

The impact of high serum bicarbonate levels on mortality in hemodialysis patients

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Background/Aims: The optimal serum bicarbonate level is controversial for patients who are undergoing hemodialysis (HD). In this study, we analyzed the impact of serum bicarbonate levels on mortality among HD patients.

Methods: Prevalent HD patients were selected from the Clinical Research Center registry for End Stage Renal Disease cohort in Korea. Patients were categorized into quartiles according to their total carbon dioxide (tCO₂) levels: quartile 1, a tCO₂ of < 19.4 mEq/L; quartile 2, a tCO₂ of 19.4 to 21.5 mEq/L; quartile 3, a tCO₂ of 21.6 to 23.9 mEq/L; and quartile 4, a tCO₂ of ≥ 24 mEq/L. Cox regression analysis was used to calculate the adjusted hazard ratio (HR) and confidence interval (CI) for mortality.

Results: We included 1,159 prevalent HD patients, with a median follow-up period of 37 months. Kaplan-Meier analysis revealed that the all-cause mortality was significantly higher in patients from quartile 4, compared to those from the other quartiles (*p* = 0.009, log-rank test). The multivariate Cox proportional hazard model revealed that patients from quartile 4 had significantly higher risk of mortality than those from quartile 1, 2 and 3, after adjusting for the clinical variables in model 1 (HR, 1.99; 95% CI, 1.15 to 3.45; *p* = 0.01) and model 2 (HR, 1.82; 95% CI, 1.03 to 3.22; *p* = 0.04).

Conclusions: Our data indicate that high serum bicarbonate levels (a tCO₂ of ≥ 24 mEq/L) were associated with increased mortality among prevalent HD patients. Further effort might be necessary in finding the cause and correcting metabolic alkalosis in the chronic HD patients with high serum bicarbonate levels.

Keywords: Renal dialysis; Bicarbonates; Alkalosis; Mortality

INTRODUCTION

The current guidelines for managing metabolic acidosis suggest that patients with chronic kidney disease (CKD)

and serum bicarbonate concentrations of < 22 mmol/L should be treated with oral bicarbonate supplementation to maintain their serum bicarbonate concentration within the normal range, unless this treatment is con-

traindicated [1]. However, there is no clear consensus regarding the level of serum bicarbonate that should be targeted during hemodialysis (HD). Furthermore, the optimal serum bicarbonate level in HD patients has not been fully clarified.

Intradialytic metabolic alkalosis is induced by high dialysate bicarbonate concentrations, volume contraction, or chronic hypoventilation [2,3]. High serum bicarbonate levels have also been associated with the correction of metabolic acidosis [3] and improvements in protein turnover and serum branched-chain amino acid levels [4]. However, metabolic alkalosis may also contribute to adverse outcomes. The rapid change in serum bicarbonate levels leads to faster decreases in serum potassium and ionized calcium levels, which can subsequently result in cardiac arrhythmia and prolongation of the corrected QT interval [5,6]. This change also results in increased neuromuscular excitability, reduced cerebral blood flow, respiratory suppression, and hemodynamic instability [7,8]. Furthermore, it is associated with increased interdialytic weight gain, which could be caused by exposure to higher sodium bicarbonate levels during HD, and these elevated levels subsequently result in intradialytic hypotension [2]. Finally, several studies have reported that serum bicarbonate levels are associated with mortality in end-stage renal disease (ESRD) [3,9-11]. Therefore, in this study, we investigated the impact of stratified serum bicarbonate levels on mortality among HD patients from the Clinical Research Center (CRC) registry for ESRD cohort in Korea.

METHODS

Study cohort

All patients in this study participated in the CRC registry for ESRD, which is an ongoing observational prospective cohort study of patients with ESRD at 31 Korean centers. The cohort was started in April 2009, and includes adult (> 18 years old) dialysis patients. A total of 1,812 prevalent HD patients were enrolled in this cohort, although 653 patients whose total carbon dioxide (tCO₂) at enrollment could not be ascertained were excluded from the present analysis. Thus, 1,159 HD patients were included in the present analysis.

Demographic data and clinical data were collected at

enrollment, and the assessment of dialysis characteristics and health measurements was performed every 6 months until the end of follow-up. Dates and causes of mortality were immediately reported throughout the follow-up period. The CRC registry for ESRD was approved by the medical ethics committees of all of the participating hospitals, and informed consent was obtained from all patients before their inclusion.

Baseline demographic and clinical data included age, sex, height, weight, body mass index (BMI), causes of ESRD, duration of dialysis, comorbidities, laboratory test results, and therapeutic characteristics. Serum levels of hemoglobin, albumin, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, ferritin, intact parathyroid hormone, and tCO₂ were determined using the patients' blood samples. Prevalent HD patients were categorized into quartiles according to their tCO₂ levels: quartile 1, a tCO₂ of < 19.4 mEq/L; quartile 2, a tCO₂ of 19.4 to 21.5 mEq/L; quartile 3, a tCO₂ of 21.6 to 23.9 mEq/L; and quartile 4, a tCO₂ of ≥ 24 mEq/L.

Cardiovascular disease was defined as the presence of coronary heart disease, peripheral vascular disease, and cerebrovascular disease. The normalized protein catabolic rate (nPCR) was calculated using the following urea kinetic modeling formula; PCR (g/day) = 0.22 + (0.036 × intradialytic rise in BUN × 24) / (intradialytic interval); nPCR (g/kg/day) = PCR / standard weight; standard weight = total body water / 0.58 [12].

Outcomes

The primary clinical outcome of this study was all-cause mortality. All patients were followed until death (event) or the end of the study, with censoring of data at the time the patient underwent renal transplantation, was lost to follow-up, refused to continue participating, or was transferred to a nonparticipating hospital. For each death, the clinical center's principal investigator completed a form that included the cause of death, defined according to the CRC for ESRD study classification.

Statistical analysis

Data for continuous and normally distributed variables were presented as mean ± standard deviation (SD), and those for non-normally distributed continuous variables were presented as median and range, as appropriate. Student *t* test and the Mann-Whitney *U* test were

Table 1. Baseline characteristics of the study population according to total CO₂

| Characteristic | Serum tCO ₂ , mEq/L | | | | p value |
|------------------------------------|---------------------------------|------------------------------------|------------------------------------|-------------------------------|---------|
| | Quartile 1 (≤ 19.3, n = 289) | Quartile 2 (19.4–21.5, n = 285) | Quartile 3 (21.6–23.9, n = 284) | Quartile 4 (≥ 24, n = 301) | |
| tCO ₂ , mEq/L | 17.4 ± 1.5 | 20.5 ± 0.6 | 22.6 ± 0.6 | 26.2 ± 2.2 | < 0.001 |
| Age, yr | 57 ± 13 | 61 ± 12 | 59 ± 13 | 59 ± 13 | 0.009 |
| Male sex | 147 (50.9) | 154 (54.0) | 167 (58.8) | 197 (65.4) | 0.002 |
| Duration of dialysis, mon | 51 ± 52 | 46 ± 51 | 44 ± 52 | 38 ± 39 | 0.018 |
| No RRF | 124 (71.3) | 113 (64.9) | 134 (77.0) | 143 (72.2) | 0.098 |
| Causes of ESRD | | | | | 0.054 |
| Diabetes mellitus | 126 (44.5) | 123 (43.3) | 135 (48.0) | 161 (53.7) | |
| Glomerulonephritis | 35 (12.4) | 44 (15.5) | 29 (10.3) | 32 (10.7) | |
| Others/unknown | 122 (43.1) | 117 (41.2) | 117 (41.6) | 107 (35.6) | |
| Comorbidities | | | | | |
| Diabetes mellitus | 118 (47.4) | 116 (49.6) | 124 (52.1) | 134 (55.1) | 0.351 |
| Cardiovascular disease | 53 (21.3) | 58 (24.8) | 59 (24.8) | 75 (30.9) | 0.105 |
| Systolic blood pressure, mmHg | 145 ± 20 | 139 ± 21 | 140 ± 21 | 140 ± 20 | 0.006 |
| Diastolic blood pressure, mmHg | 77 ± 13 | 73 ± 13 | 75 ± 13 | 76 ± 12 | 0.005 |
| Body mass index, kg/m ² | 22.7 ± 3.6 | 22.4 ± 3.0 | 22.3 ± 3.3 | 22.0 ± 3.1 | 0.067 |
| Hemoglobin, g/dL | 10.8 ± 1.1 | 10.6 ± 1.2 | 10.5 ± 1.1 | 10.5 ± 1.4 | 0.003 |
| Serum albumin, g/dL | 3.9 ± 0.4 | 3.8 ± 0.4 | 3.9 ± 0.4 | 3.9 ± 0.5 | 0.201 |
| Serum creatinine, mg/dL | 10.1 ± 2.8 | 9.4 ± 2.6 | 9.5 ± 2.7 | 8.5 ± 2.9 | < 0.001 |
| Serum calcium, mg/dL | 8.6 ± 0.6 | 8.8 ± 0.8 | 8.9 ± 0.8 | 9.1 ± 0.8 | < 0.001 |
| Serum phosphorus, mg/dL | 5.5 ± 1.5 | 4.8 ± 1.4 | 4.9 ± 1.5 | 4.4 ± 1.4 | < 0.001 |
| Ferritin | 277 ± 285 | 296 ± 323 | 306 ± 320 | 321 ± 357 | 0.443 |
| iPTH, pg/mL | 173.3 (74.3–18.0) | 165.6 (79.5–291.5) | 148.0 (68.1–279.1) | 123.2 (56.2–211.2) | < 0.001 |
| nPCR, g/kg/day | 0.94 ± 0.28 | 0.90 ± 0.25 | 0.91 ± 0.22 | 0.86 ± 0.25 | 0.039 |
| spKt/V | 1.52 ± 0.32 | 1.52 ± 0.31 | 1.52 ± 0.35 | 1.51 ± 0.32 | 0.975 |
| Dialysate HCO ₃ , mEq/L | | | | | 0.012 |
| 25 | 0 | 6 (2.7) | 1 (0.5) | 2 (1.2) | |
| 30 | 142 (57.3) | 127 (57.2) | 133 (65.8) | 115 (69.7) | |
| 31 | 20 (8.1) | 8 (3.6) | 16 (7.9) | 8 (4.8) | |
| 32 | 60 (24.2) | 59 (26.6) | 39 (19.3) | 29 (17.6) | |
| 34 | 26 (10.5) | 22 (9.9) | 13 (6.4) | 11 (6.7) | |

Values are presented as mean ± SD, number (%), or medians (interquartile range). No RRF means 24 hours residual urine volume < 100 mL. The albumin-corrected serum calcium was calculated as: [4 – serum albumin (mg/dL)] × 0.8 + unadjusted serum calcium (mg/dL).

tCO₂, total carbon dioxide; RRF, residual renal function; ESRD, end-stage renal disease; iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; spKt/V, single pool Kt/V.

used, as appropriate, to evaluate differences in the continuous variables. Categorical variables were presented as percentages, and Pearson chi-square test or Fisher exact test was used to evaluate differences in the cate-

gorical variables.

Absolute mortality rates were calculated per 100 person-years of follow-up. The survival curves were estimated using the Kaplan-Meier method and compared

between quartiles 1, 2, 3, and 4 using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazard regression model were performed to calculate the hazard ratio (HR) with 95% confidence interval (CI) for all-cause mortality; the reference category was defined as quartile 3 (a tCO₂ of 21.6 to 23.9 mEq/L).

For categorical variables, the assumption of proportional hazards over time was assessed by visual inspection of the log-minus-log survival plot. The Cox proportional hazard model was used to calculate the HR with 95% CI for all-cause mortality. Analyses were adjusted for potential confounders using two models. Model 1 was adjusted for age, sex, BMI, diabetes mellitus, and cardiovascular disease, while model 2 was adjusted for model 1 plus serum hemoglobin levels, serum albumin levels, and serum phosphorus levels and nPCR.

All statistical analyses were performed using SPSS version 19.0 (IBM Co., Armonk, NY, USA), and a *p* < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 1,159 prevalent HD patients were included in the present analysis. The mean patient age was 59 ± 13 years and the mean tCO₂ was 21.7 ± 3.5 mEq/L. The main causes of ESRD were diabetes mellitus (48%), glomerulonephritis (12%), and other or unknown causes (40%). The baseline characteristics of the study population according to tCO₂ are shown in Table 1. Quartile 1 contained 289 patients (24.9%), quartile 2 contained 285 patients (24.6%), quartile 3 contained 284 patients (24.5%), and quartile 4 contained 301 patients (26%). The mean

tCO₂ was 17.4 ± 1.5 mEq/L for patients in quartile 1, 20.5 ± 0.6 mEq/L for patients in quartile 2, 22.6 ± 0.6 mEq/L for patients in quartile 3, and 26.2 ± 2.2 mEq/L for patients in quartile 4. Compared to the patients in other quartiles, the patients in quartile 4 were more likely to be male, have a shorter duration of dialysis, and have lower levels of serum hemoglobin, phosphorus, and intact parathyroid hormone. However, there was no difference in the prevalence of comorbidities, BMI, serum albumin, ferritin, single pool Kt/V, and dialysate bicarbonate concentrations when the quartiles were compared.

All-cause mortality according total CO₂

The median follow-up period was 37 months (interquartile range, 24 to 55), and 266 patients were censored the study during the follow-up period. The reasons for censoring included transfer to a nonparticipating hospital (*n* = 102), kidney transplantation (*n* = 80), refusal to continue participating (*n* = 32), and other reasons (*n* = 52).

There were 112 deaths during the follow-up period, and the leading causes of deaths were cardiovascular diseases (44.6% of all deaths) and infectious diseases (16.1% of all deaths). Table 2 shows the causes of deaths in each group, all-cause mortality and cardiovascular mortality were significantly higher in quartile 4 (*p* = 0.021).

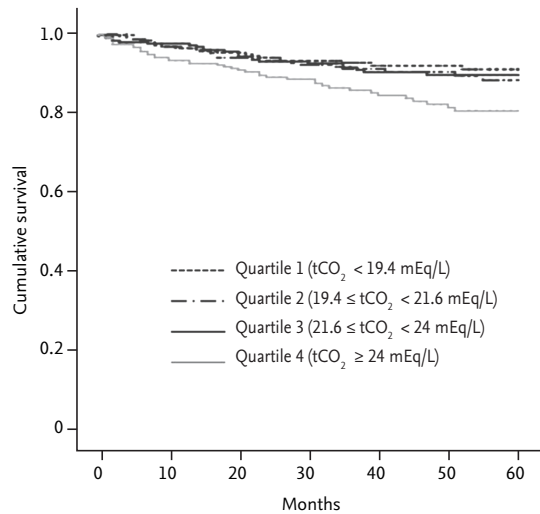
The absolute mortality rate during the median follow-up period of 37 months was 3.17 deaths per 100 person-years. Fig. 1 shows the Kaplan-Meier survival curve for mortality according to tCO₂, and mortality was observed to be significantly higher in patients from quartile 4 compared to those from the other quartiles (*p* = 0.009, log-rank test).

In the univariate Cox regression analysis, all-cause mortality was significantly associated with old age (> 65

Table 2. Causes of deaths in each group

| Diseases | Serum tCO ₂ , mEq/L | | | | <i>p</i> value |
|-------------------------|--|---|---|--------------------------------------|----------------|
| | Quartile 1 (≤ 19.3, <i>n</i> = 289) | Quartile 2 (19.4–21.5, <i>n</i> = 285) | Quartile 3 (21.6–23.9, <i>n</i> = 284) | Quartile 4 (≥ 24, <i>n</i> = 301) | |
| Cardiovascular diseases | 8 (38.1) | 12 (48.0) | 8 (33.3) | 22 (52.4) | 0.021 |
| Infectious diseases | 5 (23.8) | 2 (8.0) | 5 (20.8) | 6 (14.3) | 0.599 |
| Others | 8 (38.1) | 11 (44.0) | 11 (45.8) | 14 (33.3) | 0.695 |
| Total | 21 (18.8) | 25 (22.3) | 24 (21.4) | 42 (37.5) | 0.029 |

Values are presented as number (% of deaths). tCO₂, total carbon dioxide.



| Patients at risk, n | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
|---|-----|-----|-----|-----|-----|-----|-----|
| Quartile 1 (tCO ₂ < 19.4) | 289 | 256 | 238 | 224 | 216 | 211 | 208 |
| Quartile 2 (19.4 ≤ tCO ₂ < 21.6) | 285 | 257 | 232 | 217 | 213 | 205 | 203 |
| Quartile 3 (21.6 ≤ tCO ₂ < 24) | 284 | 258 | 234 | 217 | 204 | 198 | 198 |
| Quartile 4 (tCO ₂ ≥ 24) | 301 | 249 | 217 | 196 | 183 | 173 | 171 |

Figure 1. Kaplan-Meier survival curve for mortality according to total carbon dioxide (tCO₂) in prevalent hemodialysis patients (*p* = 0.009, log-rank).

years), male sex, diabetes mellitus, cardiovascular disease, BMI, serum hemoglobin, serum albumin, serum creatinine, serum phosphorus, and nPCR. Relative to quartile 3, the HR for all-cause mortality in quartile 4 was 1.85 (95% CI, 1.12 to 3.05; *p* = 0.02). All-cause mortality was positively correlated with old age, diabetes mellitus, and cardiovascular disease, and was negatively correlated with serum levels of hemoglobin, albumin, creatinine, and phosphorus (Table 3).

To evaluate tCO₂ as an independent predictor for all-cause mortality, multivariate Cox regression analysis was performed (Table 4). All-cause mortality was not significantly different when we compared quartile 1, 2, and 3 (the reference category), after adjusting for age, sex, BMI, diabetes mellitus, and cardiovascular disease (model 1) or for age, BMI, diabetes mellitus, cardiovascular disease, serum levels of albumin, hemoglobin, phosphorus and nPCR (model 2). However, quartile 4 had a significantly higher risk of all-cause mortality, compared to quartile 1, 2, and 3 in model 1 (HR, 1.99; 95% CI, 1.15 to 3.45; *p* = 0.01) and model 2 (HR, 1.82; 95% CI, 1.03 to 3.22; *p* = 0.04).

Table 3. Univariate Cox regression analysis of mortality

| Variable | HR | 95% CI | <i>p</i> value |
|---|------|-----------|----------------|
| Quartile 1 (tCO ₂ < 19.4) | 0.86 | 0.48–1.55 | 0.62 |
| Quartile 2 (19.4 ≤ tCO ₂ < 21.6) | 1.05 | 0.60–1.84 | 0.86 |
| Quartile 3 (21.6 ≤ tCO ₂ < 24) | | Reference | |
| Quartile 4 (tCO ₂ ≥ 24) | 1.85 | 1.12–3.05 | 0.02 |
| Age, yr | 1.06 | 1.04–1.08 | < 0.01 |
| Male (vs. female) | 1.44 | 0.98–2.13 | 0.07 |
| Duration of dialysis, mon | 1.00 | 0.99–1.00 | 0.97 |
| Diabetes mellitus (vs. none) | 1.82 | 1.20–2.78 | < 0.01 |
| Cardiovascular disease (vs. none) | 2.15 | 1.43–3.22 | < 0.01 |
| Body mass index, kg/m ² | 0.93 | 0.88–0.99 | 0.03 |
| Hemoglobin, g/dL | 0.80 | 0.69–0.94 | < 0.01 |
| Serum albumin, g/dL | 0.31 | 0.21–0.45 | < 0.01 |
| Serum creatinine, g/dL | 0.84 | 0.78–0.90 | < 0.01 |
| Serum phosphorus, mg/dL | 0.84 | 0.73–0.96 | < 0.01 |
| Dialysate HCO ₃ , mEq/L | 0.92 | 0.79–1.08 | 0.29 |
| nPCR, g/kg/day | 0.35 | 0.13–0.95 | 0.039 |

HR, hazard ratio; CI, confidence interval; tCO₂, total carbon dioxide; nPCR, normalized protein catabolic rate.

Table 4. Multivariate Cox regression analysis of mortality

| Variable | Model 1 ^a | | | Model 2 ^b | | |
|--------------------------|----------------------|-----------|---------|----------------------|-----------|---------|
| | HR | 95% CI | p value | HR | 95% CI | p value |
| tCO ₂ , mEq/L | | | | | | |
| < 19.4 | 1.16 | 0.61–2.21 | 0.65 | 1.27 | 0.66–2.44 | 0.47 |
| 19.4–21.5 | 1.09 | 0.59–2.02 | 0.78 | 1.11 | 0.60–2.07 | 0.74 |
| 21.6–23.9 | 1 (reference) | | | 1 (reference) | | |
| ≥ 24 | 1.99 | 1.15–3.45 | 0.01 | 1.82 | 1.03–3.22 | 0.04 |
| tCO ₂ , mEq/L | | | | | | |
| < 19.4 | 1 (reference) | | | 1 (reference) | | |
| 19.4–21.5 | 0.94 | 0.50–1.77 | 0.85 | 0.88 | 0.46–1.67 | 0.68 |
| 21.6–23.9 | 0.86 | 0.45–1.64 | 0.65 | 0.79 | 0.41–1.51 | 0.47 |
| ≥ 24 | 1.71 | 0.97–3.03 | 0.06 | 1.43 | 0.77–2.66 | 0.25 |
| tCO ₂ , mEq/L | | | | | | |
| < 19.4 | 1.06 | 0.56–2.01 | 0.85 | 1.14 | 0.60–2.18 | 0.68 |
| 19.4–21.5 | 1 (reference) | | | 1 (reference) | | |
| 21.6–23.9 | 0.92 | 0.50–1.69 | 0.78 | 0.90 | 0.48–1.67 | 0.74 |
| ≥ 24 | 1.82 | 1.06–3.13 | 0.03 | 1.64 | 0.92–2.93 | 0.10 |
| tCO ₂ , mEq/L | | | | | | |
| < 19.4 | 0.58 | 0.33–1.03 | 0.06 | 0.70 | 0.38–1.29 | 0.25 |
| 19.4–21.5 | 0.55 | 0.32–0.94 | 0.03 | 0.61 | 0.34–1.09 | 0.10 |
| 21.6–23.9 | 0.50 | 0.29–0.87 | 0.01 | 0.55 | 0.31–0.97 | 0.04 |
| ≥ 24 | 1 (reference) | | | 1 (reference) | | |

tCO₂, total carbon dioxide; HR, hazard ratio; CI, confidence interval.

^aModel 1: multivariate model including age, sex, body mass index, diabetes mellitus, and cardiovascular disease.

^bModel 2: multivariate model including model 1 + albumin, hemoglobin, phosphorus level, and normalized protein catabolic rate.

DISCUSSION

As serum bicarbonate levels continuously decrease during the interdialytic interval, HD patients may experience intermittent metabolic acidosis and intradialytic alkalosis. In this prospective observational study of the impact of high serum bicarbonate levels on mortality among HD patients, we found that the group with a tCO₂ of ≥ 24 mEq/L had a significantly higher risk of mortality compared with the reference group.

The association between serum bicarbonate levels and mortality remains controversial. Bommer et al. [9] have reported that a U-curve best represented the association between predialysis serum bicarbonate levels and the risk of mortality or hospitalization and in their study, both high (> 24 mEq/L) and low (< 19 mEq/L) serum bi-

carbonate levels were associated with an increased risk of mortality and hospitalization. In addition, other studies reported that a low serum bicarbonate in dialysis patients is a surrogate of better nutritional status with greater survival [3,10]. Unlike previous reports, we observed increased mortality in the group with a tCO₂ of ≥ 24 mEq/L independent from nPCR, a nutritional marker. Healthy diets usually include high protein intake, which increases acid load and contributes to predialysis metabolic acidosis. High protein intake is also accompanied by high phosphorus intake, as suggested by the discovery of an inverse correlation between serum bicarbonate and serum phosphorus levels. Uribarri et al. [4] have reported that tCO₂ was negatively correlated with the nPCR, which suggests that patients with higher tCO₂ levels have lower protein intake. In our study,

nPCR was related to the mortality of the chronic HD patients in univariate analysis ($p = 0.04$); however, was not related to the mortality in the multivariate analysis ($p = 0.361$). Our data showed that the $t\text{CO}_2$ of ≥ 24 mEq/L level was associated with the increased mortality independent from the nPCR level in the chronic HD patients. Therefore, increased mortality in the group with a $t\text{CO}_2$ of ≥ 24 mEq/L level might be associated with metabolic alkalosis itself.

In some reports, high dialysate bicarbonate concentrations may contribute to adverse outcomes through the development of postdialysis metabolic alkalosis and the higher dialysate to serum bicarbonate gradients results in higher bicarbonate transfer during dialysis [2,13,14]. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), the average dialysate bicarbonate concentration was 35.5 ± 2.3 mEq/L [2]. However, in our study, the dialysate bicarbonate concentrations did not affect the association between high serum bicarbonate levels and increased mortality. Due to the lack of high dialysate bicarbonate concentrations in Korea, the dialysate bicarbonate concentrations are relatively low (30.9 ± 1.6 mEq/L).

In our study, all-cause mortality and cardiovascular mortality were significantly higher in the $t\text{CO}_2$ of ≥ 24 mEq/L group. In this context, intradialytic metabolic alkalosis might result in hemodynamic instability, because of the decreased levels of serum potassium and ionized calcium, as well as muscle cramps and respiratory suppression [5,6].

In addition, our results indicate that serum $t\text{CO}_2$ levels were negatively correlated with hemoglobin and phosphorus levels. It is well known that albumin and BMI are associated strongly and inversely associated with mortality and hospitalization [15-17]. Furthermore, related comorbidities may alter the acid load and affect the association between mortality and acidosis in dialysis patients, as these comorbidities frequently reduce appetite, leading to decreased protein intake and eventually to a reduced serum albumin level, which is a strong predictor for increased risk of mortality.

Our study has several potential limitations. First, there was lack of data on the exact timing of the blood sampling for predialysis $t\text{CO}_2$ (at the beginning of the week or midweek). Predialysis serum bicarbonate levels are known to be significantly higher on Wednesdays

and Fridays, compared to those obtained on Mondays. The timing of blood sampling affects the predialysis $t\text{CO}_2$ levels, which may have influenced our findings. For example, Bommer et al. [9] collected midweek $t\text{CO}_2$ data, and their patients with midweek $t\text{CO}_2$ levels of 20.1 to 21.0 mEq/L would commonly leave the dialysis units with normal acid-base balance or a mild metabolic alkalosis. Second, our study did not fully consider the patients' nutritional status, such as calorie intake and dietary protein intake. Third, we did not consider physical activity, such as respiratory function, and we did not exclude patients with chronic lung disease. Fourth, we did not consider medications that might affect the acid-base balance, such as Sevelamer hydrochloride, which is a non-calcium based phosphate binder. Each Sevelamer molecule includes an amount of nitrogen and chloride, which may lead to a decrease in the bicarbonate levels and an increase in the calculated normalized protein nitrogen appearance [10,18]. These results indicate an inverse association between serum bicarbonate and serum phosphorus. Fifth, despite the multicenter design of this study, the cohort consisted exclusively of Korean patients. Thus, it is unclear whether our results can be generalized to other ethnic groups.

In conclusion, high serum bicarbonate levels (a $t\text{CO}_2$ of ≥ 24 mEq/L) were associated with increased mortality among prevalent HD patients. Our results suggest that further research might be necessary to find the cause of metabolic alkalosis in order to correct metabolic alkalosis, especially, in the chronic HD patients with high serum bicarbonate levels.

KEY MESSAGE

1. High serum bicarbonate levels (a total carbon dioxide of ≥ 24 mEq/L) were associated with increased mortality among prevalent hemodialysis (HD) patients.
2. Further effort might be necessary in finding the cause and correcting metabolic alkalosis in the chronic HD patients with high serum bicarbonate levels.

Conflict of interest

No potential conflict of interest relevant to this article

was reported.

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