

# Pre-dialysis Hyponatremia and Change in Serum Sodium Concentration During a Dialysis Session Are Significant Predictors of Mortality in Patients Undergoing Hemodialysis



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**Background:** Previous studies have shown that hyponatremia is associated with greater mortality in hemodialysis (HD) patients. However, there have been few reports regarding the importance of the change in serum sodium (SNa) concentration ( $\Delta$ SNa) during dialysis sessions. To investigate the relationships of pre-dialysis hyponatremia and  $\Delta$ SNa during a dialysis session with mortality, we analyzed data from a national registry of Japanese patients with end-stage kidney disease.

**Methods:** We identified 178,114 patients in the database who were undergoing HD 3 times weekly. The study outcome was 2-year all-cause mortality, and the baseline SNa concentrations were categorized into quintiles. We evaluated the relationships of SNa concentration and  $\Delta$ SNa with mortality using Cox proportional hazards models.

**Results:** During a 2-year follow-up period, 25,928 patients died. Each 1-mEq/l reduction in pre-HD SNa concentration was associated with a cumulatively greater risk of all-cause mortality (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.05–1.06). In contrast, a larger  $\Delta$ SNa was associated with higher all-cause mortality (HR for a 1-mEq/l increase in  $\Delta$ SNa, 1.02; 95% CI 1.01–1.02). The combination of low pre-HD SNa concentration and large  $\Delta$ SNa was also associated with higher mortality (HR 1.09; 95% CI 1.05–1.13). Participants with the lowest SNa concentration ( $\leq 136$  mEq/L) and the highest  $\Delta$ SNa ( $>4$  mEq/L) showed higher mortality than those with an intermediate pre-HD SNa concentration (137–140 mEq/L) and the lowest  $\Delta$ SNa ( $\leq 2$  mEq/L).

**Conclusions:** Lower pre-HD SNa concentration and higher  $\Delta$ SNa are associated with a greater risk of mortality in patients undergoing HD.

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KEYWORDS: hemodialysis; hyponatremia; mortality; prospective cohort

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SNa plays an important role in the maintenance of the osmotic equilibrium in the extracellular space and determines the distribution of water between the intracellular and extracellular compartments. Previous

studies have shown that HD patients with hyponatremia have a higher mortality rate,<sup>1–5</sup> and indeed hyponatremia is a relatively common electrolyte disorder in dialysis patients. Recently, several studies have shown that low SNa concentration in HD patients is an important factor in their survival,<sup>6,7</sup> and consistent associations have been shown between low baseline SNa and higher mortality. In contrast, Rhee *et al.*<sup>7</sup> have reported a U-shaped relationship between pre-dialysis SNa and all-cause mortality in HD patients. However, low SNa before HD may be the result of the interplay of a number of risk factors for dysnatremia,

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including substantial inter-dialytic weight gain, poor nutritional status and low food intake, and comorbidities predisposing to excess thirst, that are also individually associated with a greater risk of mortality. However, hyponatremia may have a direct effect to increase mortality.<sup>2</sup> Although the brain seems to be the main target for hyponatremia, especially in acute hyponatremia, other organs, for example the lungs and bones, also may be affected by hyponatremia.<sup>8</sup> Furthermore, it has been reported that patients with both pneumonia and hyponatremia are more likely to die.<sup>9</sup>

However, few studies have characterized the change in SNa concentration ( $\Delta$ SNa: post-HD SNa – pre-HD SNa) during an HD session. Although Hecking *et al.*<sup>6</sup> reported an association between predialysis SNa and dialysate sodium concentration,  $\Delta$ SNa was not calculated. Therefore, we aimed to obtain pre- and post-HD SNa concentrations from a national registry of patients with end-stage kidney disease in Japan, and to determine the relationships of SNa and  $\Delta$ SNa during HD with mortality.

## METHODS

### Database and Patient Selection

The data were extracted from the Japanese Society for Dialysis Therapy Renal Data Registry, which has previously been described in detail.<sup>10</sup> Briefly, the Japanese Society for Dialysis Therapy has conducted annual questionnaire-based surveys of dialysis facilities throughout Japan since 1968, with questionnaires being filled out by medical staff in each facility. Because the response rate has exceeded 95% every year, the database covers nearly all the patients undergoing dialysis in Japan. Because SNa concentration data were only collected during 2008, the datasets for 2008, 2009, and 2010 were combined and analyzed in the present study. We included patients who (i) were aged  $\geq 18$  years, (ii) had undergone in-center hemodialysis 3 times a week, and (iii) had SNa data recorded pre- and post-HD. The study protocol was approved by the Ethics Committee of the Japanese Society for Dialysis Therapy (JSDT approval number 20).

### Baseline Covariates

Data were collected regarding demographics (age, sex, body mass index), the primary kidney disease (diabetic or nondiabetic), the duration of HD, the number of hours of HD per session, and the pre- and post-HD body weight. In addition, predialysis albumin, urea nitrogen, pre- and post-SNa, calcium, phosphate, total cholesterol, C-reactive protein, and hemoglobin were measured. Furthermore, normalized protein catabolic rate (nPCR), a marker of dialysis adequacy (Kt/V), was

calculated, the presence of cardiovascular disease (myocardial infarction, cerebral infarction, cerebral hemorrhage, or amputation of an extremity) was recorded, and the dialysate sodium concentration was measured. Dialysis doses were measured using the single-pool Kt/V method and nPCR was calculated using Shinzato's formula.<sup>11</sup>

### Study Outcomes

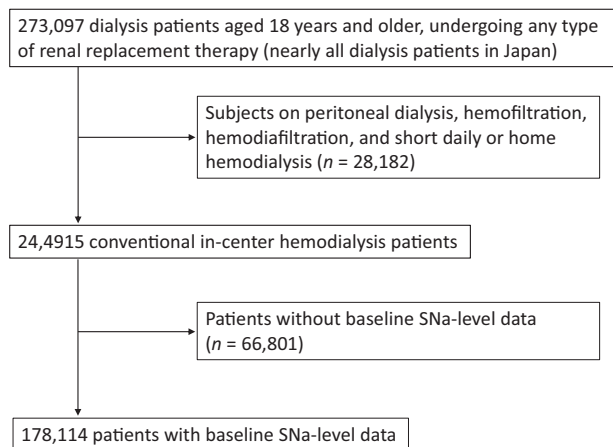
The main outcome measure was time to all-cause mortality during the 2-year observation period. As a secondary outcome, we also evaluated the time to the development of cardiovascular disease, defined as the onset of myocardial infarction, cerebral infarction, or cerebral hemorrhage, or amputation of an extremity.

### Statistical Analysis

Data are presented as numbers (percentages) for categorical variables, and as means (SDs) for continuous variables with a normal distribution or medians (interquartile ranges) for those with a skewed distribution. The distributions of baseline characteristics, stratified according to SNa quintile, were compared using trend analysis. We calculated the change in SNa concentration ( $\Delta$ SNa: post-HD SNa – pre-HD SNa) during an HD session.

Cox proportional hazards models were constructed to calculate the HR and 95% CI for all-cause, cardiovascular-related, infectious, and other mortality, in which the lowest quintiles were used as the reference groups.

We constructed 3 multivariate models: model 1, which was adjusted for age, sex, duration of HD, and number of hours of HD treatment per session; model 2, which was adjusted for the variables adjusted for in model 1, plus the hemoglobin, calcium, phosphate, and total cholesterol concentrations,  $\Delta$ BW% ( $[(\text{pre-HD body weight} - \text{post-HD body weight}) / \text{pre-HD body weight} \times 100]$ ),  $\Delta$ SNa, and dialysate concentration; and model 3, which was adjusted for the variables adjusted for in model 2, plus the concentrations of total cholesterol, albumin, and C-reactive protein, nPCR, and a past history of myocardial infarction, brain infarction, brain hemorrhage, amputation of an extremity, or hip fracture. We also evaluated the possibility of a continuous, nonlinear relationship between the SNa concentration and mortality using a fully adjusted, restricted cubic spline (RCS) model with 4 knots. We also examined the association of SNa concentration and  $\Delta$ SNa with the onset of cerebral infarction and lower limb amputation, using a logistic regression model. Logistic regression models were constructed to calculate the odds ratio and 95% CI for cerebral infarction and lower limb amputation.



**Figure 1.** Patient selection flow chart. SNa, serum sodium concentration.

All the reported *P* values are 2-sided and  $P < 0.05$  was considered to represent statistical significance. Statistical analysis was performed using JMP Statistics version 11.0 (SAS Institute, Tokyo, Japan) and the SAS software package version 9.2 (SAS Institute, Cary, NC).

## RESULTS

### Study Participants

The study enrollment process is summarized in [Figure 1](#). Of the total of 273,097 dialysis patients, those on renal replacement therapy other than HD conducted in a facility ( $n = 28,182$ ) were excluded. Of the remaining 244,915 HD patients, baseline pre- and post-HD SNa data were available for 178,114 (66,801 were excluded.). The mean (SD) pre- and post-HD SNa concentrations of the participants were 139.0 (2.9) mEq/l and 139.6 (2.1) mEq/l ([Figure 2a](#) and [b](#)). The baseline characteristics of the participants according to quintiles of SNa concentration are summarized in [Table 1](#). Lower SNa concentration was significantly associated with older age, lower albumin, calcium, phosphate, nPCR, and hemoglobin concentrations, higher C-reactive protein, prior history of cardiovascular disease, amputation of an extremity, and hip fracture.

### The Relationship Between Dialysate Sodium Concentration and Pre-HD SNa

A dialysate sodium concentration of 140 mEq/l was used in 148,388 patients (85.9%), whereas 8462 patients (4.9%) were dialyzed with dialysate containing  $>140$  mEq/l sodium and 15,879 patients (8.9%) were dialyzed with dialysate containing  $<140$  mEq/l sodium. In addition, the dialysate concentration was unknown for 5385 patients. The dialysate sodium concentration used was distributed nearly identically in all 5 of the mean SNa categories, with very similar percentages of patients having a dialysate sodium concentration

of  $<140$  mEq/l, exactly 140 mEq/l, or  $>140$  mEq/l ([Figure 2c](#)). However,  $>80\%$  of the participants had a dialysate sodium concentration of exactly 140 mEq/l.

### Risk of Mortality and Complications Associated With Pre-HD SNa Concentration

After 2 years, a total of 25,928 deaths had occurred, of which 11,347 (43.8%) had been attributed to cardiovascular disease, 4789 (18.5%) to infectious disease, and 9792 (37.8%) to other diseases. A crude analysis showed a significant L-shaped relationship between SNa quintile and the study outcomes ([Table 2](#)).

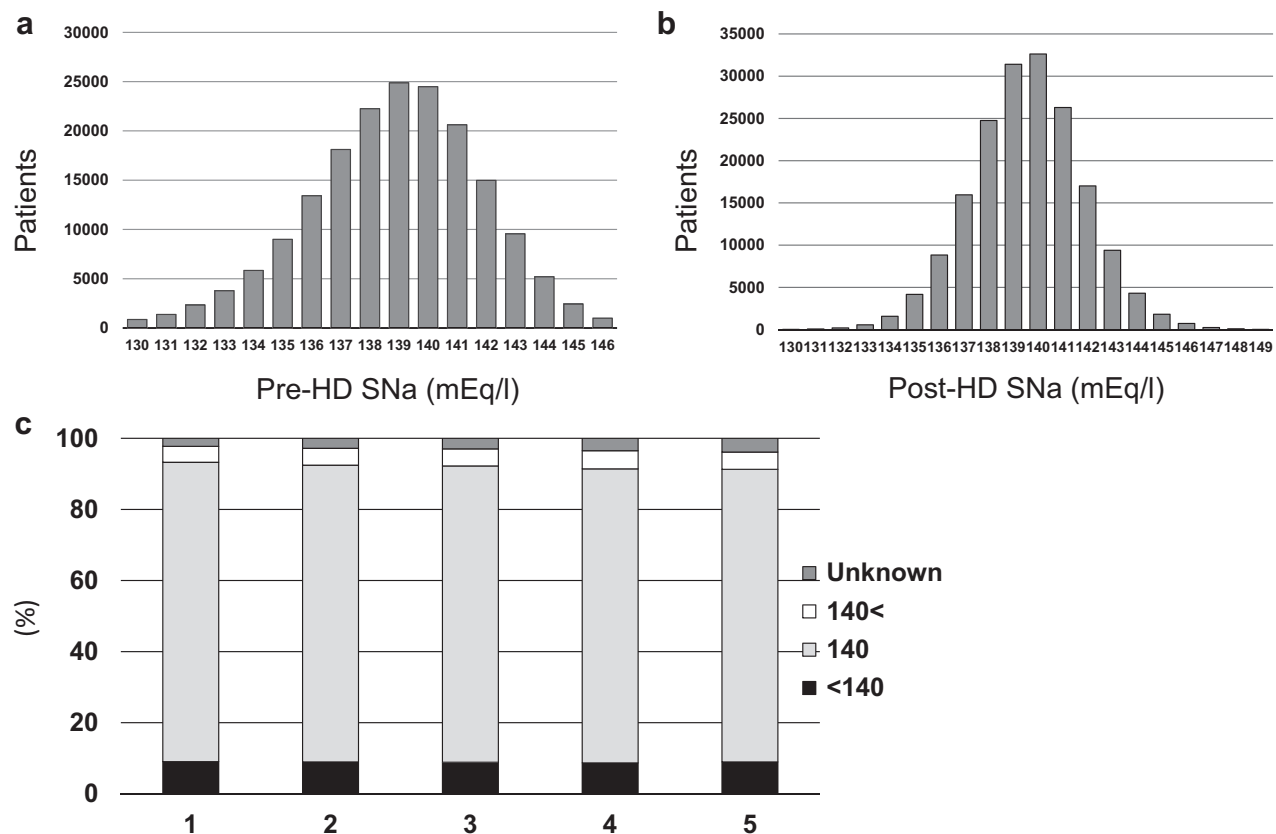
Unadjusted Kaplan-Meier curves for overall survival are shown in [Figure 3](#). These associations were somewhat attenuated after adjustment for clinically relevant demographic factors, but they remained statistically significant (the fully adjusted HR [95% CI] of the lowest quintiles was 1.44 [1.34–1.56],  $P < 0.0001$ , for all-cause mortality; 1.42 [1.27–1.59],  $P < 0.0001$ , for cardiovascular mortality; and 1.90 [1.58–2.28],  $P < 0.0001$  for mortality related to infection; [Table 2](#)). The continuous, fully adjusted association between the SNa concentration and all-cause mortality was similar. Multivariable-adjusted RCS revealed that low Pre-HD SNa was associated with a higher HR for all-cause mortality ([Figure 4a](#)). To determine the influence of low SNa on the risk of coronary heart disease, cerebral hemorrhage, cerebral infarction, amputation of a lower extremity, and hip fracture, we used multivariable-adjusted RCS, which showed that as SNa decreased, the odds ratios for cerebral infarction ([Figure 4b](#)), lower limb amputation ([Figure 4c](#)), and hip fracture ([Supplementary Figure S3A](#)) also increased.

### Risk of Mortality and Complications Associated With $\Delta$ SNa

Multivariable-adjusted RCS revealed that as  $\Delta$ SNa increased, so did the HR for all-cause mortality ([Figure 5a](#)) and the odds ratio for cerebral infarction ([Figure 5b](#)), lower limb amputation ([Figure 5c](#)), and hip fracture ([Supplementary Figure S3B](#)). However, such a relationship was not identified for coronary artery disease ([Supplementary Figure S1B](#)) in multivariable-adjusted RCS.

### Risk of Mortality Associated With Pre-HD SNa by $\Delta$ SNa Level

The combination of low pre-HD SNa concentration and large  $\Delta$ SNa was also associated with higher mortality (HR 1.09; 95% CI 1.05–1.13). Participants with the lowest SNa concentration ( $\leq 136$  mEq/l) and the highest  $\Delta$ SNa ( $>4$  mEq/l) showed higher mortality than those with an intermediate pre-HD SNa concentration (137–140 mEq/l) and the lowest  $\Delta$ SNa ( $\leq 2$  mEq/l) ([Table 3](#)).



**Figure 2.** Distribution of baseline serum sodium concentrations (SNa). (a) Serum sodium concentration before a hemodialysis (HD) session (pre-HD SNa). (b) Serum sodium concentration after an HD session (post-HD SNa). (c) Relationship between dialysate sodium concentration and pre-dialysis serum sodium concentration. Distribution of dialysate sodium concentration according to the mean predialysis serum sodium (Pre-HD SNa) category. Categories: 1, SNa ≤ 136 mEq/l; 2, 136 < SNa ≤ 138 mEq/l; 3, 138 < SNa ≤ 140 mEq/l; 4, 140 < SNa ≤ 141 mEq/l; 5, 141 mEq/l < SNa.

**Table 1.** Baseline characteristics of the participants

Characteristics	Total n = 178,114	1 SNa ≤ 136 n = 34,588	2 136 < SNa ≤ 138 n = 39,968	3 138 < SNa ≤ 140 n = 49,076	4 140 < SNa ≤ 141 n = 20,537	5 141 < SNa n = 33,945	P
Male/female							
Age (years)	65.2 ± 12.5	66.51 ± 12.76	65.04 ± 12.66	64.78 ± 12.42	64.93 ± 12.24	65.04 ± 12.03	<0.001
HD vintage (years)	7.2 ± 7.2	6.42 ± 6.43	7.04 ± 6.90	7.30 ± 7.23	7.60 ± 7.45	7.99 ± 7.79	<0.001
HD time (min)	235.7 ± 31.6	234.89 ± 32.85	236.57 ± 31.88	236.06 ± 30.48	235.72 ± 31.04	235.23 ± 30.52	0.299
Pre-HD Hb (g/dl)	10.4 ± 1.3	10.39 ± 1.37	10.45 ± 1.28	10.40 ± 1.24	10.37 ± 1.22	10.30 ± 1.23	<0.001
Pre-HD Alb (g/dl)	3.7 ± 0.4	3.59 ± 0.48	3.69 ± 0.43	3.72 ± 0.41	3.73 ± 0.41	3.72 ± 0.42	<0.001
Pre-HD Ca (mg/dl)	9.0 ± 0.8	8.91 ± 0.86	8.98 ± 0.83	8.97 ± 0.82	8.98 ± 0.81	8.96 ± 0.81	<0.001
Pre-HD P (mg/dl)	5.3 ± 1.4	5.22 ± 1.57	5.33 ± 1.47	5.32 ± 1.41	5.29 ± 1.38	5.25 ± 1.38	0.0082
Pre-HD T-Chol (mg/dl)	153.2 ± 37.0	150.86 ± 37.69	152.91 ± 37.14	153.80 ± 36.74	154.57 ± 36.70	154.41 ± 36.15	<0.001
Pre-HD CRP (mg/dl)	0.5 ± 1.6	0.84 ± 2.20	0.56 ± 1.64	0.47 ± 1.30	0.43 ± 1.35	0.40 ± 1.18	<0.001
Kt/V (single pool)	1.4 ± 0.3	1.38 ± 0.31	1.39 ± 0.30	1.39 ± 0.30	1.39 ± 0.31	1.39 ± 0.30	<0.001
nPCR	0.87 ± 0.18	0.88 ± 0.19	0.88 ± 0.18	0.88 ± 0.18	0.87 ± 0.18	0.86 ± 0.18	<0.001
ΔBW%	4.18 ± 11.07	4.41 ± 13.29	4.36 ± 6.18	4.18 ± 8.90	3.94 ± 15.56	3.86 ± 12.51	<0.001
Past history							
MI (%)	5230 (2.9)	1012 (2.9)	1262 (2.5)	1406 (2.9)	592 (2.9)	958 (2.8)	<0.001
BI (%)	21898 (12.3)	5440 (15.7)	4911 (9.8)	5579 (11.4)	2269 (11.0)	3699 (10.9)	<0.001
BH (%)	7840 (4.4)	1730 (5.0)	1520 (4.4)	1823 (3.6)	699 (3.4)	1222 (3.6)	<0.001
Amputation (%)	4297 (2.4)	1312 (3.8)	971 (1.9)	1042 (2.1)	386 (1.9)	586 (1.7)	<0.001
Hip fracture (%)	3844 (2.6)	1105 (3.2)	827 (1.7)	929 (1.9)	391 (1.9)	592 (1.7)	<0.001

Alb, serum albumin; BH, brain hemorrhage; BI, brain infarction; BW, body weight; Ca, calcium; CRP, C-reactive protein; CVD, cardiovascular disease; Hb, hemoglobin; HD, hemodialysis; MI, myocardial infarction; nPCR, normal protein catabolic rate; P, phosphate; SNa, serum sodium; T.Chol, total cholesterol. Values are presented as means ± SDs.

**Table 2.** Cox proportional hazards models for the rate of all-cause and cause specific mortality

Serum sodium category	Unadjusted			Adjusted								
	HR	95% CI	P	Model 1			Model 2			Model 3		
				HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
<b>All-cause</b>												
1	2.04	1.95–2.13	<.0001	1.90	1.82–1.99	<.0001	1.71	1.61–1.82	<.0001	1.44	1.34–1.56	<.0001
2	1.26	1.20–1.32	<.0001	1.26	1.20–1.32	<.0001	1.20	1.13–1.27	<.0001	1.14	1.06–1.22	0.0004
3	1.07	1.02–1.12	0.0064	1.08	1.03–1.13	0.002	1.06	1.00–1.12	0.03	1.05	0.98–1.12	0.21
4	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
5	0.98	0.93–1.03	0.45	0.98	0.93–1.03	0.34	1.00	0.94–1.06	0.96	1.00	0.93–1.08	0.99
<b>CVD</b>												
1	1.07	1.05–1.09	<.0001	1.91	1.78–2.05	<.0001	1.61	1.47–1.76	<.0001	1.42	1.27–1.59	<.0001
2	1.02	1.00–1.04	0.048	1.25	1.17–1.35	<.0001	1.12	1.03–1.22	0.01	1.09	0.98–1.21	0.12
3	1.00	0.99–1.02	0.60	1.08	1.01–1.16	0.03	1.03	0.95–1.12	0.41	1.03	0.93–1.15	0.53
4	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
5	1.00	0.98–1.02	0.92	0.94	0.87–1.02	0.15	0.96	0.88–1.05	0.40	1.00	0.89–1.12	0.99
<b>Infection</b>												
1	2.45	2.19–2.73	<.0001	2.25	2.02–2.51	<.0001	2.29	1.98–2.64	<.0001	1.90	1.58–2.28	<.0001
2	1.40	1.25–1.57	<.0001	1.39	1.24–1.55	<.0001	1.41	1.23–1.62	<.0001	1.38	1.16–1.64	0.002
3	1.08	0.96–1.21	0.18	1.09	0.97–1.22	0.13	1.11	0.97–1.27	0.11	1.14	0.96–1.35	0.12
4	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
5	1.06	0.93–1.19	0.38	1.04	0.92–1.18	0.48	1.07	0.93–1.24	0.33	1.05	0.87–1.26	0.63
<b>Others</b>												
1	1.87	1.74–2.02	<.0001	1.75	1.62–1.88	<.0001	1.07	1.05–1.10	<.0001	1.27	1.12–1.44	0.0001
2	1.22	1.13–1.31	<.0001	1.21	1.12–1.31	<.0001	1.02	1.00–1.04	0.13	1.09	0.97–1.22	0.14
3	1.06	0.98–1.14	0.13	1.07	0.99–1.15	0.08	0.66	0.99–1.02	0.66	1.01	0.91–1.13	0.82
4	Ref.	-	-	Ref.	-	-	Ref.	-	-	Ref.	-	-
5	0.99	0.91–1.07	0.77	0.98	0.90–1.06	0.65	1.00	0.98–1.02	0.90	0.98	0.87–1.11	0.80

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

Model 1 was adjusted for age, sex, duration of hemodialysis, and the length of a dialysis session.

Model 2 was adjusted for Model 1 variables + (hemoglobin, calcium, phosphate,  $\Delta$ BW% [(pre-HD body weight – post-HD body weight) / pre-HD body weight  $\times$  100], change in sodium during dialysis, dialysate sodium concentration, and Kt/V).

Model 3 was adjusted for Model 2 variables + (total cholesterol, albumin, C-reactive protein, and normal protein catabolic rate) + (past history of myocardial infarction, brain infarction, brain hemorrhage, amputation of an extremity, and hip fracture).

Values are presented as means  $\pm$  SDs.

Serum sodium categories: 1,  $S_{Na} \leq 136$  mEq/l; 2,  $136 < S_{Na} \leq 138$  mEq/l; 3,  $138 < S_{Na} \leq 140$  mEq/l; 4,  $140 < S_{Na} \leq 141$  mEq/l; 5,  $141$  mEq/l  $< S_{Na}$ .

## DISCUSSION

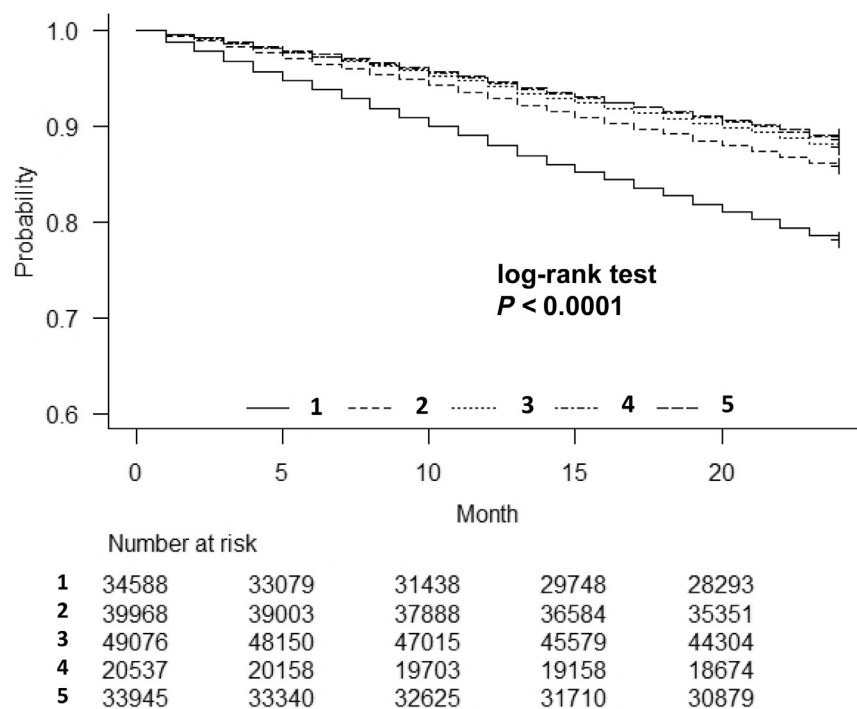
The present results indicated a relationship between better survival in HD patients and  $S_{Na} > 136$  mEq/l. The major finding of this study is that high  $\Delta S_{Na}$  is a significant and independent predictor of mortality in HD patients. To the best of our knowledge, this is the first published study to demonstrate an adverse effect of hyponatremia and fluctuations in  $S_{Na}$  concentration during a dialysis session. We also found significant associations between higher  $\Delta S_{Na}$  and stroke and amputation of an extremity. The principal strength of the study is that we have demonstrated a dose-response relationship between serum sodium and prognosis using a very large cohort of patients undergoing HD.

Several possible mechanisms may explain the greater mortality in patients with hyponatremia.<sup>2</sup> First, acute and chronic hyponatremia with progressive cerebral edema could contribute to mortality. Second, hyponatremia is also a marker of the severity of the underlying disease. Several studies have found that hyponatremia occurs alongside markers of the progression of heart

failure.<sup>12,13</sup> Third, severe underlying disease causes chronic hyponatremia and contributes to higher mortality, and hyponatremia further increases the risk of mortality. These mechanisms are consistent with the findings of recent studies that hyponatremia is associated with mortality.<sup>1,14,15</sup> In addition, when the present data were adjusted for nutritional status (serum albumin, nPCR) and body weight gain ( $\Delta$ BW%), the association between hyponatremia and all-cause mortality remained. Furthermore, hyponatremia predisposes to infections, fractures, and cognitive dysfunction, which affect the prognosis of HD patients.

Recent reports have suggested that hyponatremia increases the risk of infections,<sup>15</sup> especially tuberculosis<sup>16</sup> and pneumonia,<sup>9</sup> and associations between hyponatremia and greater mortality from these diseases have also been identified. The mechanism involves mucous membrane edema that develops due to extracellular hypotonicity and osmosis into the intracellular space, which compromises the microbial barrier function of the mucosa in the respiratory, gastrointestinal, and urinary tracts.<sup>15</sup> In HD patients with

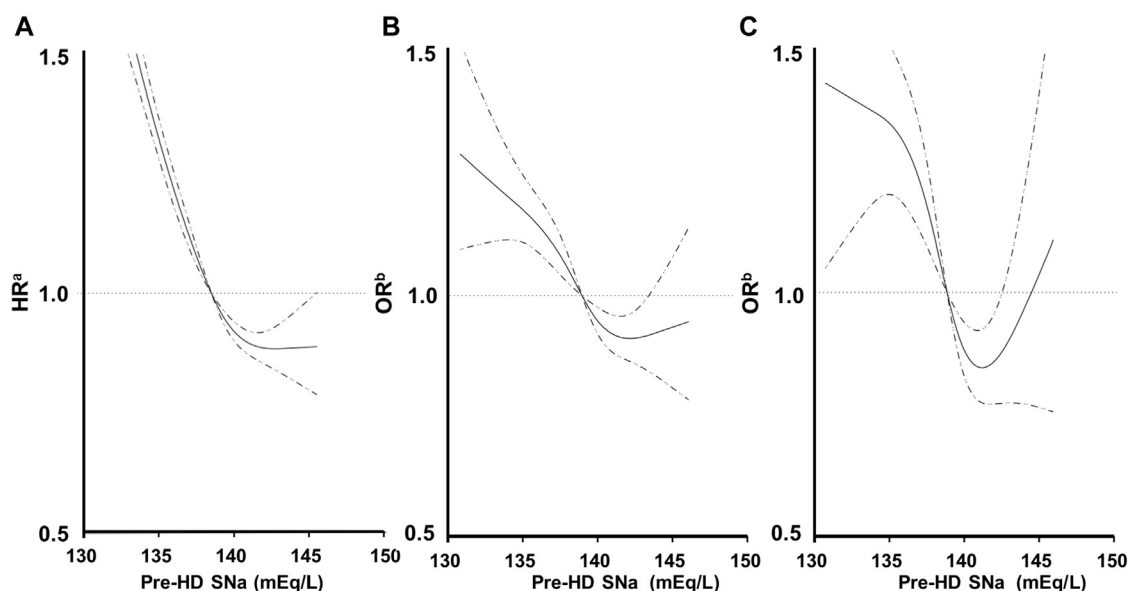




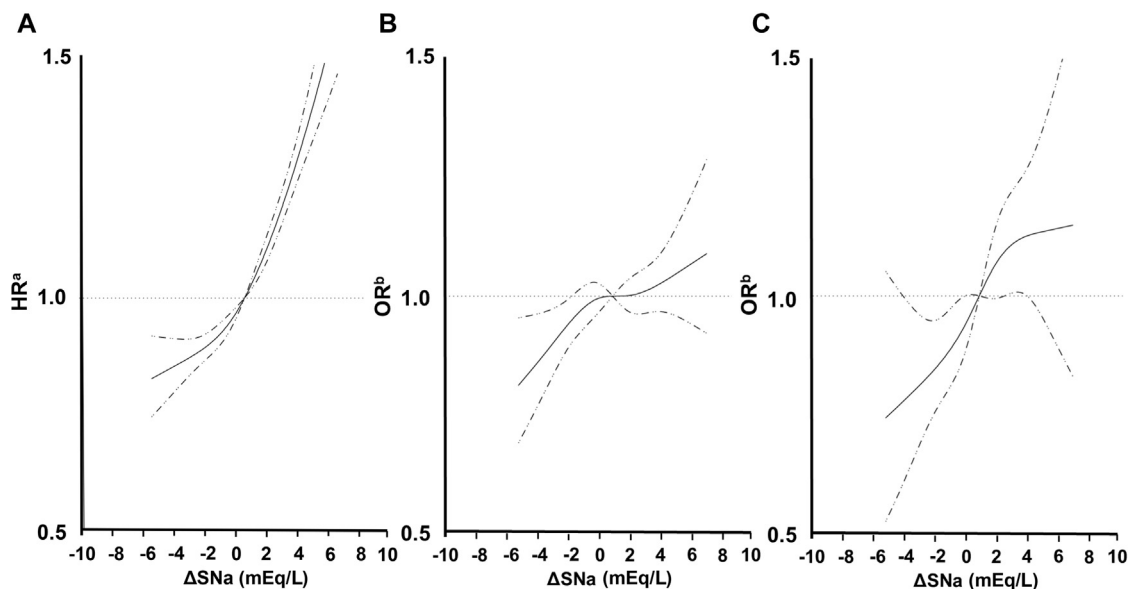
**Figure 3.** Kaplan–Meier plots for survival rates in the 5 groups during the 2-year follow-up period: univariate analysis. Categories: 1,  $SNa \leq 136$  mEq/l; 2,  $136 < SNa \leq 138$  mEq/l; 3,  $138 < SNa \leq 140$  mEq/l; 4,  $140 < SNa \leq 141$  mEq/l; 5,  $141$  mEq/l  $< SNa$ .

hyponatremia, bone turnover abnormalities are also universal, and chronic hyponatremia has recently been reported to be a risk factor for osteoporosis.<sup>8</sup> In addition, hyponatremia leads to cognitive dysfunction,<sup>17,18</sup> disequilibrium, gait disturbances, falls, and bone fractures,<sup>19</sup> all of which have a substantial influence on

the prognosis of HD patients. The present data show independent associations between hyponatremia and high risks of death from infectious disease, hip fracture, and amputation of a lower extremity. However, the mechanisms linking hyponatremia with prognosis in these patients remain unclear.



**Figure 4.** Multivariable-adjusted restricted cubic spline plots of (a) the hazard ratios (HR) for all-cause mortality according to serum sodium concentration before an HD session (pre-HD SNa). Multivariable-adjusted restricted cubic spline plots of the odds ratios (OR) for (b) cerebral infarction and (c) lower limb amputation according to pre-HD SNa. The solid line represents the HR and OR, and the dotted line represents the 95% confidence interval. The multivariable-adjusted model (a) Cox model and (b) logistic model was adjusted for age, sex, duration of HD, length of an HD session, dialysate sodium, history of CVD, Hb, Alb,  $\Delta SNa$ , Ca, P, T-Chol, Kt/V, CRP, nPCR,  $\Delta BW\%$ . Alb, serum albumin; BW, body weight; Ca, calcium; CRP, C-reactive protein; Hb, hemoglobin; HD, hemodialysis; P, phosphate; nPCR, normal protein catabolic rate; T.Chol., total cholesterol.



**Figure 5.** Multivariable-adjusted restricted cubic spline plots of (a) the hazard ratios (HR) for all-cause mortality according to post-dialysis serum sodium concentration (SNa)– pre-dialysis SNa ( $\Delta$ SNa). Multivariable-adjusted restricted cubic spline plots of the odds ratios (OR) for (b) cerebral infarction and (c) lower limb amputation according to  $\Delta$ SNa. The solid line represents the HR and OR, and the dotted line represents the 95% confidence interval. The multivariable-adjusted model (a) Cox model and (b) logistic model was adjusted for age, sex, duration of HD, length of an HD session, dialysate sodium, history of cardiovascular disease (CVD), Hb, Alb, SNa, Ca, P, T-Chol, Kt/V, CRP, nPCR, and  $\Delta$ BW%. Alb, serum albumin; BW, body weight; Ca, calcium; CRP, C-reactive protein; Hb, hemoglobin; HD, hemodialysis; P, phosphate; nPCR, normal protein catabolic rate; T.Chol., total cholesterol.

We also studied the significance of fluctuations in SNa concentration during HD ( $\Delta$ SNa) and investigated the relationship between  $\Delta$ SNa during HD and mortality. To date, there have been few similar studies. One previous study<sup>20</sup> showed that higher pre-HD SNa variability, indicated by measurements of mean (SD) SNa, mean variability, and mean directional range, was associated with greater all-cause mortality. Specifically, the mean directional range of SNa, representing the difference between the minimum and maximum values during 2 years of follow-up, was associated with mortality. The strength of the present study is that we measured the change in SNa between pre-HD and post-HD samples, finding that the larger the  $\Delta$ SNa, the higher the all-cause mortality, and incidences of cerebral infarction, amputation of a lower extremity, and hip fracture. A larger  $\Delta$ SNa may cause organ damage,

but the detailed mechanism involved remains to be determined. We also found that pre-hemodialysis hypernatremia was not a mortality risk in this study. In the DOPPS Study,<sup>6</sup> the effect of hypernatremia on mortality could not be ascertained. However, a U-shaped association between serum sodium and mortality has been observed in incident HD patients.<sup>7</sup>

In the central nervous system, an overly rapid correction of serum sodium can lead to osmotic demyelination syndrome, and chronic hyponatremia causes water to enter astrocytes in larger quantities.<sup>21</sup> Osmotic demyelination syndrome is usually caused by overly rapid correction of serum sodium levels in patients with chronic hyponatremia, and involves demyelination, especially of the central basis pontis (pontine myelinolysis). The reasons why hyponatremia predisposes to other central nervous system disorders

**Table 3.** Adjusted mortality risk associated with pre-HD SNa by  $\Delta$ SNa level

Serum sodium category	$\Delta$ SNa category		
	0 < $\Delta$ SNa $\leq$ 2 HR (95% CI)	2 < $\Delta$ SNa $\leq$ 4 HR (95% CI)	4 < $\Delta$ SNa HR (95% CI)
SNa $\leq$ 136	- (N = 0)	1.046 (0.998–1.096)	1.089 <sup>a</sup> (1.053–1.126)
136 < SNa $\leq$ 140	1 (reference)	1.007 (0.975–1.040)	1.014 (0.981–1.048)
140 < SNa	0.987 (0.954–1.021)	0.995 (0.962–1.030)	0.991 (0.939–1.046)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HD, hemodialysis; HR, hazard ratio; SNa, serum sodium.

<sup>a</sup> < 0.0001

Cox model adjusted for age, sex, HD vintage, HD time, dialysate sodium, history of cardiovascular disease, hemoglobin, albumin, calcium, phosphate, total cholesterol, Kt/V, C-reactive protein, normal protein catabolic rate,  $\Delta$ BW% [(pre-HD body weight – post-HD body weight) / pre-HD body weight  $\times$  100].

are unknown, but the present findings show a significant association between high  $\Delta$ SNa and stroke.

The major strength of our data is that they were derived from a large national cohort, and by analyzing data from various regions of Japan, we have been able to show that SNa and  $\Delta$ SNa are independent risk factors for all-cause, cardiovascular, and infectious disease-related mortality. From the results of this study, changes in plasma sodium concentration from pre- to post-dialysis may lead to organ damage. However, several limitations of the study should be acknowledged. First, the study was observational in nature, which means we cannot draw conclusions regarding cause and effect regarding the relationship between  $\Delta$ SNa and mortality. Second, plasma glucose concentrations were not available for all the participants; plasma glucose influences plasma osmolality, particularly in diabetic patients, and would affect SNa and  $\Delta$ SNa.<sup>22</sup> Third, we did not have exact data regarding interdialytic weight gain and dry weight data; therefore, we could not determine the influence of interdialytic water retention. Instead, we used water removal amount per body weight ( $\Delta$ BW%) to adjust the analyses. Fourth, this study did not have the data that patients were taking the drugs. We did not consider the possible effect of pharmacological interference. Fifth, in this study, the exact cause of hyponatremia could not be identified; however, a previous study<sup>23</sup> reported that malnutrition and inflammation were associated with a higher likelihood of hyponatremia (sodium < 135 mEq/l), whereas fluid overload was associated with a lower likelihood of hyponatremia. Sixth,  $\Delta$ SNa in this study reflects the same tonicity change for HD patients. As a result, this sodium gradient may affect an HD patient's prognosis and illness. In this regard, a new hemodialysis machine with the aim to achieve no sodium gradient in HD and online HDF treatments was tested in the form of a prospective clinical trial.<sup>24–26</sup> Advances in these devices, automated sodium and tonicity management tool embedded in hemodialysis machine, have the potential to solve the problem in the future. Finally, this study used data from 2008 to 2010 in Japan; therefore, applying our findings to current dialysis patients may be inappropriate. In addition, baseline variables in this study were derived only from the 2008 database and were based on a single measurement.

In conclusion, we have shown that low pre-HD SNa concentration and high  $\Delta$ SNa are associated with a greater risk of death in HD patients. This finding may have implications for the management of dialysis in patients with hyponatremia; however, further study of these associations and the mechanisms involved is required.

## DISCLOSURES

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Figure S1.** Multivariable-adjusted restricted cubic spline plots of the odds ratios (OR) for coronary heart disease according to (A) serum sodium concentration before an HD session (Pre-HD SNa) and (B) post-dialysis SNa – pre-dialysis SNa ( $\Delta$ SNa).

**Figure S2.** Multivariable-adjusted restricted cubic spline plots of the odds ratios (OR) for cerebral hemorrhage according to (A) serum sodium concentration before an HD session (Pre-HD SNa) and (B) post-dialysis SNa – pre-dialysis SNa ( $\Delta$ SNa).

**Figure S3.** Multivariable-adjusted restricted cubic spline plots of the odds ratios (OR) for hip fracture according to (A) serum sodium concentration before an HD session (Pre-HD SNa) and (B) post-dialysis SNa – pre-dialysis SNa ( $\Delta$ SNa).

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