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Association between sodium-to-potassium ratio in spot urine and hospitalization due to heart failure in high-risk Japanese patients☆

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ABSTRACT

Background: In Japanese cardiovascular (CV) high-risk patients, the ESPRIT (**E**valuation of **S**odium Intake for the **Pre**dict**i**on of Cardiovascular Events in Japanese High-risk Patients) study showed that high sodium excretion (≥4.0 g/day) was associated with a composite CV events of heart failure (HF) hospitalization, acute coronary syndrome, cerebrovascular events, and CV deaths. In this context, the sodium-to-creatinine (Na/Cr) ratio in spot urine was found to be significantly associated with HF hospitalizations. Since a stable potassium balance plays a particularly relevant role for CV patients, this post-hoc study was designed to investigate the extent to which consideration of the sodium-to-potassium (Na/K) ratio represents a better predictor of HF hospitalizations in the ESPRIT study population.
Methods: This is a post-hoc analysis of a previously reported ESPRIT study (n = 520, 60 HF hospitalizations).
Results: Receiver operating curve analysis yielded optimal Na/K ratio cut-off value of 2.9 for detecting HF hospitalization. Kaplan–Meier curve showed that high Na/K ratio in spot urine was associated with increased HF hospitalization ($p < 0.001$). Cox proportional hazards model analysis revealed that high Na/K ratio was associated with HF hospitalization with a hazard ratio of 2.97 (confidence interval: 1.67–5.61). An association between high Na/K ratio and HF hospitalization remained after adjustments for Na/Cr ratio in spot urine or the use of diuretics.
Conclusion: The Na/K ratio in spot urine is associated with HF hospitalization in high-risk Japanese patients.

1. Introduction

Dietary salt reduction and/or increase in potassium intake have been shown to reduce blood pressure, leading to reduced cardiovascular (CV) mortality [1,2]. A randomized controlled trial conducted in Taiwan [3] reported that patients who were assigned to receive potassium-enriched salt (49 % sodium chloride and 49 % potassium chloride) showed a significant reduction (41 %) in CV mortality as compared to the patients who received regular salt, suggesting that increased potassium intake plays a substantial role in addition to reduced sodium intake. Several studies have reported a positive association between the sodium-to-potassium (Na/K) ratio and hypertension and CV disease [1,2,4–12]. Furthermore, a stronger association was found between the Na/K ratio and CV disease than between sodium and potassium alone [1,2]. However, few studies have reported the association between the Na/K ratio and specific CV diseases except for stroke [10,11] and ischemic heart disease [12].

In this study, we evaluated whether the Na/K ratio in spot urine samples was associated with CV events, focusing on heart failure (HF) hospitalizations, using a previously reported cohort study of Japanese high-risk patients for CV events [13], because considerable number of patients experienced HF hospitalizations in this cohort [14].

2. Methods

This was a post-hoc analysis of a previously reported ESPRIT (**E**valuation of **s**odium Intake for the **predict**ion of cardiovascular events in Japanese high-risk patients) study [13]. The study protocol of the ESPRIT conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Ethics Committee of Ueki Hospital. Written informed consent was obtained from all patients. Briefly, the ESPRIT study was a single-center, prospective, observational

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the presented data and their discussed interpretation.

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study that included 520 patients who visited the cardiology clinic with at least one of the following CV conditions: 1) stable and compensated HF; 2) reduced left ventricular ejection fraction (<50 %); 3) brain natriuretic peptide (BNP) levels ≥ 100 pg/mL for any reason; 4) documented coronary artery disease; 5) cerebrovascular disease; 6) chronic kidney disease, estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2; and 7) atrial fibrillation (97 permanent, 87 paroxysmal). Follow-up was initiated at the time of entry (Fig. 1). During a median follow-up period of 5.2 years, 105 (20 %) patients experienced composite CV events (60 patients with HF hospitalization, 9 patients with acute coronary syndrome, 21 patients with cerebrovascular events, and 15 patients with CV deaths), which were predominantly driven by 60 (12 %) HF hospitalizations.

Na (mEq/L), K (mEq/L), and creatinine (Cr, mmol/L) concentrations were measured in spot urine samples, and the Na/K ratio was calculated. Na intake was estimated using the Tanaka method [15]. The measurements were conducted at the time of entry and were repeated at least every 6 months. The average of all data from each patient was used for the analysis (median 14 measurements).

2.1. Statistical analysis

Data were presented as the mean ± standard deviation, median (interquartile range), or percentages, as appropriate. Event frequencies were compared using the chi-square test. Other data comparisons between two groups were performed using the Student's *t*-test or the Mann–Whitney *U* test, as appropriate. The optimal Na/K ratio cutoff point was determined by receiver operating characteristic (ROC) curve analysis. Outcomes were displayed using Kaplan–Meier curves and compared using log-rank tests. The prognostic values of the Na/K ratio and clinical variables were analyzed using Cox proportional hazards models and hazard ratios (HRs) were described with a 95 % confidence interval (CI). For multivariable analyses, the Na/Cr ratio in spot urine (used in a previous study [14]), left ventricular ejection fraction, or the use of diuretics were used for adjustments. Statistical significance was set at $p < 0.05$. All analyses were performed using the JMP statistical software (version 11; SAS Institute, Cary, NC, USA).

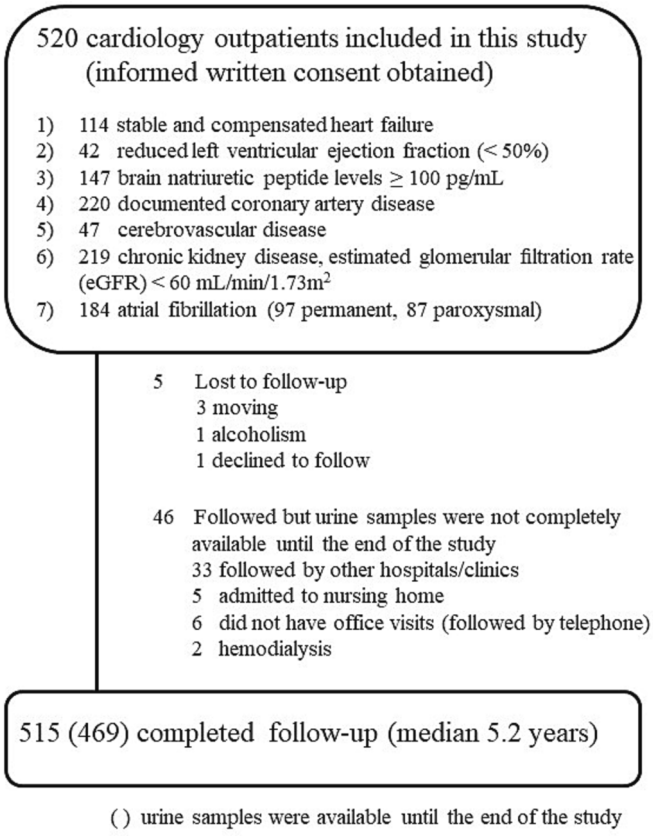

Fig. 1. Flow chart illustrating the inclusion and follow-up of the original study.

3. Results

3.1. Baseline characteristics

Table 1 summarizes baseline characteristics of the patients below and above Na/K ratio cutoff point (see below for the cutoff value). Average sodium excretion and average Na/Cr ratio were high in patients with a Na/K ratio ≥ 2.9. Mean left ventricular ejection fraction were lower in patients with a Na/K ratio ≥ 2.9. Diuretics were more commonly used in patients with high Na/K ratios; however, doses of furosemide were low and comparable between these groups.

3.2. Cutoff value of the Na/K ratio to detect CV events and HF hospitalization

With the ROC analysis (Fig. 2, Table 2), the optimum cutoff point of

Table 1
Characteristics of the study patients according to urine Na/K ratios.

	all patients	Na/K ratio < 2.9	Na/K ratio ≥ 2.9	p value
N	520	240	280	
Event: HF hospitalization	60	14 (5.8 %)	46 (16 %)	<0.001
Average sodium excretion (g/day)	3.52 ± 0.67	3.20 ± 0.58	3.79 ± 0.62	<0.001
Average Na/Cr ratio	19.5 ± 10.2	14.6 ± 6.6	23.8 ± 10.8	<0.001
Average Na/K ratio	3.13 ± 1.22	2.13 ± 0.55	3.99 ± 0.97	<0.001
Measurement (times)	14 (9–20)	13 (9–19)	14 (9–20)	0.54
Age (y/o)	73 ± 10	73 ± 10	74 ± 10	0.82
Gender (female)	199 (38 %)	96 (40 %)	103 (37 %)	0.45
Body weight (kg)	60 ± 13	61 ± 12	60 ± 13	0.50
Systolic Blood pressure (mmHg)	123 ± 15	123 ± 15	123 ± 16	0.60
Diastolic Blood pressure (mmHg)	70 ± 11	69 ± 10	70 ± 11	0.71
LVEF (%)	70 ± 12	72 ± 9	68 ± 13	<0.001
LVEF < 50 %	42 (8.1 %)	8 (3.3 %)	34 (12 %)	<0.001
LVEF < 40 %	19 (3.7 %)	2 (0.8 %)	17 (6.1 %)	<0.01
Hypertension	384 (74 %)	172 (72 %)	212 (76 %)	0.30
Atrial fibrillation (permanent)	97 (19)	39 (16)	58 (21)	0.21
eGFR (mL/min/1.73 m^2)	64 ± 18	64 ± 16	63 ± 20	0.48
BNP (pg/mL)	53 (24–115)	50 (23–96)	57 (24–137)	0.14
Diabetes mellitus	129 (25 %)	61(25 %)	68 (24 %)	0.77
Diuretics	125 (24 %)	29 (12 %)	96 (34 %)	<0.001
Loop diuretics (furosemide/ azosemide)	92 (18 %)	18 (7.5 %)	74 (27 %)	<0.001
Dose of furosemide equivalents (mg)	20 ± 10	20 ± 10	21 ± 10	0.60
Smoking status				
current	30(5.8 %)	10 (4.2 %)	20 (7.1 %)	
former	246 (47 %)	110 (46 %)	136 (49 %)	
never	244 (47 %)	120 (50 %)	124 (44 %)	0.21

BNP: B-type natriuretic peptide, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction
() indicate percentage or median (interquartile range). azosemide 30 mg = furosemide 20 mg.

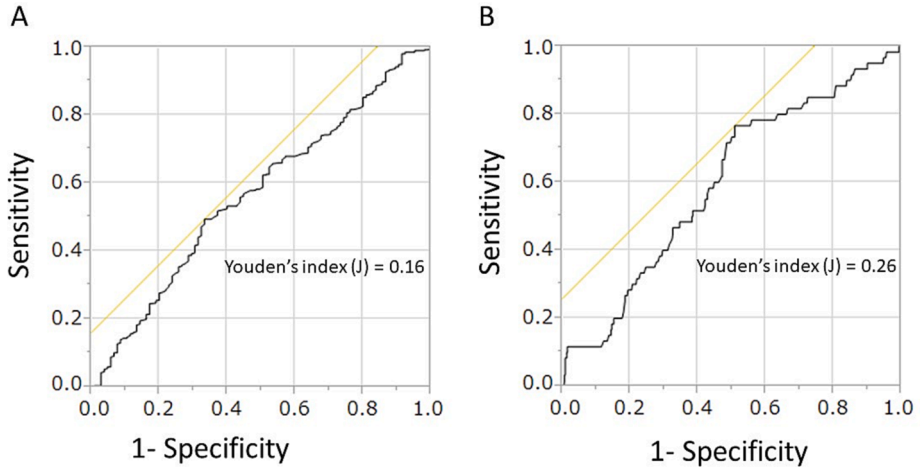

Fig. 2. Receiver operating curve for the Na/K rations in spot urine to detect composite CV events (A) and HF hospitalizations (B).

Table 2
Na/K ratios with (+) or without (-) events and AUC for Na/K ratio to detect these events.

	N	Na/K ratios	p value	AUC	p value
Composite cardiovascular events	(+) 105	3.38 ± 1.34	0.033	**0.57**	0.022
	(-) 415	3.07 ± 1.18			
Heart failure hospitalizations	(+) 60	3.53 ± 3.08	<0.01	**0.60**	<0.01
	(-) 460	3.08 ± 1.19			
Cerebrovascular events	(+) 21	3.21 ± 1.40	0.80	**0.53**	0.77
	(-) 499	3.12 ± 1.22			
Acute coronary syndrome	(+) 9	3.36 ± 0.98	0.51	**0.57**	0.58
	(-) 511	3.13 ± 1.23			
Cardiovascular deaths	(+) 15	3.00 ± 1.33	0.71	**0.55**	0.68
	(-) 505	3.14 ± 1.22			
Cardiovascular events other than heart failure hospitalizations	(+) 45	3.17 ± 1.28	0.83	**0.51**	0.83
	(-) 475	3.13 ± 1.22			

Composite cardiovascular events: heart failure hospitalizations + Cerebrovascular events + Acute coronary syndrome + Cardiovascular deaths, AUC: area under the curve (receiver operating curve).

the Na/K ratio in spot urine using a median of 14 (9–20) measurements, yielded 2.9 to detect composite CV events (area under the curve [AUC] 0.57, p = 0.022, sensitivity 49 %, and specificity 67 %), and also 2.9 to detect HF hospitalization (AUC: 0.60, p < 0.01, sensitivity 77 %, and specificity 49 %).

3.3. The Na/K ratio in spot urine and CV events

The Na/K ratios in spot urine were significantly higher in patients with composite CV events and HF hospitalization than those in patients without these events (Table 2). The Na/K ratios were not different in patients with and without cerebrovascular disease, acute coronary syndrome, CV deaths, and these three combinations (i.e., CV events other than HF hospitalizations). Composite CV events observed in patients with an average Na/K ratio ≥ 2.9 were higher than in those with an average Na/K ratio < 2.9 (70[25 %] vs. 35[15 %], p < 0.01). HF hospitalizations observed in patients with an average Na/K ratio ≥ 2.9 were higher than in those with an average Na/K ratio < 2.9 (46[16 %] vs. 14[5.8 %], p < 0.001). Kaplan–Meier curves for the Na/K ratio showed that an elevated Na/K ratio was significantly associated with both composite CV events and HF hospitalization (Fig. 3A and 3B). Cox proportional hazards model analysis revealed that a Na/K ratio ≥ 2.9 was associated with composite CV events with a HR of 1.86. An association between high Na/K ratio and composite CV events remained after adjustments for Na/Cr ratio, or left ventricular ejection fraction. However, this association was not observed after adjustment for the use of diuretics (Table 3). Similarly, Cox proportional hazards model analysis revealed that a Na/K ratio ≥ 2.9 was associated with HF hospitalization with a HR of 2.97. An association between high Na/K ratio and HF hospitalization remained after adjustments for Na/Cr ratio, left ventricular ejection fraction, or the use of diuretics (Table 3).

3.4. Combination of Na/K ratio and Na/Cr ratio for heart failure hospitalization

Based on the high and low Na/K ratios (cutoff value of 2.9) and Na/Cr ratios (cutoff value of 24.8, as previously reported [14]), patients were divided into four categories. A total of 11 (4.9 %) HF hospitalizations were observed in patients with an average Na/Cr ratio < 24.8 and a Na/K ratio < 2.9. Moreover, 26 (14.5 %), 20 (19.8 %), and 3 (21.4 %) hospitalizations were observed in patients with Na/Cr ratio < 24.8 and Na/K ratio ≥ 2.9, Na/Cr ratio ≥ 24.8 and Na/K ratio ≥ 2.9, and Na/Cr ratio ≥ 24.8 and Na/K ratio < 2.9, respectively. Kaplan–Meier curves showed that Na/Cr ratio < 24.8 and Na/K ratio < 2.9 were significantly associated with fewer HF hospitalization (Fig. 4, p < 0.001). Furthermore, in patients with a low Na/Cr ratio (<24.8, n = 408), Cox proportional hazards analysis revealed that high Na/K ratio was associated with HF hospitalization (HR: 2.93, 1.48–6.20, p < 0.01). In contrast, the Na/K ratio was not associated with HF hospitalization in patients with a high Na/Cr ratio (n = 112, p = 0.79).

4. Discussion

This post-hoc analysis of the ESPRIT study [13] found that a high Na/K ratio in spot urine samples was associated with HF hospitalization in high-risk Japanese patients. There was a significant but weak association between Na/K ratio and composite CV events; however, CV events other than HF hospitalization was very small and no associations were observed between Na/K ratios and these events (Table 2). The association between the Na/K ratio and composite CV events were substantially driven by HF hospitalizations. Therefore only the association between Na/K ratio and HF hospitalizations could be assessed. The strength of

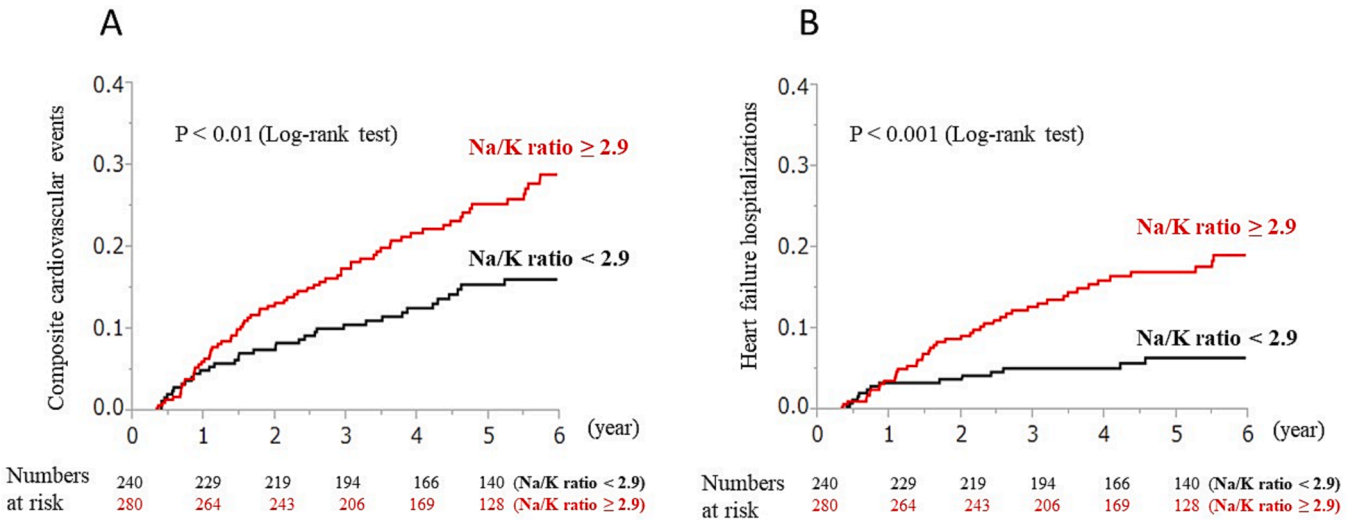

Fig. 3. Kaplan–Meier composite CV events (A) and HF hospitalizations (B) curves for the Na/K ratio in spot urine.

Table 3
Hazard ratio of urinary Na/K ratio ≥ 2.9.

Composite cardiovascular events	
	(Hazard ratio, 95 % confidence interval)
Unadjusted	**1.86** (1.22–2.77), p < 0.001
Adjusted for Na/Cr ratio	**1.73** (1.12–2.72), p = 0.014
Adjusted for left ventricular ejection fraction	**1.61** (1.08–2.46), p = 0.020
Adjusted for the use of diuretics	1.27 (0.83–1.97), p = 0.28
Heart failure hospitalizations	
	(Hazard ratio, 95 % confidence interval)
Unadjusted	**2.97** (1.67–5.61), p < 0.001
Adjusted for Na/Cr ratio	**2.70** (1.45–5.28), p < 0.00 l
Adjusted for left ventricular ejection fraction	**2.43** (1.36–4.64), p < 0.01
Adjusted for the use of diuretics	**1.88** (1.03–3.65), p = 0.041

this subanalysis is that a simple marker of the Na/K ratio in spot urine, when measured repeatedly, was associated with HF hospitalizations, independent of the Na/Cr ratio, which was previously reported to be associated with HF hospitalization. The Na/K ratio in spot urine samples was significantly associated a HF hospitalization in patients with low Na/Cr ratio, but not in patients with a high Na/Cr ratio. The inconclusive fact that patients with a high Na/Cr but low Na/K value had a similarly high HF hospitalization rate as patients with higher ratios for both parameters is most likely due to the very low number of patients with this specific constellation (n = 14).

Sodium intake (excretion) are considerably different in several population, ranging from 0.2 mmol/24 h (Yanomamo Indians, Brazil) to 242 mmol/24 h (north China), corresponding the Na/K ratios of 0.01 and 7.58, respectively [1]. Mean (median) Na/K ratios in Western and Asian population were approximately 1–3 and 3–5 [16]. In the population survey, the mean Na/K ratios were 1.0–1.3 in the National Health and Nutritional Examination Survey (NHANES, using 24-h dietary recalls [17]) in USA, 1.8 in Norway (24-h urine) [18], 2.40 in Iran (spot urine) [19], 4.1 in China (24-h urine) [20], 2.5 (spot urine) [8] and 5.4 (spot urine) [7] in Japan. Based on the results of the INTERSALT study findings using 24-h urinary collection, Stamler, et al recommended the Na/K target level of 1.0 to reduce the risk of CV diseases [21]. However, it is impractical in a Japanese population. In fact, mean Na/K ratio in this study was 3.13 (range 0.38–8.25) and patients with the Na/K ratio < 1.0 was only 8 (1.5 %). Because of the large difference in the Na/K ration in Japan and Western countries, the INTERMAP research group analyzed the data of 1145 Japanese participants and recommended a cutoff Na/K ratio level of 2 based on the Japanese Dietary Reference Intake, using dietary recalls and 24-h urine collection data [22]. However, participants included in INTERMAP study in Japan were middle-aged (40–59) men and women and the number of high-risk patients for CV diseases, such as heart disease (7.9 %) and stroke (0.08 %), were small [23]. Therefore, the target Na/K ratio level of 2 might not be applied to older high-risk patients in this study. The Na/K cutoff value of 2.9 obtained in this study might be an interim goal for the reduction of HF hospitalization in high-risk Japanese patients. However, it may not be applicable to the low-risk populations and other races other than Japanese. Averill et al., using the MESA (Multi-Ethnic Study of Atherosclerosis) study, reported that the spot urinary Na/K ratio was associated with stroke, but not HF or CV diseases (myocardial infarction, angina, transient ischemic attack, death due to coronary heart disease) [11]. The MESA included only patients with no clinical CV diseases, the average Na/K ratio was 1.30, and the cutoff value of Na/K ratio was 1.0, which might have contributed to the differences in the results.

We believe that this method can aid in predicting HF hospitalization together with the Na/Cr ratio and known clinical factors such as an increase in body weight, peripheral edema, and HF symptoms in real-world practice.

5. Limitations

This study had several limitations. First, this was a post-hoc analysis of a single-center study, which might have contributed to several selection biases. It is of note that the marked heterogeneity of the included patients in the original ESPRIT study [13] (Fig. 1) was a major concern. Second, repeated 24-h urine collection is the gold standard for estimating an individual's daily salt and potassium intake [1], which is not always feasible in everyday practice. In contrast, spot urine collection is less burdensome and repeated measurement of the Na/K ratio is a good alternative for 1–2-day 24-h urinary Na/K ratio [24,25]. Third, the number of included patients and HF hospitalizations were still small. Therefore, some important factors could not be adjusted for. Specifically, the number of patients with high Na/Cr and low Na/K ratios was small and the results of this population were inconclusive. Fourth, the AUC in ROC analysis was relatively low (0.60); the ability of the Na/K ratio to discriminate HF hospitalization may not be so high (Fig. 2). However, the results of Kaplan–Meier curves (Fig. 3) revealed clear discriminatory ability and thus this method may be feasible. Finally, because the original ESPRIT study was conducted between 2011 and

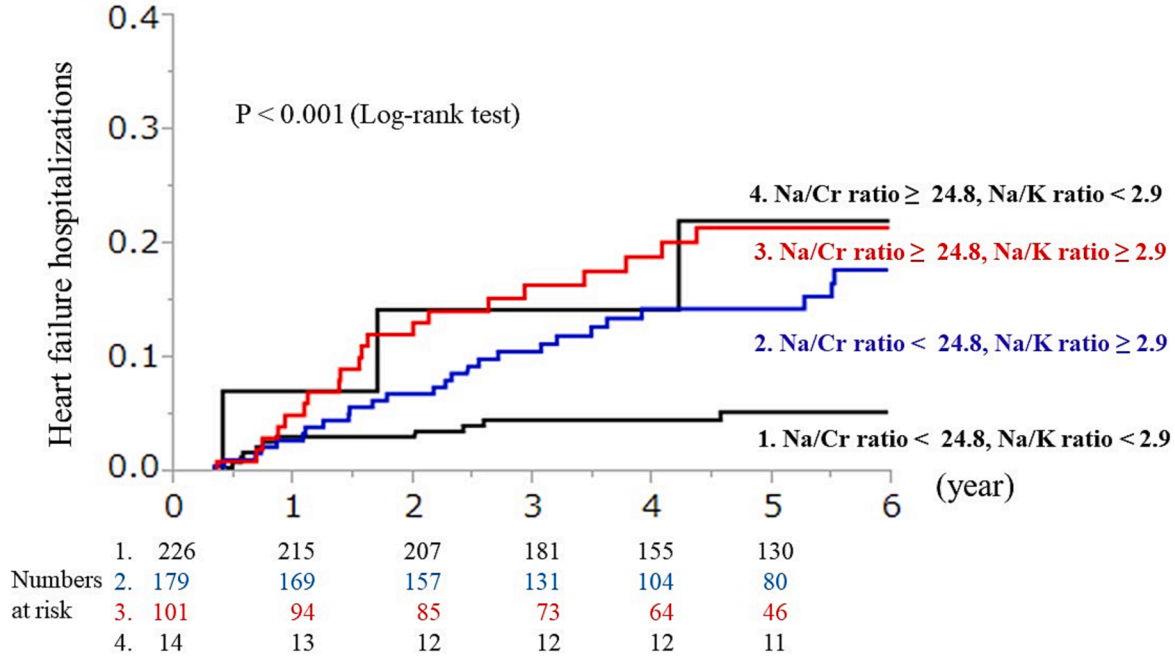

Fig. 4. Kaplan–Meier HF hospitalizations curves for the Na/K ratios and Na/Cr ratios in spot urine. 1. Na/Cr ratio < 24.8 and Na/K ratio < 2.9, 2. Na/Cr ratio < 24.8 and Na/K ratio ≥ 2.9. 3. Na/Cr ratio ≥ 24.8 and Na/K ratio ≥ 2.9, 4. Na/Cr ratio ≥ 24.8 and Na/K ratio < 2.9.

2015, sacubitril/valsaltan and sodium-glucose transport protein 2 inhibitors, which were widely used in patients with HF, were not available.

6. Conclusion

The Na/K ratio in spot urine is associated with HF hospitalization in high-risk Japanese patients. However, further studies are needed to validate this finding.

CRediT authorship contribution statement

Tsuneaki Sadanaga: . **Shinichi Hirota:** Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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