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ORIGINAL RESEARCH

# Prognostic Value of Fractional Excretion of Urea Nitrogen at Discharge in Acute Decompensated Heart Failure

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**BACKGROUND:** Maintaining euvolemia is crucial for improving prognosis in acute decompensated heart failure (ADHF). Although fractional excretion of urea nitrogen (FEUN) is used as a body fluid volume index in patients with acute kidney injury, the clinical impact of FEUN in patients with ADHF remains unclear. This study aimed to investigate whether FEUN can determine the long-term prognosis in patients with ADHF.

**METHODS AND RESULTS:** We retrospectively identified 466 patients with ADHF who had FEUN measured at discharge between April 2011 and December 2018. The primary endpoint was post-discharge all-cause death. Patients were divided into two groups according to a FEUN cut-off value of 35%, commonly used in pre-renal failure. The FEUN <35% (low-FEUN) group included 224 patients (48.1%), and the all-cause mortality rate for the total cohort was 37.1%. The log-rank test revealed that the low-FEUN group had a significantly higher rate of all-cause death compared to the FEUN equal to or greater than 35% (high-FEUN) group ($P$<0.001). Multivariate Cox proportional hazards model analysis revealed that low-FEUN was associated with post-discharge all-cause death, independently of other heart failure risk factors (hazard ratio, 1.467; 95% CI, 1.030–2.088, $P$=0.033). The risk of low-FEUN compared to high-FEUN in post-discharge all-cause death was consistent across all subgroups; however, the effects tended to be modified by renal function (threshold: 60 mL/min/1.73 m$^2$, interaction $P$=0.069).

**CONCLUSIONS:** Our study suggests that FEUN may be a novel surrogate marker of volume status in patients with ADHF requiring diuretics.

**Key Words:** diuretic ■ fractional excretion of urea nitrogen ■ heart failure ■ prognosis



Congestion due to volume overload is one of the main causes of hospitalization in patients with acute decompensated heart failure (ADHF) and is an important therapeutic target. Treatment with diuretics is the mainstay of therapy in the management of fluid congestion.[1] The correction of volume overload in patients with ADHF is a double-edged sword as correcting volume overload to improve congestion in patients with ADHF has been shown to have favorable effects on symptoms, re-hospitalization rate, and survival;[2–6] however, overcorrection and excess fluid removal with diuretics have been shown to impair renal function and increase mortality risk in these patients.[7–10] It is crucial to maintain the euvolemic state by controlling the dose of diuretics appropriately using a clinically useful surrogate marker of volume status to improve the long-term prognosis of ADHF. However, clinically useful surrogate markers for this purpose are lacking.

The fractional excretion of sodium (FENa) is frequently used to identify the causes of acute kidney

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## CLINICAL PERSPECTIVE

### What Is New?

- Fractional excretion of urea nitrogen (FEUN) has been used as an index of body fluid volume in the setting of acute kidney injury using diuretics, however the clinical impact of FEUN in patients with acute decompensated heart failure (ADHF) has not been shown.
- We provide new insight into the adjustment of diuretic therapy and discharge timing in patients with ADHF based on imprecise volume status markers such as symptom improvement, physical and laboratory examinations, urine output, and weight loss.
- We show that low-FEUN was independently associated with poor prognosis and may be a novel surrogate marker of volume status in patients with ADHF.

### What Are the Clinical Implications?

- Our study presents a new possible method of monitoring the crucial euvolemic status of patients with heart failure that is both cost-effective and non-invasive and could be performed even in patients on diuretic therapy.
- Using FEUN as a marker 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 low-FEUN at discharge and poor long-term prognosis.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ADHF** | acute decompensated heart failure |
| **Beta2MG** | beta 2 microglobulin |
| **BUN** | blood urea nitrogen |
| **eGFR** | estimated glomerular filtration rate |
| **FEUN** | fractional excretion of urea nitrogen |
| **SBP** | systolic blood pressure |

injury.[11,12] However, FENa should be used with caution in patients undergoing diuretic therapy since it can be affected by the renal sodium handling in tubular function.[13] Previous studies have demonstrated that urea transport does not occur directly via sodium transporters, and the effect of diuretics on the fractional excretion of urea nitrogen (FEUN) is lower than in FENa.[12,14,15] As a result, FEUN has been used as an alternative diagnostic approach and an index of body fluid volume while using diuretics. Although FEUN <35% is commonly used as an indicator of pre-renal failure in patients with acute kidney injury, the clinical impact of FEUN in patients with ADHF regardless of renal function has never been examined.[11,12]

The present study aimed to investigate whether FEUN used as an index of body fluid volume can predict long-term prognosis in ADHF, and the usefulness of FEUN 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 Registry and Analyses for Heart Failure study 4 (NARA-HF study 4) is a prospective cohort study comprised of 1012 consecutive patients emergently admitted to our department or the coronary care unit at our hospital with documented ADHF [either acute new-onset or acute-on-chronic heart failure (HF)] between April 2011 and December 2018. The diagnosis of HF was based on the Framingham Criteria.[16] Patients with acute myocardial infarction, acute myocarditis, or acute HF with acute pulmonary embolism were excluded. Our study excluded patients who died during hospitalization, those treated with dialysis, or patients whose urine urea nitrogen was not measured at discharge. We investigated the impact of FEUN on the prognosis of ADHF in 466 patients. The enrolled patients were divided into groups based on FEUN <35% (low-FEUN) and FEUN equal to or greater than 35% (high-FEUN) at discharge (Figure 1). The study protocol

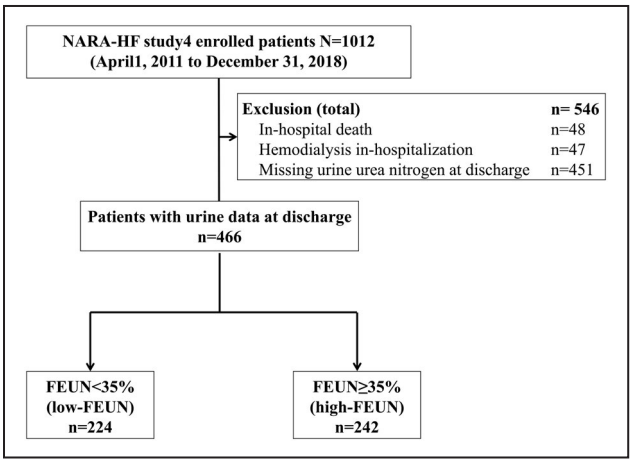


**Figure 1. Flow chart of the study cohort.**
FEUN indicates fractional excretion of urea nitrogen; and NARA-HF Study 4, Nara Registry and Analyses for Heart Failure Study 4.

was approved by the ethics committee at Nara Medical University (approval number 624), and written informed consent was obtained from all patients according to the Declaration of Helsinki ethical principles for medical research involving human subjects.

## Data Collection and Definitions

Laboratory parameters including hemoglobin (Hb), albumin, blood urea nitrogen (BUN), creatinine (Cr), estimated glomerular filtration rate (eGFR) by the modification of diet in renal disease method, cystatin C, serum electrolytes (sodium, potassium, chloride), B-type natriuretic peptide (BNP), renin, aldosterone, serum osmolality, urine osmolality, urine electrolytes (sodium, potassium, chloride), urine N-acetyl-beta-glucosaminidase, urine beta 2 microglobulin (beta2MG), and urine urea nitrogen (in collection urine samples) were measured in all patients at discharge. Vital signs, including heart rate and systolic blood pressure (SBP) at discharge, were recorded.

FEUN was calculated according to its well-defined formula:[11,12,17]

$$\text{FEUN} = \left[\text{urinary urea} \times \text{plasma creatinine}\right] / \left[\text{plasma urea} \times \text{urinary creatinine}\right] \times 100$$

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 equivalent to 20 mg of furosemide.[18,19]

## Outcomes

The primary endpoint was post-discharge all-cause death in a time-to-event analysis. The secondary endpoint was the first occurrence of readmission for worsening HF in a time-to-event analysis. The status of all patients was surveyed, and information on outcomes was obtained from patient medical records and the participating cardiologists. When this information was unavailable in the medical records, clinicians sent letters to patients' homes or telephoned the patients or their families to collect these data.

## Statistical Analysis

Data are expressed as mean and standard deviation (SD) for normally distributed data, and median with interquartile range for non-normally distributed data. The Kolmogorov-Smirnov test was performed for normality. Categorical data were expressed as numbers and percentages. The difference between the two groups was tested with Student's *t*-test for normally distributed variables and the Mann-Whitney *U* test for non-normally distributed variables. The Chi-square test was used to compare categorical variables.

First, to evaluate the association between the FEUN category and outcomes, Kaplan-Meier analyses with the log-rank test, and univariate and multivariate Cox proportional hazard analysis was performed using the value (35%) to identify the causes of acute kidney injury as a cut-off point. In the multivariate analysis, three models with the following covariates were used; model 1: adjusted for established predictive factors for ADHF including the New York Heart Association (NYHA) functional classification, age, diabetes mellitus, Hb, BNP, and left ventricular ejection fraction (LVEF) at discharge; model 2: adjusted for all factors in model 1 and sex, BUN, Cr, serum sodium, and SBP at discharge; and model 3: adjusted for all factors in model 2 and the medications at discharge associated with all-cause mortality in the previous study,[20] including angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, beta-blockers, aldosterone antagonist, and loop diuretics doses. 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 heart failure re-hospitalization.

Second, subgroup analyses were conducted by following groups: age (<75 years, equal to or older than 75 years), sex (male, female), Hb (<12 g/dL, equal to or greater than 12 g/dL), BNP (<200 pg/mL, equal to or greater than 200 pg/mL), LVEF (<50%, equal to or greater than 50%), BUN (<25 mg/dL, equal to or greater than 25 mg/dL), eGFR (<60 mL/min/1.73 $m^2$, equal to or greater than 60 mL/min/1.73 $m^2$), and new-onset HF.

Finally, multivariate logistic regression was performed to examine the factors associated with the low-FEUN. A value of $P<0.05$ was considered significant for individual comparisons. All statistical analyses were performed using R software version.3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

# RESULTS

## Patient Characteristics

Among them, the low-FEUN group included 224 patients (48.1%) and the high-FEUN group included 242 patients (51.9%). The median age was 76 (67–83) years, and 55.8% of patients were males (Table 1). There were no significant differences in age, sex, SBP, heart rate, and medication use at discharge between groups. The proportion of patients with diabetes mellitus in the low-FEUN group was significantly higher than in the high-FEUN group. Loop diuretic dose was higher in the low-FEUN group than in the high-FEUN group. Among the laboratory parameters, BUN, Cr, delta Cr, BUN/Cr ratio, delta BUN/Cr ratio, cystatin C, renin, and arginine vasopressin were significantly higher in the low-FEUN group than in the high-FEUN group. eGFR and BNP

**Table 1. Baseline Characteristics**

| | All patients (N=466) | Low-FEUN (n=224) | High-FEUN (n=242) | *P* Value |
|---|---|---|---|---|
| Age, y | 76 (67 to 83) | 77 (69 to 84) | 76 (65 to 82) | 0.108 |
| Male sex, % | 260 (55.8) | 120 (53.6) | 140 (57.9) | 0.403 |
| BMI, kg/m$^2$ | 20.9 (18.3 to 23.6) | 20.8 (18.1 to 23.3) | 20.9 (18.7 to 23.6) | 0.479 |
| delta BW, %* | –7.9 (4.3 to 13.2) | –8.8 (5.3 to 13.3) | –7.3 (3.7 to 12.6) | 0.047 |
| SBP, mmHg | 108 (98 to 120) | 108 (98 to 120) | 108 (98 to 122) | 0.562 |
| DBP, mmHg | 60 (54 to 68) | 60 (52 to 66) | 62 (55 to 68) | 0.010 |
| HR, beats/min | 70 (62 to 80) | 70 (63 to 81) | 70 (62 to 78) | 0.384 |
| NYHA at discharge, % | | | | 0.339 |
| 1 | 153 (32.8) | 72 (32.1) | 81 (33.5) | |
| 2 | 297 (63.7) | 141 (62.9) | 156 (64.5) | |
| 3 | 15 (3.2) | 10 (4.5) | 5 (2.1) | |
| 4 | 1 (0.2) | 1 (0.4) | 0 (0) | |
| Medical history, % | | | | |
| Hypertension | 341 (73.2) | 160 (71.4) | 181 (74.8) | 0.475 |
| Dyslipidemia | 200 (42.9) | 93 (41.5) | 107 (44.2) | 0.621 |
| Diabetes mellitus | 184 (39.5) | 100 (44.6) | 84 (34.7) | 0.036 |
| Cerebrovascular disease | 74 (15.9) | 28 (12.5) | 46 (19.0) | 0.073 |
| COPD | 61 (13.1) | 21 (9.4) | 40 (16.5) | 0.032 |
| Current or ex-smoker | 277 (59.4) | 132 (58.9) | 145 (59.9) | 0.902 |
| Atrial fibrillation | 204 (43.8) | 105 (46.9) | 99 (40.9) | 0.229 |
| Myocardial infarction | 106 (22.8) | 47 (21.0) | 59 (24.4) | 0.445 |
| PCI | 92 (19.7) | 38 (17.0) | 54 (22.3) | 0.183 |
| CABG | 20 (4.3) | 8 (3.6) | 12 (5.0) | 0.610 |
| Valvular surgery | 18 (3.9) | 10 (4.5) | 8 (3.3) | 0.683 |
| Medication at discharge, % | | | | |
| ACEI or ARB | 413 (88.6) | 201 (89.7) | 212 (87.6) | 0.564 |
| Beta blocker | 366 (78.5) | 179 (79.9) | 187 (77.3) | 0.562 |
| Aldosterone antagonist | 223 (47.9) | 107 (47.8) | 116 (47.9) | 1.000 |
| Statin | 191 (41.0) | 90 (40.2) | 101 (41.7) | 0.805 |
| Diuretic | 372 (79.8) | 185 (82.6) | 187 (77.3) | 0.189 |
| Loop diuretic | 356 (76.4) | 174 (77.7) | 182 (75.2) | 0.604 |
| Loop diuretic dose, mg | 25.4 ± 21.4 | 28.4 ± 24.2 | 22.7 ± 18.0 | 0.004 |
| Tolvaptan | 40 (8.6) | 20 (8.9) | 20 (8.3) | 0.928 |
| Aspirin | 168 (36.1) | 75 (33.5) | 93 (38.4) | 0.310 |
| Oral Anticoagulation | 215 (46.1) | 97 (43.3) | 118 (48.8) | 0.277 |
| Antiarrhythmic drug | 71 (15.2) | 29 (12.9) | 42 (17.4) | 0.232 |
| Diabetes mellitus drug | 139 (29.8) | 77 (34.4) | 62 (25.6) | 0.050 |
| Non-drug therapy | | | | |
| Pacemaker | 26 (5.6) | 12 (5.4) | 14 (5.8) | 0.960 |
| ICD | 7 (1.5) | 4 (1.8) | 3 (1.2) | |
| CRT | 11 (2.4) | 5 (2.2) | 6 (2.5) | |
| Laboratory data at discharge | | | | |
| Hb, g/dL | 11.6 (10.3 to 13.3) | 11.4 (10.2 to 13.0) | 11.9 (10.6 to 13.7) | 0.017 |
| Alb, g/dL | 3.7 (3.4 to 4.0) | 3.7 (3.4 to 4.0) | 3.7 (3.4 to 4.0) | 0.880 |
| BUN, mg/dL | 25.0 (18.0 to 38.0) | 31.5 (22.0 to 45.0) | 21.0 (15.3 to 29.0) | <0.001 |
| Cr, mg/dL | 1.14 (0.86 to 1.62) | 1.21 (0.89 to 1.67) | 1.08 (0.84 to 1.49) | 0.043 |
| delta Cr, % † | 7.3 (–7.2 to 23.8) | 13.0 (–0.8 to 31.8) | 2.3 (–11.3 to 17.3) | <0.001 |

(*Continued*)

**Table 1. Continued**

| | All patients (N=466) | Low-FEUN (n=224) | High-FEUN (n=242) | *P* Value |
|---|---|---|---|---|
| BUN/Cr | 22.1 (17.0 to 27.7) | 25.9 (21.9 to 32.4) | 18.1 (15.2 to 22.9) | <0.001 |
| delta BUN/Cr, % ‡ | 9.0 (–16.1 to 38.4) | 21.0 (–6.2 to 54.7) | 0.3 (–21.4 to 20.4) | <0.001 |
| eGFR, mL/min/1.73 $m^2$ | 44.2 (29.2 to 58.7) | 40.1 (27.5 to 55.7) | 47.4 (32.4 to 61.1) | 0.017 |
| Cystatin C, mg/L | 1.62 (1.21 to 2.21) | 1.79 (1.30 to 2.41) | 1.48 (1.16 to 1.99) | <0.001 |
| Serum sodium, mEq/L | 139 (136 to 141) | 138 (135 to 141) | 139 (137 to 141) | 0.088 |
| Serum potassium, mEq/L | 4.3 ± 0.5 | 4.3 ± 0.6 | 4.3 ± 0.5 | 0.938 |
| Serum chloride, mEq/L | 101 (98 to 104) | 100 (97 to 103) | 102 (99 to 104) | <0.001 |
| BNP, pg/mL | 259 (134 to 478) | 212 (124 to 444) | 281 (146 to 508) | 0.046 |
| delta BNP, %§ | –68.9 (45.5 to 82.2) | –68.7 (46.3 to 81.7) | –69.1 (45.3 to 82.6) | 0.816 |
| Renin, ng/mL/hr | 4.1 (1.4 to 11.8) | 5.7 (1.8 to 14.8) | 2.9 (1.0 to 9.1) | <0.001 |
| Aldosterone, pg/mL | 103.1 (70.8 to 158.9) | 97.0 (68.4 to 148.1) | 107.7 (72.5 to 173.0) | 0.088 |
| AVP, pg/mL‖ | 2.3 (1.2 to 4.0) | 2.9 (1.4 to 4.8) | 1.9 (1.1 to 3.2) | 0.007 |
| Serum osmolality, mOsm/kg·$H_2O$ | 287 ± 12 | 289 ± 12 | 285 ± 12 | <0.001 |
| Urine osmolality, mOsm/kg·$H_2O$ | 427 ± 166 | 439 ± 168 | 417 ± 163 | 0.174 |
| Urine sodium, mEq/L | 67 (49 to 83) | 69 (51 to 85) | 66 (48 to 81) | 0.300 |
| Urine potassium, mEq/L | 21 (15 to 27) | 22 (16 to 29) | 19 (14 to 26) | 0.001 |
| Urine chloride, mEq/L | 51 (36 to 69) | 54 (37 to 71) | 49 (36 to 68) | 0.130 |
| Urine NAG, U/L | 6.5 (4.2 to 9.8) | 7.1 (4.5 to 10.9) | 5.8 (3.7 to 8.7) | 0.011 |
| Urine beta2MG, μg/L | 114 (51 to 375) | 96 (50 to 291) | 120 (66 to 555) | 0.001 |
| FENa, % | 0.92 (0.55 to 1.50) | 0.91 (0.52 to 1.62) | 0.92 (0.60 to 1.44) | 0.598 |
| FEUN, % | 35.3 (28.8 to 42.2) | 28.6 (25.1 to 32.0) | 42.1 (38.1 to 46.5) | <0.001 |
| LVEF, % | 44 (33 to 60) | 45 (34 to 60) | 43 (32 to 60) | 0.441 |

Data are expressed as mean and SD for normally distributed variables and as median with interquartile range for non-normally distributed data. Categorical data are expressed as numbers and percentages.

ACEI indicates angiotensin-converting enzyme inhibitor; Alb, albumin; ARB, angiotensin II receptor blocker; AVP, arginine vasopressin; beta2MG, beta2microglobulin; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; BW, body weight; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FENa, fractional excretion of sodium.; FEUN, fractional excretion of urea nitrogen; Hb, hemoglobin; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NAG, N-acetyl-b-D-glucosaminidase; NYHA, New York Heart Association functional classification; PCI, percutaneous coronary intervention; and SBP, systolic blood pressure;.

*Delta BW=[discharge – admission] BW / admission BW ×100.

†Delta Cr=[discharge – admission] Cr / admission Cr ×100.

‡Delta BUN/Cr=[discharge – admission] BUN/Cr / admission BUN/Cr ×100.

§Delta BNP=[discharge – admission] BNP / admission BNP ×100.

‖Data on AVP was available for 246 patients (low-FEUN: 111 patients, high-FEUN: 135 patients).



were significantly lower in the low-FEUN group than in the high-FEUN group.

## Clinical Outcomes

During a median follow-up period of 28.1 months, there were 173 all-cause deaths (37.1%) and 83 (17.8%) due to cardiovascular causes in overall, 104 all-cause deaths (46.4%) and 43 (19.2%) due to cardiovascular causes in the low-FEUN group, and 69 all-cause deaths (28.5%) and 40 (16.5%) due to cardiovascular causes in the high-FEUN group. The log-rank test demonstrated that the low-FEUN group had a significantly higher rate of all-cause death than the high-FEUN group (log-rank test, $P<0.001$) (Figure 2A). However, the low-FEUN was not significantly associated with HF readmission (log-rank test, $P=0.073$) (Figure 2B). A competing-risk analysis was performed to assess the effect of death as a competing risk and similar result was observed (Gray test, $P=0.140$) (Figure S1).

In univariate Cox regression models, low-FEUN was associated with all-cause death compared to high-FEUN (hazard ratio, 1.747; 95% CI, 1.288–2.369; $P<0.001$). In multivariable Cox regression models adjusted for established prognostic factors for ADHF (NYHA classification, age, diabetes mellitus, Hb, BNP, LVEF, BUN, Cr, serum sodium, SBP, and sex), low-FEUN was independently associated with higher all-cause mortality in the total population (Table 2, model 1 and 2). The medications that were significantly associated

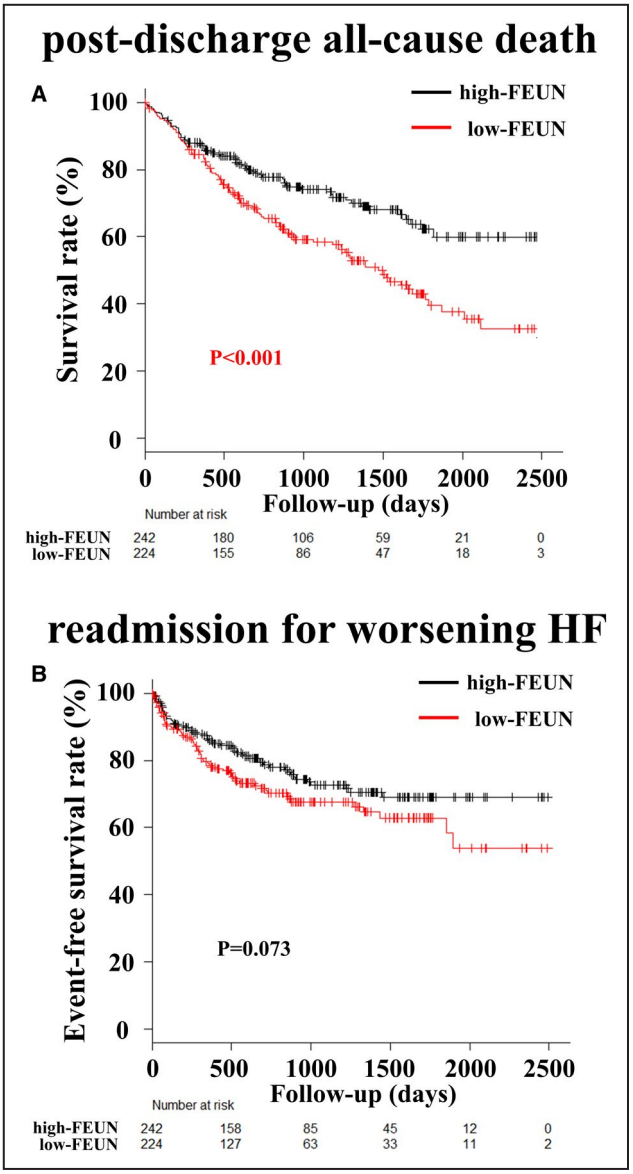


**Figure 2. Kaplan–Meier analyses of FEUN at discharge for post-discharge all-cause mortality and readmission for worsening HF.**

Kaplan-Meier survival curves show time to all-cause death (**A**) and HF readmission (**B**) in the FEUN<35% and FEUN equal to or greater than 35% groups. The log-rank test demonstrated that the FEUN<35% group had a significantly higher rate of all-cause death compared to the FEUN equal to or greater than 35% group (log-rank test, *P*<0.001), with a HR, 1.747; 95% CI, 1.288–2.369. Furthermore, the FEUN<35% group had a strong trend toward a higher risk of HF readmission (log-rank test, *P*=0.073), with a HR, 1.383; 95% CI, 0.967–1.977. FEUN indicates fractional excretion of urea nitrogen; and HF, heart failure.

with all-cause mortality in the previous study[20] were added for adjustment, which also demonstrated that low-FEUN was independently associated with higher all-cause mortality in the same manner as in models 1 and 2 (Table 2, model 3).

Hb, BNP, loop diuretic dose, and renin but not age, LVEF, and Cr at discharge were independent risk factors for low-FEUN (Table 3). The risk of low-FEUN compared to high-FEUN in post-discharge all-cause death was consistent across all subgroups; however, the effects tended to be modified by renal function (threshold: 60 mL/min/1.73 $m^2$, interaction *P*=0.069) (Figure 3).

## DISCUSSION

This study examined the association between FEUN at discharge and long-term prognosis in patients with ADHF. The main finding of the present study was that low-FEUN at discharge was independently associated with higher post-discharge all-cause mortality in patients with ADHF (based on multivariate analysis). To the best of our knowledge, this is the first report to reveal that low-FEUN at discharge was a strong prognostic predictor of long-term outcomes in patients with ADHF. The impact of low-FEUN was consistent across various subgroups; however, the effects tended to be modified by renal function.

In patients with ADHF, it is well known that the correction of volume overload improves prognosis, although excess fluid removal with diuretics has been shown to cause worsening renal function and may increase mortality risk in these patients.[7–10] However, there have been no reliable clinical tests that can determine euvolemia. Since about 80% of patients in this study used diuretics, such as in many previous studies,[5,21] FEUN was used as an index of body fluid volume instead of FENa. In the present study, there was no significant difference in LVEF and SBP between the low-FEUN and high-FEUN groups. However, the BNP level was significantly lower, and the BUN/Cr ratio, delta BUN/Cr ratio and delta-BW were significantly higher in the low-FEUN group than in the high-FEUN group. These findings suggest that low-FEUN may represent intravascular dehydration rather than low output compared to high-FEUN, and FEUN may be an index for determining euvolemia.

In this study, low-FEUN at discharge was an independent prognostic factor for higher post-discharge all-cause mortality in patients with ADHF. The precise reason for low-FEUN being independently associated with higher post-discharge all-cause mortality in patients with ADHF remains unclear. A possible mechanism underlying the association between low-FEUN and higher post-discharge all-cause mortality in patients with ADHF is the effect of neurohormonal activation, which is an aggravating factor for HF.

Pre-renal diseases, such as dehydration and increased plasma osmolality, cause vasopressin release.

**Table 2. Cox Regression Analysis for All-Cause Death in Patients With ADHF**

| | Univariate | | Multivariate | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Model1 | | Model2 | | Model3 | |
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| FEUN<35% | 1.747 (1.288–2.369) | <0.001 | 1.564 (1.146–2.136) | 0.005 | 1.422 (1.003–2.015) | 0.048 | 1.467 (1.030–2.088) | 0.033 |
| NYHA | 1.720 (1.268–2.334) | <0.001 | 1.319 (0.959–1.813) | 0.088 | 1.182 (0.855–1.633) | 0.312 | 1.148 (0.829–1.589) | 0.407 |
| Age | 1.058 (1.042–1.076) | <0.001 | 1.045 (1.028–1.063) | <0.001 | 1.044 (1.026–1.063) | <0.001 | 1.043 (1.024–1.062) | <0.001 |
| Diabetes mellitus | 1.031 (0.760–1.397) | 0.847 | 0.965 (0.705–1.320) | 0.822 | 0.953 (0.692–1.312) | 0.768 | 0.993 (0.716–1.377) | 0.967 |
| Hb | 0.758 (0.696–0.826) | <0.001 | 0.807 (0.732–0.889) | <0.001 | 0.817 (0.740–0.901) | <0.001 | 0.813 (0.736–0.898) | <0.001 |
| BNP, 100 pg/mL | 1.078 (1.047–1.110) | <0.001 | 1.070 (1.035–1.107) | <0.001 | 1.076 (1.039–1.116) | <0.001 | 1.078 (1.039–1.118) | <0.001 |
| LVEF | 1.008 (0.999–1.018) | 0.085 | 1.000 (0.990–1.010) | 0.944 | 1.005 (0.995–1.016) | 0.315 | 1.004 (0.993–1.015) | 0.467 |
| BUN | 1.023 (1.015–1.031) | <0.001 | | | 1.005 (0.993–1.017) | 0.432 | 1.005 (0.993–1.017) | 0.459 |
| Cr | 1.125 (0.984–1.286) | 0.085 | | | 0.944 (0.734–1.214) | 0.653 | 0.946 (0.738–1.214) | 0.664 |
| Serum Na | 0.933 (0.901–0.967) | <0.001 | | | 0.972 (0.936–1.009) | 0.136 | 0.975 (0.938–1.013) | 0.198 |
| SBP | 0.986 (0.977–0.995) | 0.003 | | | 0.990 (0.980–1.001) | 0.065 | 0.990 (0.980–1.001) | 0.074 |
| Male | 1.101 (0.814–1.490) | 0.532 | | | 1.368 (0.987–1.894) | 0.060 | 1.390 (1.002–1.928) | 0.049 |
| ACEI or ARB | 0.592 (0.403–0.867) | 0.008 | | | | | 0.803 (0.529–1.218) | 0.302 |
| Beta blocker | 0.617 (0.443–0.859) | 0.004 | | | | | 0.902 (0.620–1.314) | 0.592 |
| Aldosterone antagonist | 1.121 (0.831–1.511) | 0.455 | | | | | 1.116 (0.809–1.539) | 0.503 |
| Loop diuretic dose, mg | 1.004 (0.998–1.011) | 0.186 | | | | | 0.997 (0.990–1.004) | 0.439 |

ACEI indicates angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; FEUN, fractional excretion of urea nitrogen; Hb, hemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional classification; and SBP, systolic blood pressure.

**Table 3. Predictors of FEUN<35% in the Multivariate Logistic Regression Analysis**

| | Odds ratio | 95% CI | *P* Value |
|---|---|---|---|
| Age, y | 1.010 | 0.992–1.030 | 0.304 |
| Hb, g/dL | 0.863 | 0.773–0.963 | 0.008 |
| Plasma BNP, 100 pg/mL | 0.913 | 0.857–0.973 | 0.005 |
| Loop diuretic dose, mg | 1.010 | 1.010–1.020 | 0.003 |
| LVEF, % | 1.000 | 0.987–1.010 | 0.988 |
| Cr, mg/dL | 0.974 | 0.770–1.230 | 0.828 |
| Renin, ng/mL/hr | 1.030 | 1.010–1.050 | 0.002 |

Hb, BNP, Loop diuretic dose, LVEF, eGFR, and Renin values are at the time of discharge. BNP indicates B-type natriuretic peptide; Cr, creatinine; FEUN, fractional excretion of urea nitrogen; Hb, hemoglobin; and LVEF, left ventricular ejection fraction.

Additionally, activated vasopressin enhances urea nitrogen reabsorption by urea-transporter proteins (UT-A1 and UT-A3) in inner medullary collecting ducts, resulting in the reduction of FEUN.[22–24]

In this study, plasma vasopressin levels and plasma osmolality were significantly higher in the low-FEUN group than in the high-FEUN group. This suggests that low-FEUN represents an increased vasopressin secretion caused by decreased plasma volume, which may lead to a poor prognosis. We further assessed the plasma renin activity in this study. The plasma renin activity was significantly higher in the low-FEUN group than in the high-FEUN group. In patients with ADHF, low-FEUN suggests increased activation of the renin-angiotensin-aldosterone system, which may also contribute to poor prognosis. Although low Hb was

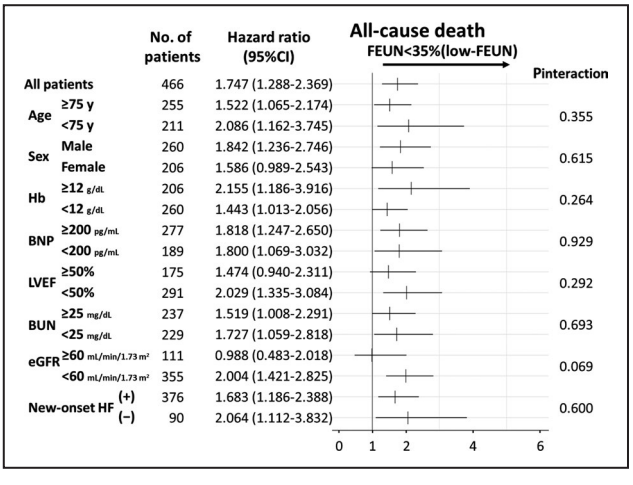


**Figure 3. Subgroup analysis of all-cause death by baseline characteristics.**
Hazard ratios for 7 predefined subgroups. Horizontal bars represent 95% CI. *P* values are for the tests of subgroup heterogeneity (tests of interactions). BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hb indicates hemoglobin; and LVEF, left ventricle ejection.

an independent risk factor for low-FEUN, the precise reason was unclear. Renal dysfunction is common in patients with HF and closely associated with the development of anemia.[25,26] In the present study, renal function was worse in low-FEUN than in high-FEUN, which may lead that low Hb was an independent risk factor for low-FEUN.

Generally, the administration of loop diuretics increases the activation of the renin-angiotensin- aldosterone system because urine loss with loop diuretics is exclusively through extracellular fluid. In contrast, the V2 receptor antagonist increases urinary excretion from intracellular fluids (two-thirds) and extracellular fluids (one-third). As a result, renin-angiotensin- aldosterone system is apparently less activated with V2 receptor antagonists than with loop diuretics.[27] Therefore, in patients with ADHF and low-FEUN at discharge, it may be necessary to reduce the loop diuretic dose. This may suppress neurohormonal activation and consequently improve long-term prognosis.

Subgroup analysis of all-cause death did not show significant interactions but nearly significant interactions in the subgroup by eGFR probably because of a small number of patients, and low-FEUN was not associated with all-cause death in eGFR equal to or greater than 60 mL/min/1.73 $m^2$. Therefore, we think that FEUN is more useful in patients with ADHF with eGFR less than 60 mL/min/1.73 $m^2$ and may not be available in patients with ADHF with eGFR equal to or greater than 60 mL/min/1.73 $m^2$.

These findings suggest that FEUN at discharge in patients with ADHF can be a novel surrogate marker of volume status that can allow maintenance of the euvolemic condition using diuretics. Moreover, measuring FEUN is non-invasive and repeatable, and of low cost, making this a practical and feasible indicator for euvolemia in the clinical setting. Further research is necessary to confirm our findings and to elucidate the reason for low-FEUN at discharge in patients with ADHF leading to poor long-term prognosis.

This study has several limitations that should be acknowledged. First, this was a single-center study involving a relatively small number of patients with ADHF. Second, this study was a retrospective analysis of prospectively collected data. Third, we had to exclude a large number of patients owing to missing data on FEUN, and as such, the possibility of selection bias cannot be denied. Fourth, non-neurohormonal factors that influence urea reabsorption, such as diet and protein catabolism, may have introduced potential uncontrolled confounding. Fifth, indices of renal function, such as serum BUN and Cr, are included in the FEUN formula. Therefore, we cannot exclude the possibility of the influence of renal function on FEUN. Sixth, we could not directly evaluate association between FEUN

and volume depletion because we did not usually perform right heart catheterization by the swan-ganz catheter during hospitalization.

## CONCLUSIONS

Low-FEUN at discharge was independently associated with higher post-discharge all-cause mortality in patients with ADHF. Our study suggests that FEUN at discharge in patients with ADHF may be a novel surrogate marker of volume status even in patients actively on diuretic therapy.

## ARTICLE INFORMATION

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### Supplementary Material

Figure S1

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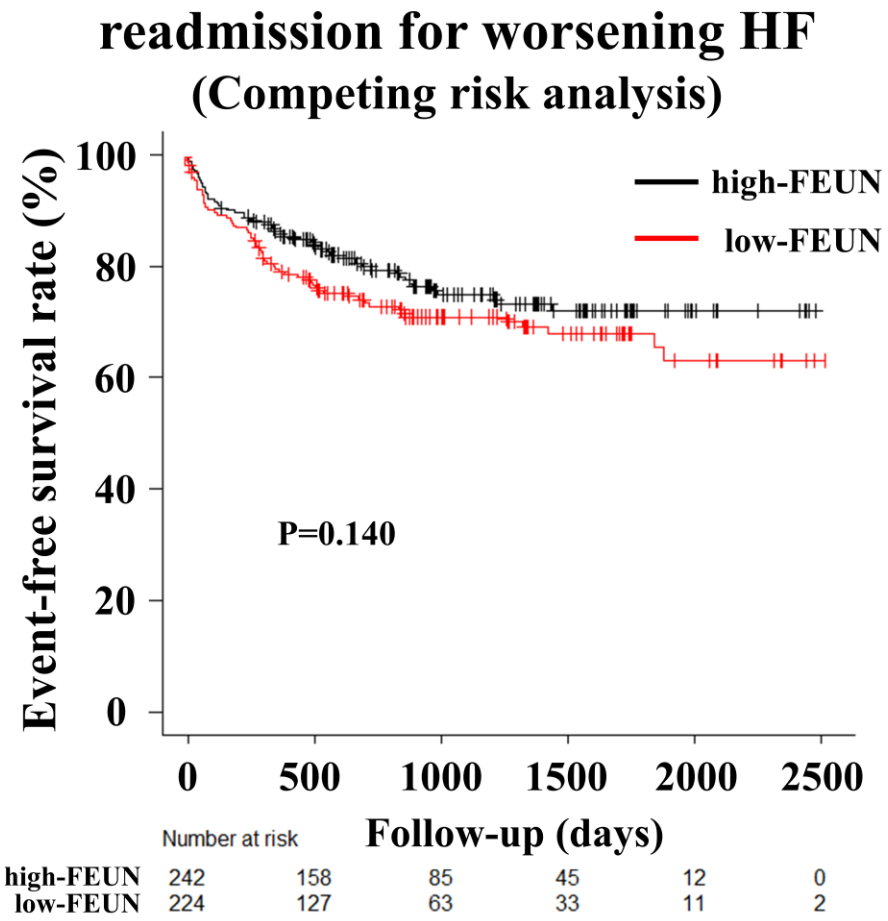
# SUPPLEMENTAL MATERIAL

**Figure S1. Kaplan–Meier analyses of FEUN at discharge for readmission for worsening HF without death (Competing risk analysis).**




Kaplan-Meier survival curves show time to HF readmission in the FEUN<35% and FEUN equal to or greater than 35% groups in a competing-risk analysis (Gray test, P=0.140).