Groups

	High-FEUN low-ePVS (n=134)	High-FEUN high-ePVS (n=108)	Low-FEUN low-ePVS (n=99)	Low-FEUN high-ePVS (n=125)	P value
IVS, mm	10 (9–12)	11 (9–12)	10 (9–12)	10 (9–12)	0.848
LVPW, mm	10 (9–11)	10 (9–11)	10 (9–12)	10 (9–12)	0.635
AOD, mm	32 (29–34)	31 (29–33)	31 (29–34)	31 (29–34)	0.635
LAD, mm	44 (38–48)	43 (40–46)	42 (38–47)	44 (40–50)	0.102
LVEDD, mm	54 (48–62)	50 (45–56)	52 (47–59)	51 (45–57)	<0.01* <0.05‡
LVESD, mm	44 (34–53)	36 (30–44)	41 (34–48)	36 (29–46)	<0.001* <0.01‡ <0.05\$
LVEDV, mL	140 (102–191)	122 (97–146)	104 (83–136)	104 (70–137)	<0.001‡‡ <0.05*†
LVEDVi, mL/m ²	96.7 (73.1–116.0)	84.5 (68.8–106.9)	69.2 (55.8–90.2)	72.3 (51.5–96.4)	<0.001†‡ <0.01\$†
LVESV, mL	83 (47–125)	55 (35–88)	60 (40–95)	52 (29–82)	<0.001† <0.01* <0.05†
LVESVi, mL/m ²	55.3 (32.3–77.7)	39.3 (23.6–61.8)	40.3 (28.1–59.6)	34.5 (20.6–57.5)	<0.001† <0.05*†
Valvular regurgitation					
MR severity grade	2.0±1.1	1.9±1.0	1.9±1.0	2.1±1.0	0.470
AR severity grade	1.0±1.1	1.1±1.0	0.9±1.0	1.1±1.1	0.449
TR severity grade	1.6±0.8	1.8±0.9	1.6±0.9	1.9±1.0	<0.05†
TRPG, mmHg	22 (16–30)	27 (21–33)	22 (17–29)	27 (21–36)	<0.001† <0.01‡\$
E/A	0.90 (0.66–1.37)	0.73 (0.60–1.20)	0.80 (0.60–1.10)	0.80 (0.66–1.20)	0.348
E/e'	15.4 (12.5–19.0)	18.8 (12.7–24.6)	15.2 (11.5–20.0)	17.8 (13.5–22.7)	<0.05\$†
e'	4.6 (3.6–5.7)	4.2 (3.2–5.4)	4.6 (3.5–6.0)	4.1 (3.3–5.3)	0.205
DCT, ms	207 (163–248)	224 (180–263)	199 (175–236)	219 (174–262)	0.117
LVEF, %	39 (29–52)	53 (39–64)	41 (32–50)	48 (36–64)	<0.001* <0.01‡\$ <0.05†
Stroke volume, ml	57 (45–70)	60 (49–72)	42 (33–51)	47 (36–61)	<0.001†‡\$† <0.01‡
SVI, mL/m ²	36.6 (29.5–43.9)	41.2 (35.2–48.5)	27.9 (22.7–32.0)	32.0 (25.6–43.3)	<0.001‡\$† <0.01*†
Heart rate at echocardiography	77 (66–90)	71 (63–79)	65 (56–72)	62 (55–70)	<0.001†‡† <0.01*‡
Cardiac output, L/min	4.33 (3.40–5.21)	4.08 (3.32–4.96)	2.60 (2.12–3.29)	2.85 (2.13–3.99)	<0.001†‡\$†

(Continued)

Table 2. (Continued)

	High-FEUN low-ePVS (n=134)	High-FEUN high-ePVS (n=108)	Low-FEUN low-ePVS (n=99)	Low-FEUN high-ePVS (n=125)	P value
Cardiac index, L/min/m ²	2.73 (2.17–3.57)	2.84 (2.40–3.35)	1.73 (1.41–2.17)	1.99 (1.54–2.65)	<0.001 ^{†,‡,§,¶}
RVDd, mm	35 (32–40)	34 (32–37)	34 (31–38)	33 (29–37)	0.059
Maximum IVC diameter, mm	14.9±4.1	15.1±4.6	14.4±4.2	15.5±5.6	0.400
IVC collapsibility index	0.46±0.11	0.48±0.13	0.46±0.14	0.49±0.13	0.282
sPAP, mmHg	27 (21–34)	32 (25–39)	27 (20–33)	33 (25–42)	<0.001 [†] <0.01 [‡] <0.05 [§]

P value refers to comparisons of the means or median among the groups by 1-way ANOVA and Kruskal–Wallis tests with Bonferroni post hoc analysis. AOD, aorta diameter; AR, aortic regurgitation; DCT, deceleration time; e', early diastolic mitral annular velocity; E/A, early mitral inflow velocity; E/e', early mitral inflow velocity to early diastolic mitral annular velocity; IVC, inferior vena cava; IVS, interventricular septum; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESVi, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVPW, left ventricular posterior wall; MR, mitral regurgitation; RVDd, right ventricular diastolic diameter; sPAP, systolic pulmonary artery pressure; SVI, stroke volume index; TR, tricuspid regurgitation; and TRPG, tricuspid regurgitation pressure gradient.

[†]High-FEUN/low-ePVS vs high-FEUN/high-ePVS.

[‡]High-FEUN/low-ePVS vs low-FEUN/low-ePVS.

[§]High-FEUN/low-ePVS vs low-FEUN/high-ePVS.

[¶]High-FEUN/high-ePVS vs low-FEUN/low-ePVS.

^{‡‡}High-FEUN/high-ePVS vs low-FEUN/high-ePVS.

^{§§}Low-FEUN/low-ePVS vs low-FEUN/high-ePVS.

In the echocardiographic parameters, the levels of the left ventricular end-diastolic diameter and left ventricular end-systolic diameter in the high-FEUN/low-ePVS group were significantly higher compared with those of the high-FEUN/high-ePVS and low-FEUN/high-ePVS groups. The levels of the left ventricular end-diastolic volume and left ventricular end-systolic volume in the high-FEUN/low-ePVS group were significantly higher compared with those of the other 3 groups. The levels of transtricuspid pressure gradient, early mitral inflow velocity to early diastolic mitral annular velocity (E/e'), and systolic pulmonary artery pressure in the high-FEUN/high-ePVS and low-FEUN/high-ePVS groups were significantly higher compared with those of the low-FEUN/low-ePVS group. The levels of left ventricular ejection fraction in the high-FEUN/high-ePVS and low-FEUN/high-ePVS groups was significantly higher compared with that of the high-FEUN/low-ePVS and low-FEUN/low-ePVS groups. The levels of stroke volume, cardiac output, and cardiac index in the high-FEUN/low-ePVS and high-FEUN/high-ePVS groups were significantly higher compared with those of the low-FEUN/low-ePVS and low-FEUN/high-ePVS groups (Table 2).

Clinical Outcomes

During a median follow-up period of 28.1 months, there were 173 all-cause deaths (37.1%), 83 cardiovascular deaths (17.8%), and 121 HF readmissions (26.0%). The incidences of both all-cause deaths and HF readmissions were the highest in the low-FEUN/high-ePVS group (58.4% [n=73] and 34.4% [n=43], respectively) and the lowest in the high-FEUN/low-ePVS group (17.1% [n=23] and 18.7% [n=25], respectively) (Table 3).

The Kaplan–Meier curve analyses showed that the low-FEUN/high-ePVS group had much higher rates of all-cause death (log-rank test, $P<0.001$) and composite end points (log-rank test, $P<0.001$) than the high-FEUN/low-ePVS and low-FEUN/low-ePVS groups, and HF readmissions (log-rank test, $P=0.003$) than the high-FEUN/low-ePVS group overall (Figure 3A through 3C). In patients with eGFR<60 mL/min per 1.73 m², the Kaplan–Meier curve analyses showed that the low-FEUN/high-ePVS group had much higher rates of all-cause death than the other 3 groups (log-rank test with Bonferroni post hoc analysis, versus the high-FEUN/low-ePVS group: $P<0.001$, versus the low-FEUN/low-ePVS group: $P=0.002$, versus the high-FEUN/high-ePVS group: $P=0.032$) (Figure S1–S2A). In patients with eGFR ≥60 mL/min per 1.73 m², the Kaplan–Meier curve analyses showed that there were no significant differences in the all-cause death between the low-FEUN/high-ePVS group and the other 3 groups (Figure S1–S2B).

A competing-risk analysis was performed to assess the effect of death as a competing risk, and a similar result was observed (Gray test, $P=0.022$) (Figure S2).

Table 3. Incidence of All-Cause Death and HF Readmission After Discharge in the 4 Groups

	High-FEUN low-ePVS (n=134)	High-FEUN high-ePVS (n=108)	Low-FEUN low-ePVS (n=99)	Low-FEUN high-ePVS (n=125)	P value
All-cause death, %	23 (17.1)	47 (43.6)	30 (30.3)	73 (58.4)	<0.001 ^{*,†,§}
Cardiovascular death, %	11 (8.2)	30 (27.8)	14 (14.1)	28 (22.4)	<0.001 [*] <0.05 [†]
Infection, %	2 (1.5)	8 (7.4)	3 (3.0)	14 (11.2)	<0.05 [†]
Malignancy, %	3 (2.2)	6 (5.6)	5 (5.1)	10 (8.0)	0.196
Others, %	7 (5.2)	3 (2.8)	8 (8.1)	21 (16.8)	<0.01 [‡] <0.05 [†]
HF readmission, %	25 (18.7)	32 (29.6)	21 (21.2)	43 (34.4)	<0.05 [†]

P value refers to comparisons of the proportions among the groups by the Pearson Chi-square tests with Bonferroni post hoc analysis. e, early diastolic mitral annular velocity; E/A, early mitral inflow velocity; E/e', early mitral inflow velocity to early diastolic mitral annular velocity; ePVS indicates estimated plasma volume status; FEUN, fractional excretion of urea nitrogen; and HF, heart failure.

*High-FEUN/low-ePVS vs high-FEUN/high-ePVS.

†High-FEUN/low-ePVS vs low-FEUN/high-ePVS.

‡High-FEUN/high-ePVS vs low-FEUN/high-ePVS.

§Low-FEUN/low-ePVS vs low-FEUN/high-ePVS.

In the univariate Cox regression analyses, the low-FEUN/low-ePVS, high-FEUN/high-ePVS, and low-FEUN/high-ePVS groups were associated with a higher all-cause mortality than the high-FEUN/low-ePVS group (Table 4). In the multivariable Cox regression models adjusted for established prognostic factors for ADHF (age, sex, New York Heart Association functional classification, diabetes, BNP, left ventricular ejection fraction, BUN, creatinine, serum sodium, systolic blood pressure at discharge, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and aldosterone antagonists at discharge), the low-FEUN/low-ePVS, high-FEUN/high-ePVS, and low-FEUN/high-ePVS groups were associated with a higher all-cause mortality than the high-FEUN/low-ePVS group (HR, 1.89 [95% CI, 1.07–3.33; $P=0.029$]; HR, 2.51 [95% CI, 1.46–4.26; $P<0.001$]; HR, 2.92 [95% CI, 1.73–4.92; $P<0.001$], respectively) (Table 4).

Similarly, the low-FEUN/high-ePVS group was associated with the composite outcome and HF readmissions (Table 4).

DISCUSSION

This study investigated the effect of the 4 hemodynamic categories according to the high and low FEUN and ePVS values at discharge and long-term prognosis in patients with ADHF. The main findings of the present study were that (1) the all-cause mortality was lower in the high-FEUN/low-ePVS group than in any other groups, and (2) low-FEUN/high-ePVS group was associated independently with higher HF readmissions than the high-FEUN/low-ePVS group. To the best of our knowledge, this was the first report that investigated the use of the combined assessment of the FEUN and ePVS values at discharge to predict the long-term prognosis of patients with ADHF. These findings may be applied to clinical practice.

In patients with ADHF, it has been shown that persistent congestion before discharge is associated with a higher risk of HF readmission and mortality.²¹ Furthermore, low cardiac output attributable to primary cardiac dysfunction has also been shown to lead to a life-threatening condition of tissue hypoperfusion, which can lead to multiple organ failure and death.²² Previous studies have shown that a classification based on congestion and perfusion status provides clinically relevant information for targeted strategies that may improve the outcomes.^{21,23}

The hemodynamic classification in HF was proposed originally by Forrester and Waters^{24,25} and then adapted clinically by Nohria et al.²⁶ The Forrester classification is easy for everyone to understand because it is based on objective values, such as pulmonary artery wedge pressure and cardiac index measured using the Swan-Ganz catheter; however, it has the disadvantage of requiring invasive procedures, whereas the Nohria-Stevenson classification uses the 4 hemodynamic profiles according to physical assessments and has the advantage that it can be assessed easily at the bedside for all patients. However, different clinicians may vary in their physical assessments. In addition, it is difficult to assess mild congestion or hypoperfusion that is not clinically apparent; therefore, it is used mainly in the worsening phase of HF and may not be suitable for use in the pre-discharge assessment.^{26,27}

In the present study, we focused on the ePVS that is associated with congestion¹² and the FEUN that is associated with renal perfusion in patients with ADHF.^{8,11} These indices are minimally invasive and do not vary in interpretation among clinicians because they are objective results that are measured using blood or urine tests. However, no studies have evaluated the association between the combined assessment of the FEUN and ePVS values at discharge and the long-term prognosis in patients with ADHF. In the present study, the

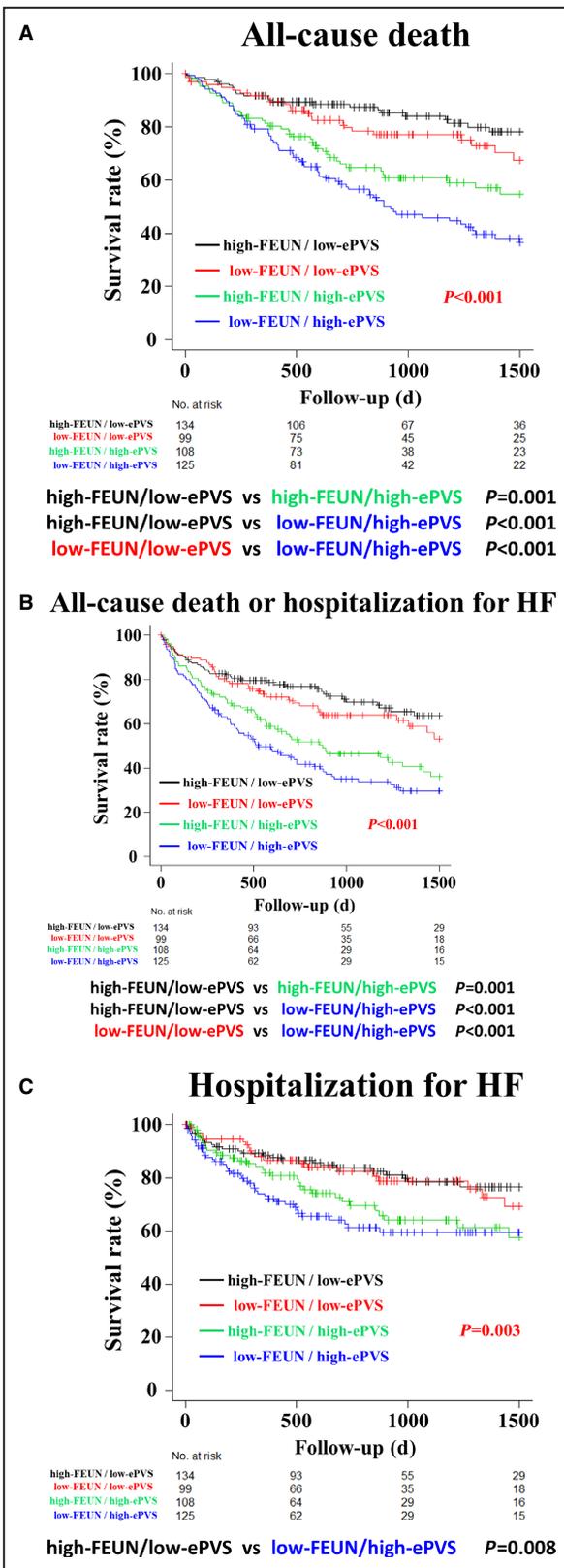


Figure 3. Kaplan–Meier analyses of the 4 hemodynamic profiles based on the combined assessment of FEUN and ePVS values at discharge for postdischarge all-cause mortality, composite end point, and heart failure readmission.

Kaplan–Meier curve analyses showed that the low-FEUN/high-ePVS group had much higher rates of all-cause death (log-rank test, $P<0.001$) and composite end points (log-rank test, $P<0.001$) than the high-FEUN/low-ePVS and low-FEUN/low-ePVS groups, and HF readmissions (log-rank test, $P=0.003$) than the high-FEUN/low-ePVS group in overall (A through C). ePVS indicates estimated plasma volume status; FEUN, fractional excretion of urea nitrogen; and HF, heart failure.

high-FEUN group. In short, these findings suggested that a high-ePVS value may represent an excessive congestive status, and a low-FEUN value may represent a hypoperfusion status. Therefore, in the present study, we categorized 4 hemodynamic profiles as follows: (1) high-FEUN/low-ePVS; (2) high-FEUN/high-ePVS; (3) low-FEUN/low-ePVS; and (4) low-FEUN/high-ePVS (Figure 1).

The Kaplan–Meier curves and the adjusted Cox proportional hazards regression model showed that the lowest rates of all-cause death were observed in the patients classified as having “high-FEUN/low-ePVS”. Based on this result, it is important to transfer the patients from the other 3 groups to the high-FEUN/low-ePVS group. Therefore, it is necessary to understand the status of each group correctly before considering treatment methods. In the present study, the BUN/creatinine ratio, plasma renin activity, and vasopressin levels as the indicators of hypoperfusion were significantly higher and the cardiac index was significantly lower in the low-FEUN/low-ePVS group compared with the high-FEUN/low-ePVS group. This suggested that the low-FEUN/low-ePVS profile may indicate hypoperfusion because of excessive dehydration. Therefore, in the low-FEUN/low-ePVS group, it may be necessary to reduce the use of diuretics to transfer the patients to the high-FEUN/low-ePVS profile. Moreover, the trans-tricuspid pressure gradient, E/e', and systolic pulmonary artery pressure as indicators of congestion were significantly higher in the high-FEUN/high-ePVS group compared with the high-FEUN/low-ePVS group. This suggested that the high-FEUN/high-ePVS profile may indicate residual clinical congestion. Therefore, in the high-FEUN/high-ePVS group, we should remove residual congestion more aggressively to transfer the patients to the high-FEUN/low-ePVS profile. Furthermore, in the present study, the BUN/creatinine ratio, trans-tricuspid pressure gradient, E/e', and systolic pulmonary artery pressure values were significantly higher, and the cardiac index was significantly lower in the low-FEUN/high-ePVS group compared with the high-FEUN/low-ePVS group. These findings suggested that the low-FEUN/high-ePVS profile may represent a combination of hypoperfusion and congestion, that is, the

BNP level, transtricuspid pressure gradient, and E/e' were significantly higher in the high-ePVS group than in the low-ePVS group, and the cardiac index was significantly lower in the low-FEUN group than in the

Table 4. Independent Predictors of All-Cause Death, All-Cause Death or HF Readmission, and HF Readmission After Discharge

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
All-cause death				
High-FEUN/low-ePVS	1 (reference)		1 (reference)	
Low-FEUN/low-ePVS	1.88 (1.09–3.24)	0.023	1.89 (1.07–3.33)	0.029
High-FEUN/high-ePVS	3.00 (1.82–4.94)	<0.001	2.51 (1.46–4.26)	<0.001
Low-FEUN/high-ePVS	4.16 (2.60–6.65)	<0.001	2.92 (1.73–4.92)	<0.001
All-cause death or HF readmission				
High-FEUN/low-ePVS	1 (reference)		1 (reference)	
Low-FEUN/low-ePVS	1.40 (0.90–2.18)	0.132	1.47 (0.93–2.33)	0.102
High-FEUN/high-ePVS	2.22 (1.49–3.31)	<0.001	1.92 (1.25–2.94)	0.003
Low-FEUN/high-ePVS	2.94 (2.02–4.29)	<0.001	2.15 (1.41–3.28)	<0.001
HF readmission				
High-FEUN/low-ePVS	1 (reference)		1 (reference)	
Low-FEUN/low-ePVS	1.21 (0.67–2.15)	0.527	1.29 (0.70–2.36)	0.410
High-FEUN/high-ePVS	1.85 (1.10–3.13)	0.021	1.58 (0.90–2.77)	0.112
Low-FEUN/high-ePVS	2.34 (1.43–3.83)	<0.001	1.79 (1.02–3.14)	0.043

Univariate and multivariate Cox proportional hazard analyses were performed among groups adjusted for age, sex, the New York Heart Association functional classification, diabetes, BNP, left ventricular ejection fraction at discharge, BUN, creatinine, serum sodium, systolic blood pressure at discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, beta-blockers, and aldosterone antagonist. BNP indicates brain natriuretic peptide; BUN, blood urea nitrogen; ePVS, estimated plasma volume status; FEUN, fractional excretion of urea nitrogen; HF, heart failure; HR, hazard ratio; and SBP, systolic blood pressure.

state of Forester IV group. To improve the outcomes of patients who belong to this profile, intensive treatment such as medical therapies that include not only cardioprotective and vasoactive agents, but also invasive procedures such as mechanical circulatory support, may be necessary.

Subgroup analyses of all-cause death showed that the low-FEUN/high-ePVS group had much higher rates of all-cause death than the high-FEUN/high-ePVS group in patients with eGFR <60 mL/min per 1.73 m², but not in patients with eGFR ≥60 mL/min per 1.73 m². These results were similar to the previous study showing that FEUN was more useful in patients with eGFR <60 mL/min per 1.73 m².¹¹ However, given the small number of patients with eGFR ≥60 mL/min per 1.73 m² in the present study, it is not yet clear whether the differences of the renal function affect the combined assessment of the FEUN and ePVS values. Therefore, generalizing our results to all patients with ADHF might be limited.

The hemodynamic classification using the combined assessment of the FEUN and ePVS values at discharge will lead to an understanding of the status of the patients with HF, before treatment methods are considered. However, the impact of the 4 hemodynamic categories according to the combined assessment of the FEUN and ePVS values should be further evaluated in prospective studies.

This study had several potential limitations that should be acknowledged. First, this was a single-center

study with a relatively small number of patients with ADHF and it has not been validated in an independent cohort. Second, we excluded a large number of patients with missing data on FEUN and ePVS values, patients who died in-hospital because we targeted postdischarge prognosis, and patients on hemodialysis because we used urinary data. These aspects of the study could be both selection and sampling bias. Third, we could not directly evaluate the association between the combined assessment of the FEUN and ePVS values at discharge and the invasive hemodynamic measurements, because we did not routinely perform right heart catheterization using the Swan-Ganz catheter at discharge. Finally, in the present study, we only included stable patients with ADHF at discharge because both FEUN and ePVS are clearly dynamic through the course of cardiorenal illness. Therefore, we need to be careful in our interpretation if the combined assessment of the FEUN and ePVS values is used in the unstable general condition, such as immediately after HF hospitalization. This new classification might be more appropriate for predischarged patients with eGFR <60 mL/min per 1.73 m² than those with preserved GFR.

CONCLUSIONS

Classifying patients with ADHF according to the combined assessment of the FEUN and ePVS values at discharge enabled the identification of significant

differences in all-cause mortality and HF readmissions among the profiles. The new classification of the 4 hemodynamic profiles using the FEUN and ePVS values may play an important role in the implementation of targeted strategies to improve outcomes.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S2

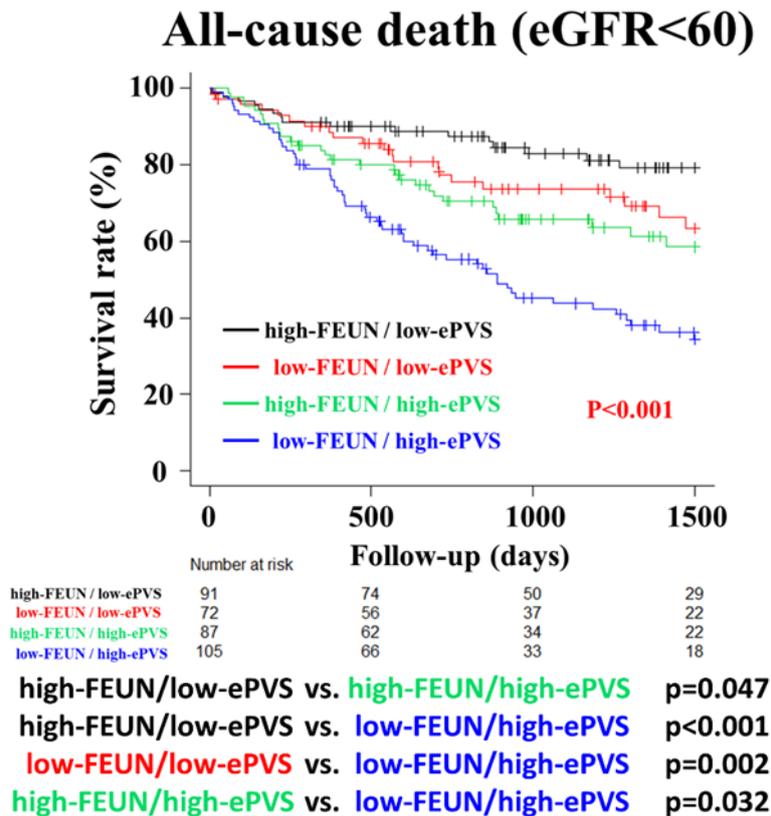
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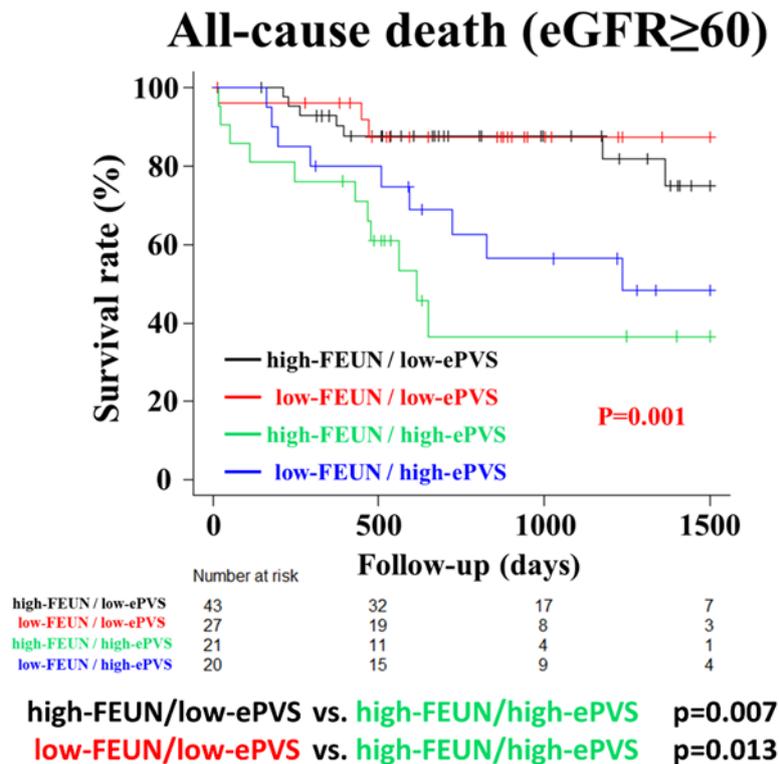
SUPPLEMENTAL MATERIAL

Figure S1A. Kaplan–Meier analyses of the four hemodynamic profiles based on the combined assessment of FEUN and ePVS values at discharge for post-discharge all-cause mortality in patients with eGFR < 60 mL/min/1.73 m².



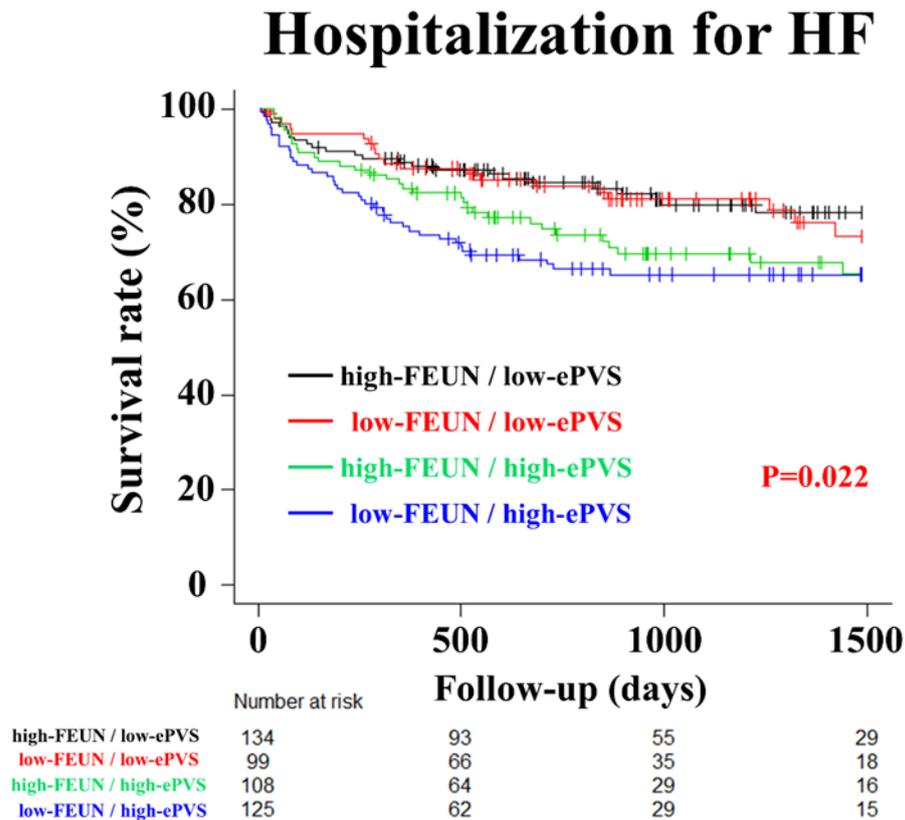
In patients with eGFR<60 mL/min/1.73 m², the Kaplan–Meier curve analyses showed that the low-FEUN/high-ePVS group had much higher rates of all-cause death than the other three groups (log-rank test with Bonferroni post hoc analysis, vs. the high-FEUN/low-ePVS group : $P < 0.001$, vs. the low-FEUN/low-ePVS group : $P = 0.002$, vs. the high-FEUN/high-ePVS group : $P = 0.032$).

Figure S1B. Kaplan–Meier analyses of the four hemodynamic profiles based on the combined assessment of FEUN and ePVS values at discharge for post-discharge all-cause mortality in patients with $eGFR \geq 60$ mL/min/1.73 m².



In patients with $eGFR \geq 60$ mL/min/1.73 m², the Kaplan–Meier curve analyses showed that there were no significant differences in the all-cause death between the low-FEUN/high-ePVS group and the other three groups.

Figure S2. Kaplan–Meier analyses of the four hemodynamic profiles based on the combined assessment of FEUN and ePVS values at discharge for HF readmission without death (Competing-risk analysis).



A competing-risk analysis was performed to assess the effect of death as a competing risk and similar result was observed (Gray test, $P=0.022$) (Figure S1).

Abbreviations: FEUN, fractional excretion of urea nitrogen; ePVS, estimated plasma volume status; HF, heart failure