

Sodium to creatinine ratio in spot urine is associated with heart failure hospitalization in Japanese high-risk patients

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Abstract. Our previous study [Evaluation of sodium intake for the prediction of cardiovascular events in Japanese high-risk patients (ESPRIT study)] reported that increased sodium excretion ≥ 4.0 g/day was associated with composite cardiovascular events in hospitalization for heart failure (HF), acute coronary syndrome, cerebrovascular events and documented cardiovascular-related mortality in Japanese high-risk patients with either stable and compensated HF, coronary artery disease, cerebrovascular disease, chronic kidney disease or atrial fibrillation. However, the method of estimating sodium excretion levels using spot urine is complex, requiring age, body weight, height and multiplier factors for calculation. The aim of the present study was to elucidate whether the sodium to creatinine ratio in spot urine, a key component in estimating daily sodium excretion, was associated with hospitalization for HF. The present study performed a post-hoc analysis of the ESPRIT study (n=520; 60 hospitalizations for HF). Receiver operating curve analysis yielded an optimal sodium to creatinine ratio cut-off value of 24.8 for detecting hospitalization for HF. Kaplan-Meier curve analysis revealed that a high sodium to creatinine ratio in spot urine was associated with an increased hospitalization for HF (P<0.001). Cox regression analysis revealed that a high sodium to creatinine ratio was associated with hospitalization for HF with a hazard ratio (HR) of 2.49 [95% confidence interval (95% CI), 1.47-4.16]. Following adjustment for age, sex and body weight, the HR was as high as 2.74 (95% CI, 1.51-4.71). This association remained following further adjustment for brain natriuretic peptide, estimated glomerular filtration rate, diabetes mellitus or the use of diuretics. Overall, the present study demonstrated that the sodium to creatinine ratio in spot urine is associated with hospitalization for HF in Japanese high-risk patients.

Introduction

Although the prognosis of patients with heart failure (HF) has improved considerably with the development of new strategies, including medical therapies and advances to the instrument used, it remains extremely poor (1,2); the 1 and 5-year mortality rates after diagnosis, have been reported to be 20 and 53%, respectively in the Olmsted County cohort study (3). Therefore, the prevention of HF is of utmost importance. European Society Guidelines recommended a healthy diet, avoiding excessive salt intake (>5 g/day, i.e., 2 g/day sodium); however, the optimal level of sodium intake remains unclear.

The ESPRIT study (4) (Evaluation of sodium Intake for the prediction of cardiovascular events in Japanese high-risk patients) revealed that a high sodium excretion ≥ 4.0 g/day, assessed by repeated measurements of spot urine, was associated with composite cardiovascular events in Japanese high-risk patients. During the median follow-up period of 5.2 years in 520 enrolled patients, 105 (20%) experienced composite cardiovascular events, which were predominantly driven by 60 (12%) hospitalizations due to HF.

However, the method for estimating sodium excretion using spot urine is complex requiring age, body weight, height, and multiplier factors for calculation (5).

There are certain reports comparing the sodium/creatinine (Na/Cr) ratio and 24-hr sodium excretion. Mann and Gerber (6) reported that the Na/Cr ratio of a late afternoon/early evening urine sample highly correlated with the actual 24-h sodium excretion (r=0.86, P<0.001), although the correlation was weak when using AM samples (r=0.31, P=0.06). Wan *et al* (7) reported that the Na/Cr ratio in spot urine and 24-h sodium excretion weakly correlated (r=0.26, P=0.019). A higher correlation of the Na/Cr ratio in spot urine and 24-h sodium excretion was observed (r=0.392, P<0.01) in a Korean study using a small number of 15 subjects (8). Furthermore, blood pressure and hypertension have been found to be associated with the Na/Cr ratio using a large population (n=9,674) in Korea (9). However, to the best of our knowledge, there are no reports available to date assessing the association between the Na/Cr ratio in spot urine and hospitalizations due to HF.

The aim of the present study was to elucidate whether the Na/Cr ratio in spot urine, a key component in estimating daily sodium excretion, is associated with hospitalizations due to HF.

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Patients and methods

Patient cohort. In the present study, a post hoc analysis of the previously published ESPRIT study (4) was performed. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Ethics Committee of Ueki Hospital, and informed written consent was obtained from all the patients. Briefly, the ESPRIT study was a single-center, prospective, observational study that included 520 patients who visited the cardiology clinic with at least one of the following cardiovascular conditions: i) Stable and compensated HF [having New York Heart Association (NYHA) ≥ 2 symptoms and/or congestive sign requiring loop diuretics, or a history of congestive heart failure that required continued medical treatment]; ii) reduced left ventricular ejection fraction (LVEF $< 50\%$); iii) brain natriuretic peptide (BNP) levels ≥ 100 pg/ml for any reason; iv) documented coronary artery disease; v) cerebrovascular disease; vi) chronic kidney disease (CKD), estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²; and vii) atrial fibrillation. Follow-up was commenced at the time of entry. During the median follow-up period of 5.2 years, 105 (20%) patients experienced composite cardiovascular events (hospitalization due to HF, acute coronary syndrome, cerebrovascular events and cardiovascular-related mortality), which were predominantly driven by 60 (12%) hospitalizations due to HF.

The sodium (mEq/l) and creatinine (mmol/l) concentrations were measured using spot urine and the Na/Cr ratio was calculated. Sodium intake was estimated using the Tanaka method (5). The measurements were conducted at the time of entry and repeated at least every 6 months. An average of all data from each patient was used for the analysis (median 14 measurements).

Statistical analysis. Data are presented as the mean \pm standard deviation, median (interquartile range), or percentages, as appropriate. Event frequencies were compared using a χ^2 test. Other comparisons between two groups of data were performed using an unpaired Student's t-test or the Mann-Whitney U test, as appropriate. The optimal Na/Cr ratio cut-off point was determined using receiver operating characteristic (ROC) curve analysis. The outcomes were displayed with Kaplan-Meier event-free curves and compared with the use of log-rank tests. The prognostic values of Na/Cr ratio, sodium excretion ≥ 4.0 g/day and clinical variables were analyzed using Cox-proportional hazard models and hazard ratios (HRs) were described with a 95% confidence interval (CI). For multivariate analyses, age, sex, body weight, BNP, eGFR, diabetes mellitus, and the use of diuretics were used for adjustments. $P < 0.05$ was considered to indicate a statistically significant difference. The statistical software package JMP (version 11; SAS Institute, Inc.) was used for the analyses.

Results

Cut-off values. With ROC analysis, the optimum cut-off point for Na/Cr ratio in spot urine using a median of 14 (interquartile range, 10-21) measurements, yielded 24.8 to detect hospitalization due to HF [area under the curve (AUC), 0.58, $P = 0.015$; sensitivity, 40%, specificity, 81%]. This association was not

observed when using only a Na/Cr ratio at the time of entry alone (AUC 0.52, $P = 0.81$). Similarly, this association was not observed when using the average values of first three ($n = 511$; AUC, 0.52; $P = 0.22$) or first five ($n = 495$; AUC, 0.54; $P = 0.10$) Na/Cr ratios. However, there were trends towards an association when using the average values of last five Na/Cr ratios ($n = 495$; AUC, 0.58; $P = 0.070$).

Baseline characteristics. The Baseline characteristics of the patients, below and above the cut-off point, are presented in Table I. In patients with a Na/Cr ratio ≥ 24.8 , an older age, female sex, a smaller body weight and diabetes mellitus were more prevalent, and BNP levels were higher. Additionally, diuretics were more commonly used in patients with a high Na/Cr ratio.

Hospitalization due to HF. The Na/Cr ratio was significantly higher in patients who were hospitalized due to HF than that in patients without hospitalization for HF (22.7 ± 13.0 vs. 19.1 ± 9.7 , $P < 0.01$). There were 24 (22%) hospitalizations for HF observed in patients with an average Na/Cr ratio ≥ 24.8 as compared with 36 (8.8%) such events in those with an average Na/Cr ratio < 24.8 . Kaplan-Meier free curves for hospitalization due to HF for the Na/Cr ratio revealed that an elevated Na/Cr ratio was significantly associated with hospitalization for HF ($P < 0.001$, Fig. 1). The HRs of the Na/Cr ratio ≥ 24.8 for hospitalization due to HF are presented in Table II. In the univariate analysis, a Na/Cr ratio ≥ 24.8 was associated with hospitalization for HF (HR, 2.49; CI, 1.47-4.16). Following adjustment for age, sex and body weight, a Na/Cr ratio ≥ 24.8 was also associated with hospitalization for HF (HR, 2.74; CI, 1.47-4.16). The association between high Na/Cr ratio and hospitalization for HF remained following further additional adjustments for either BNP, eGFR, diabetes mellitus, or the use of diuretics (Table II).

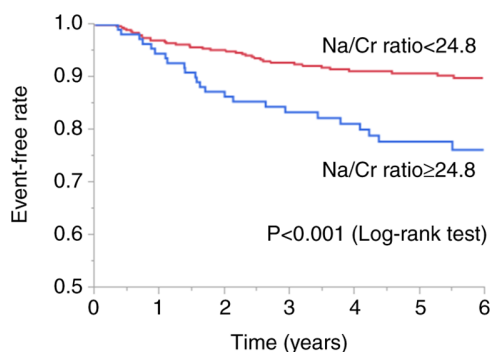
On the other hand, there were 18 (15%) hospitalizations for HF observed in patients with a sodium excretion ≥ 4.0 g/day as compared with 42 (10.5%) such events in those with an average sodium excretion < 4.0 g/day. Kaplan-Meier free curves for hospitalization for HF for a sodium excretion ≥ 4.0 g/day did not reveal a significant difference ($P = 0.16$, Fig. 2). However, Cox proportional hazard model analysis revealed that a sodium excretion ≥ 4.0 g/day was associated with hospitalization for HF following adjustment for age, sex and body weight (HR, 2.48; CI, 1.35-4.14).

Hospitalization for HF with and without stable HF. Stable 114 HF patients, defined as having NYHA ≥ 2 symptoms and/or congestive sign requiring loop diuretics, or a history of congestive HF that required continued medical treatment were enrolled in the present study. LVEF was preserved ($\geq 50\%$) in 82 (72%) patients. There were 17 (39%) hospitalizations for HF observed in patients with an average Na/Cr ratio ≥ 24.8 as compared with 23 (33%) such events in those with an average Na/Cr ratio < 24.8 . Kaplan-Meier free curves for hospitalization due to HF for the Na/Cr ratio did not reveal any differences between the groups ($P = 0.74$, Fig. 3A). However, in patients without HF ($n = 406$), there were 7 (10%) hospitalizations for HF observed in patients with an average Na/Cr ratio ≥ 24.8 as compared with 13 (3.8%) such events in those with an average Na/Cr ratio < 24.8 . Kaplan-Meier free curves

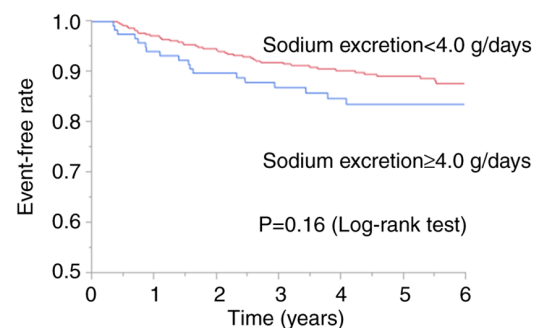
Table I. Characteristics of the study patients according to the Na/Cr ratio in spot urine.

| Variable | All patients | Na/Cr <24.8 | Na/Cr ≥24.8 | P-value |
|---------------------------------------------|---------------|---------------|---------------|---------|
| No. | 520 | 408 | 112 | |
| Event: HF hospitalization, n (%) | 60 | 36 (8.8) | 24 (22) | <0.001 |
| Sodium excretion at entry, g/day | 3.52±0.93 | 3.36±0.84 | 4.07±1.03 | <0.001 |
| Average sodium excretion, g/day | 3.52±0.67 | 3.35±0.57 | 4.13±0.67 | <0.001 |
| Na/Cr ratio at entry | 18.9±13.0 | 15.5±9.5 | 31.2±16.3 | <0.001 |
| Average Na/Cr ratio | 19.5±10.2 | 15.4±4.8 | 34.5±10.6 | <0.001 |
| Serum sodium, mEq/liter | 141±2.5 | 141±2.4 | 141±3.1 | 0.35 |
| Follow-up duration, years | 5.2 (3.2-5.7) | 5.3 (3.2-5.7) | 4.8 (2.7-5.7) | 0.65 |
| Measurement, times | 14 (10-21) | 14 (10-20) | 15 (10-22) | 0.74 |
| Age, years | 73±10 | 73±10 | 75±9 | 0.016 |
| Age >75 years, n (%) | 254 (49) | 193 (47) | 61 (54) | 0.18 |
| Female, n (%) | 199 (38) | 126 (31) | 73 (65) | <0.001 |
| Body weight, kg | 60±13 | 62±13 | 55±10 | <0.001 |
| Body weight <60 kg, n (%) | 260 (50%) | 182 (45%) | 78 (70%) | <0.001 |
| Body mass index, kg/m ² | 24±3.5 | 24±3.5 | 23±3.3 | 0.013 |
| Systolic blood pressure, mmHg | 123±15 | 124±16 | 121±15 | 0.094 |
| Diastolic blood pressure, mmHg | 70±11 | 70±11 | 68±12 | 0.15 |
| Hypertension, n (%) | 384 (74) | 302 (74) | 82 (74) | 0.86 |
| eGFR, ml/min/1.73 m ² | 64±18 | 63±18 | 65±20 | 0.23 |
| eGFR <60 ml/min/1.73 m ² , n (%) | 219 (42) | 174 (43) | 45 (40) | 0.63 |
| Cr, mg/dl | 0.87±0.28 | 0.89±0.28 | 0.79±0.24 | <0.001 |
| BNP, pg/ml | 53 (24-115) | 50 (22-105) | 67 (29-148) | 0.011 |
| BNP >100 pg/ml, n (%) | 147 (28) | 107 (26) | 40 (36) | 0.048 |
| Chronic HF, n (%) | 114 (22) | 70 (17) | 44 (39) | <0.001 |
| Permanent AF, n (%) | 97 (19) | 77 (19) | 20 (18) | 0.80 |
| HbA1c, % | 6.1±0.64 | 6.1±0.64 | 6.0±0.65 | 0.066 |
| Diabetes mellitus, n (%) | 129 (25) | 112 (27) | 17 (15) | <0.01 |
| Medications, n (%) | | | | |
| ACEI/ARBs | 330 (64) | 254 (62) | 76 (68) | 0.28 |
| β-blockers | 194 (37) | 154 (38) | 40 (36) | 0.69 |
| Calcium channel blockers | 264 (51) | 205 (50) | 59 (53) | 0.65 |
| Diuretics | 125 (24) | 76 (19) | 49 (44) | <0.001 |

Data are presented as the mean ± standard deviation, median (interquartile range) or number (percentage). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AF, atrial fibrillation; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HF, heart failure.



Na/Cr ratio <24.8 408 387 367 316 261 213
Na/Cr ratio ≥24.8 112 105 95 83 74 55



<4.0 g/days 400 381 359 311 259 205
≥4.0 g/days 120 110 103 87 76 62

Figure 1. Kaplan-Meier event-free curves for hospitalization due to heart failure according to the Na/Cr ratio. Na/Cr ratio, sodium/creatinine ratio.

Figure 2. Kaplan-Meier event-free curves for hospitalization due to heart failure according to estimated sodium excretion. Urinary sodium excretion was estimated using the Tanaka method (5).

Table II. Hazard ratios of the urinary Na/Cr ratio ≥ 24.8 for hospitalization due to heart failure.

| Analysis | Hazard ratio (95% confidence interval) | P-value |
|-------------------------------------------|-------------------------------------------|---------|
| Unadjusted (univariate analysis) | 2.49 (1.47-4.16) | <0.001 |
| Adjusted for | | |
| Age, sex and body weight (1) | 2.74 (1.51-4.71) | <0.001 |
| (1) + BNP >100 pg/ml | 2.36 (1.37-4.01) | <0.01 |
| (1) + eGFR <60 ml/min/1.73 m ² | 2.81 (1.61-4.81) | <0.001 |
| (1) + Diabetes mellitus | 2.80 (1.61-4.78) | <0.001 |
| (1) + Use of diuretics | 1.85 (1.03-3.26) | 0.037 |

Multivariate analysis was performed following adjustment for age, sex and body weight. Further additional adjustments for either BNP, eGFR, diabetes mellitus or the use of diuretics were performed. Fully-adjusted analysis was not performed due to the limited number of events. BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

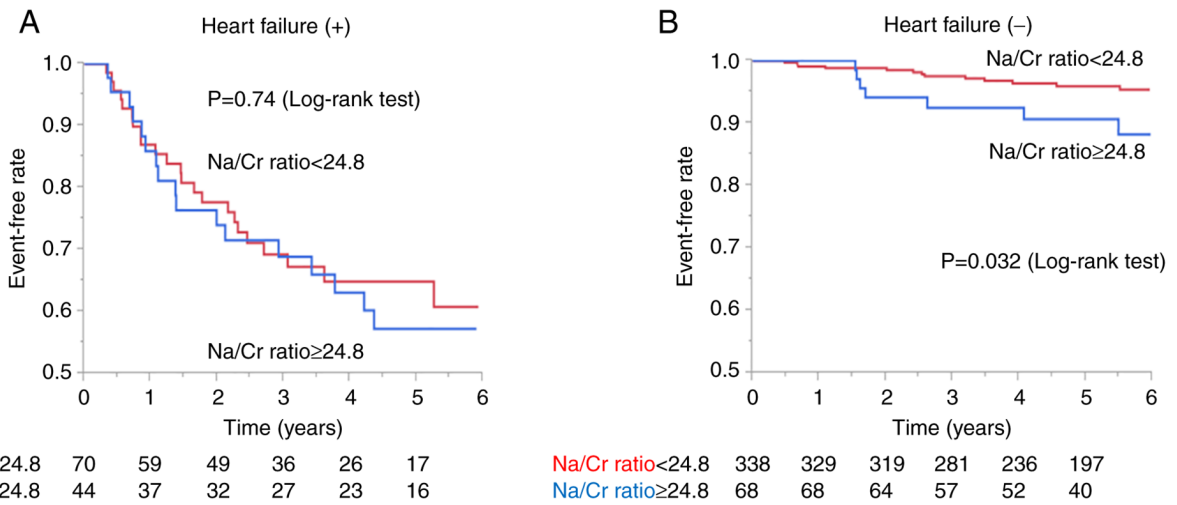


Figure 3. Kaplan-Meier event-free curves for hospitalization due to heart failure according to the Na/Cr ratio in patients (A) with stable and compensated heart failure and (B) without any history of heart failure. Na/Cr ratio, sodium/creatinine ratio.

for hospitalization due to HF for Na/Cr ratio revealed that an elevated Na/Cr ratio was significantly associated with hospitalization for HF (P=0.032, Fig. 3B).

Discussion

In the present study, a post hoc analysis of the ESPRIT study (4) was performed and it was found that a high Na/Cr ratio in spot urine was associated with hospitalization for HF in high-risk Japanese patients. The strength of this sub-analysis is that a simple marker of the Na/Cr ratio in spot urine, when measured repeatedly, was associated with hospitalizations for HF either in univariate analysis or following adjustment for several factors, such as age, sex, body weight, BNP, eGFR, diabetes mellitus, or the use of diuretics. On the other hand, a sodium excretion ≥ 4.0 g/day assessed using the method of Tanaka *et al* (5) was associated with hospitalization for HF only following adjustment for age, sex and body weight. This may be due to the fact that high sodium excretion is associated with hospitalization for HF in patients of an older age, of the female sex and a low body weight, as previously reported (10).

Of note, appropriate sodium intake in these populations is not yet well understood. Thus, it is considered that the Na/Cr ratio may be a simple and promising marker without the need for these adjustments.

Sodium excretion varies considerably from day to day and hour to hour, and, therefore, spot urine results can differ substantially from the results of 24-h collections (11-14). It is evident that the salt intake estimation from the data of spot urine may be too variable to examine an individual's absolute salt intake using only a single measurement (13,14), as may be applied to the Na/Cr ratio in spot urine. In fact, the Na/Cr ratios at the time of entry alone, the averages of the first three, and first five times were not associated with hospitalization for HF in the present study. Repeated measurements may thus be necessary. We believe this method can aid in predicting HF hospitalization along with known clinical factors, such as an increase in body weight, peripheral edema and HF symptoms in the real- world practice.

With regard to hospitalization for HF in patients with stable HF, Martens *et al* (15) reported that the urinary sodium excretion remained relatively stable over time in

patients with stable and chronic HF patients, and patients who developed acute decompensated HF exhibited a chronically lower, as opposed to a higher urinary sodium concentration. They also demonstrated a further decrease in the urinary sodium concentration during the week preceding hospitalization. It was concluded that the inability to efficiently excrete sodium, which may be due to the sustained activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, may be a sign of worsening HF. However, the urinary sodium excretion is also dependent on dietary sodium intake and this hypothesis may not be validated without the information of dietary sodium intake. Therefore, the efficacy of urinary sodium as a biomarker of HF is more complicated than it initially appears (16). In the present and previous study (10), the Na/Cr ratio and sodium excretion ≥ 4.0 g/day were not associated with HF hospitalization in patients with stable HF patients (Fig. 3A, and ref 10). The LVEF was reduced in the majority (86%) of the patients in the study by Martens *et al* (15), whereas, the LVEF was preserved in the majority (72%) of the patients in the present study; this may have contributed to the difference in the results. However, these results were at least consistent at the point that a higher urinary sodium concentration was not observed at the time of hospitalization for HF in patients with stable HF.

The present study has several limitations. A post hoc analysis of a single-center study was performed, and thus may have introduced selection bias. Second, the number of included patients and hospitalization for HF were minimal. Thus, certain crucial factors could not be fully adjusted. Third, the AUC in ROC analysis was relatively low (0.58); the ability of the Na/Cr to discriminate hospitalization for HF may not be as high. However, the results (Fig. 1) revealed clear discriminatory ability and thus this method may be feasible. Fourth, this method may not be used in patients with stable HF, as aforementioned. Fifth, the original ESPRIT study was conducted between 2011 and 2015. Thus, sacubitril/valsartan and SGLT2 inhibitors, which were widely used in patients with HF, were not available. Other limitations for the original ESPRIT study were described previously (4), in particular, the marked heterogeneity of the included patients was a major concern.

In conclusion, the present study demonstrates that Na/Cr ratio in spot urine is associated with hospitalization for HF in high-risk Japanese patients. However, these findings require further validation in the future prospective studies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TS and SH designed the study, analyzed the data and wrote the manuscript. TS and SH confirm the authenticity of all the raw data. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol of the Evaluation of sodium intake for the prediction of cardiovascular events in Japanese high-risk patients (ESPRIT) study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Ethics Committee of Ueki Hospital, and informed written consent was obtained from all of the patients. The present study performed a post hoc analysis of the ESPRIT study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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