Original Paper

Evaluation of the Predictive Value of the Serum Calcium-Magnesium Ratio for All-Cause and Cardiovascular Mortality in Incident Dialysis Patients

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Keywords

Calcium · Magnesium · Cardiovascular disease · Dialysis initiation · Vessel calcification

Abstract

Background/Aim: Cardiovascular disease is the most serious cause of death in patients on hemodialysis. Low serum magnesium (Mg) and high serum calcium (Ca) levels have been associated with poor outcome and cardiovascular mortality in patients on maintenance and initiation dialysis. As a more accurate marker is warranted, we evaluated the efficacy of a novel serum Ca-Mg marker of all-cause and cardiovascular mortality that indicates vessel calcification. **Methods:** We recruited 378 consecutive patients with end-stage renal disease who started dialysis between January 2009 and December 2015 at the Japanese Red Cross Ishinomaki Hospital. We collected data of patients' demographic characteristics and comorbidities from their electronic medical records. We retrospectively examined the association of the serum Ca-Mg ratio with all-cause and cardiovascular mortality using the Cox proportional hazard model, and determined the value that predicted cardiovascular death using the receiver operating characteristic (ROC) curve. **Results:** Overall, 253 patients with serum Mg and Ca data were analyzed. The 3-year survival rate of this group was 0.70 (95% confidence interval [CI] 0.55–0.80), and the hazard ratio for the risk of death was 3.94 (95% CI 1.37–11.31). The 3-year cardiovascular mortality rate was 0.12 (95% CI 0.05–0.23), which was significantly higher than that of the other groups. The ROC curve of cardiovascular mortality with the Ca-Mg ratio was greater than that of Mg (area under the curve 0.75 vs. 0.69, $p = 0.037$). **Conclusion:** A high Ca-Mg ratio was significantly associated with all-cause and cardiovascular mortality, and it was more accurate than serum Mg.

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Introduction

Cardiovascular disease (CVD) is the most serious complication and the leading cause of death in patients on hemodialysis (HD) in developed countries such as Japan [1]; thus, an accurate predictor of CVD events is warranted. In the field of nutritional science, several studies have reported that the calcium-magnesium (Ca-Mg) intake ratio is associated with all-cause mortality and the incidence of acute myocardial infarction [2]. Some studies have reported that the serum Ca-Mg ratio can be a useful adjuvant marker for diagnosing acute myocardial infarction; its sensitivity was 96% and its specificity 78% [3]. Herein, we focused on this new marker, which has never been evaluated in the nephrology and dialysis fields. The risks of the incidence of CVD events associated with several readily measured indicators have been evaluated, including the highly sensitive C-reactive protein level [4], increased troponin level [5], and neutrophil-lymphocyte ratio [6]. Recently, serum Mg has been reported as a predictor of all-cause and cardiovascular mortality in patients on maintenance and initial HD [7]. Serum Mg is an important factor of the retarded progression of atherosclerosis, inhibiting the formation of thrombin by reducing platelet aggregation and prolonging blood clotting time [8]. Therefore, Mg deficiency may have a negative effect on endothelial function, leading to CVD. Thus, a lower Mg level is related to coronary artery disease in normal adults. A large cohort study of 208,820 patients with end-stage renal disease (ESRD) who initiated dialysis treatment in the United States reported that a lower serum Mg level is significantly associated with a higher mortality rate [9]. Additionally, serum Ca is another factor of mortality in patients on HD. A large observational study in Japan reported that a higher serum Ca level is an independent risk factor of mortality in patients on initial HD [10]. With a higher concentration of ionized Ca, the clotting cascades are initiated and promoted, which leads to the calcification of vessels and finally causes CVD, peripheral artery disease, and ischemic and hemorrhagic stroke [8]. This Ca-related process is inhibited by serum Mg [11]; thus, it could be considered that the serum Ca and Mg levels compete with each other. We focused on electrolytes related to vascular calcification, especially higher Ca and lower Mg levels.

No study to date has established the role of the Ca-Mg ratio in patients on HD. Therefore, in this study, we evaluated the efficacy of using the Ca-Mg ratio compared to the serum Mg level as a marker of all-cause and cardiovascular mortality.

Materials and Methods

Study Population

This study was a single-center, retrospective, observational study. We initially recruited 378 patients with ESRD who were starting incident HD between January 2009 and December 2015 at the Japanese Red Cross Ishinomaki Hospital. The clinical courses of 191 patients were followed until March 2016. The primary endpoints of this study were all-cause mortality and cardiovascular mortality. Seventeen patients were lost to follow-up within the observation period (Fig. 1).

Definitions

All blood samples were collected at the beginning of the first dialysis session only once. The serum Ca-Mg ratio is calculated by dividing the corrected Ca by the Mg. If the serum albumin level was <4.0 g/dL, the serum Ca concentration was corrected by the serum albumin level as follows: corrected Ca (mg/dL) = measured Ca (mg/dL) + [4 – albumin (g/dL)]. Blood pressure was recorded for each patient before the first session of dialysis after a 5-min rest period. Hypertension was defined as the presence of a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg, or the patient currently taking antihypertensive drugs [12]. Hyperlipidemia was defined by the presence of a low-density lipoprotein level ≥140 mg/dL and/or a high-density lipoprotein level ≤40 mg/dL and/or a fasting triglyceride level ≥150 mg/dL, or the patient receiving lipid-lowering treatment [13]. We measured patients' height at the first dialysis

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Fig. 1. Flowchart of the study design. Ca, calcium; ESRD, end-stage renal disease; Mg, magnesium.

session and their weight at the final dialysis session. The body mass index was calculated by dividing the weight in kg by the height in m². We clinically examined patients for signs of fluid overload (e.g., edema, pulmonary congestion, and clinical signs of heart failure) on the day before discharge using chest radiography and ultrasound echocardiography. Data of comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, CVD (defined as a history of ischemic heart disease), congestive heart failure (defined as a patient who required hospitalization and in-patient treatment), ischemic and hemorrhagic stroke, and atrial fibrillation, were collected from the patients' electronic medical records.

Calcification Measurement

We measured the abdominal aortic calcification score using the Agatston score, which was used to quantify coronary artery calcification. We also used the calcification measurement software Ziostation2 (Ziosoft Corp.). The section from the celiac artery bifurcation to the total iliac artery bifurcation of the abdominal aorta was divided at intervals of 7 mm, and we calculated the abdominal aortic calcification score using the computed tomography value and the calcification area [14]. Next, we evaluated the aortic arch calcification on plain frontal chest radiographs. The severity of aortic arch calcification was classified into four grades (grades 0–3) [15]. Furthermore, cardiac valve calcification was evaluated according to the presence or absence of a calcified aortic valve and mitral valve [16].

Laboratory and Statistical Analysis

The study cohort comprised 253 patients who had serum Mg and Ca measured in the first dialysis session. Patients were divided into three groups of the same number of patients. The high Ca-Mg ratio group had a Ca-Mg ratio of 4.8 ± 0.7 , the middle Ca-Mg ratio group had a Ca-Mg ratio of 3.7 ± 0.2 , and the low Ca-Mg ratio group had a Ca-Mg ratio of 2.8 ± 0.4 . Values are presented as mean $\pm$ standard deviation and median with interquartile range (25th to 75th percentiles) when appropriate. The Student *t* test was used to evaluate variables with a normal distribution. The Mann-Whitney U test was used to evaluate variables with a non-normal distribution. The Fisher exact test was used to evaluate differences between categorical values, and these results are expressed as an absolute number (*n*) and percentage. The survival rate was assessed using the Kaplan-Meier analysis and evaluated using the log-rank test. The association of the Ca-Mg ratio with mortality was initially examined using the univariate Cox proportional hazards model. The independence of prognostic variables was examined using multivariate Cox proportional hazard models. Data were analyzed using the following levels of adjustment: (1) Unadjusted. (2) Model 1: adjusted demographic characteristics (sex, age, and cause of ESRD), comorbid conditions (history of heart failure, CVD, and stroke), medications (angiotensin II receptor, angiotensin-converting enzyme inhibitor, Mg oxide, proton pump inhibitor [PPI],

Table 1. Baseline characteristics of the patient population

	Low (n = 85)	Middle (n = 84)	High (n = 84)	p value
<i>Demographic</i>				
Age, years	63.5±14.6	67.9±12.5	68.8±12.3	0.02*
Body mass index	24.3±4.4	24.6±4.1	25.3±5.5	0.46
Arteriovenous fistula	67 (78.8%)	72 (85.7%)	70 (83.3%)	0.49
Total protein, g/dL	6.1±0.7	5.9±0.6	5.8±0.7	0.02*
Serum albumin, g/dL	3.5±0.6	3.3±0.6	3.1±0.7	<0.01*
Total cholesterol, mg/dL	162.3±52.5	162.8±64.8	151±41.1	0.29
Blood urea nitrogen, mg/dL	109.9±32.8	108.8±33.6	98.8±34.4	0.07
eGFR, mL/min/1.73 m ²	4.5±1.6	4.7±1.8	5.2±2.2	0.03*
Sodium, mEq/L	138.3±5.2	138.5±4.0	138.7±4.1	0.85
Potassium, mEq/L	4.7±0.9	4.8±0.9	4.6±0.9	0.39
Chloride, mEq/L	104.5±5.8	107.2±5.4	106.7±5.4	0.46
Corrected Ca, mEq/L	7.6±1.1	8.1±1.0	8.5±0.8	<0.001*
Serum phosphate, mEq/L	7.1±2.2	6.5±1.9	6.0±1.9	<0.001*
Mg, mg/dL	2.8±0.8	2.2±0.3	1.8±0.3	<0.001*
Ca-Mg ratio	2.8±0.4	3.7±0.2	4.8±0.7	<0.001*
BNP, pg/mL	820.0 [390.1–1,034.9]	280.8 [95.2–518.4]	266.4 [156.5–589.0]	<0.01*
C-reactive protein, mg/dL	0.20 [0.04–1.20]	0.18 [0.05–0.80]	0.36 [0.10–1.82]	0.15
White blood cells, ×10 ³ /μL	6,136±3,160	5,565±1,926	6,592±3,529	0.08
Hemoglobin, g/dL	8.8±1.7	9.0±1.5	8.4±1.4	0.03*
Platelets, ×10 ⁴ /mm ³	18.2±7.0	19.5±10.8	19.2±9.0	0.61
Intact PTH, pg/mL	209.0 [123.8–317.3]	222.0 [145.5–314.0]	191.5 [130.8–296.0]	0.59
Transferrin saturation, %	21.0±15.0	23.5±16.0	23.2±13.2	0.49
Ferritin, ng/mL	76.3 [29.2–154.5]	88.1 [40.5–179.5]	120.0 [70.7–198.0]	<0.01*
LVEF, %	58.1±12.5	62.8±9.3	63.2±11.3	0.06
Systolic blood pressure, mm Hg	150±28	150±22	155±25	0.33
Diastolic blood pressure, mm Hg	75±16	75±13	74±15	0.89
Pulse rate, beats/min	77±16	73±12	74±12	0.36
<i>Comorbidities</i>				
Hypertension	76 (89.4%)	76 (90.5%)	78 (92.9%)	0.73
Hyperlipidemia	19 (22.4%)	27 (32.1%)	18 (21.4%)	0.21
Atrial fibrillation	1 (1.2%)	4 (4.8%)	3 (3.6%)	0.40
Cardiovascular disease	14 (16.5%)	14 (16.7%)	11 (13.1%)	0.77
Heart failure	21 (24.7%)	20 (23.8%)	19 (22.6%)	0.95
Stroke	7 (8.2%)	8 (9.5%)	5 (6.0%)	0.69
<i>Etiology of end-stage renal disease</i>				
Diabetic nephropathy	45 (52.9%)	50 (59.5%)	44 (52.4%)	0.34
Hypertensive nephropathy	14 (16.5%)	19 (22.6%)	20 (23.8%)	
Chronic glomerular nephritis	8 (9.4%)	2 (2.4%)	3 (3.6%)	
ADPKD	2 (2.4%)	4 (4.8%)	3 (3.6%)	
Others	16 (18.8%)	9 (10.7%)	14 (16.7%)	
<i>Medication</i>				
ACEIs/ARBs	60 (70.6%)	63 (75.0%)	59 (70.2%)	0.75
Statins	19 (22.4%)	24 (28.6%)	20 (23.8%)	0.62
Oral iron	23 (27.1%)	11 (13.1%)	8 (9.5%)	<0.01*
Proton pump inhibitors	19 (22.4%)	26 (31.0%)	20 (23.8%)	0.39
Calcium carbonate	27 (37%)	17 (24.3%)	24 (33.8%)	0.24
Phosphate binders	5 (5.9%)	2 (2.4%)	1 (1.2%)	0.37
Vitamin D receptor activation	7 (8.1%)	7 (8.4%)	9 (10.7%)	0.82
Mg oxide	6 (7.1%)	2 (2.4%)	1 (1.2%)	0.09

Continuous variables are expressed as a mean ± standard deviation in normal distribution or as median with interquartile range [25th–75th percentiles]. Categorical variables are expressed as absolute number (n) and percentage. ACEIs, angiotensin-converting enzyme inhibitors; ADPKD, autosomal dominant polycystic kidney disease; ARBs, angiotensin II receptor blockers; BNP, brain natriuretic peptide; Ca, calcium; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; Mg, magnesium; PTH, parathyroid hormone. * Statistically significant (p < 0.05).

Table 2. Several types of calcification scores among the three groups

	Low Ca-Mg ratio	Middle Ca-Mg ratio	High Ca-Mg ratio	p value
Agatston score	1,474.9 [460.5–2,700.7]	1,099.9 [155.7–2,438.7]	1,352.1 [282.4–3,090.6]	0.41
AAC score				
0	26 (30.2%)	19 (22.9%)	23 (27.4%)	0.38
1	14 (16.3%)	20 (24.1%)	22 (26.2%)	
2	17 (19.8%)	17 (20.5%)	21 (25.0%)	
3	29 (33.7%)	27 (32.5%)	18 (21.4%)	
Cardiac valve calcification				
Aortic valve	20 (23.5%)	26 (31.0%)	29 (34.5%)	0.42
Mitral valve	13 (15.3%)	13 (15.5%)	12 (21.4%)	0.98

Values are presented as median with interquartile range [25th–75th percentiles] or *n* (%). AAC, abdominal aortic calcification; Ca, calcium; Mg, magnesium.

oral iron, calcium carbonate, and phosphate binder), and univariate variables with a *p* value <0.10 (estimated glomerular filtration rate and chloride). (3) Model 2: model 1 + inflammation markers (white blood cell count and C-reactive protein level) + nutrition markers (serum albumin, hemoglobin, total cholesterol, and ferritin levels). (4) Model 3: model 2 + secondary hyperparathyroidism (intact parathyroid hormone and serum phosphate levels). The receiver operating characteristic (ROC) curve was used to estimate the sensitivity and specificity of the Ca-Mg ratio and of serum Mg as a marker of all-cause and cardiovascular mortality. Cases with missing data were excluded.

All statistical analyses were performed using EZR, which is a graphical user interface for R (R Foundation for Statistical Computing). *p* values are two-sided, and the threshold for significance was *p* < 0.05.

Results

Patients' Baseline Characteristics

The mean age of the study population was 66.7 ± 13.3 years, and 166 male patients (65.6%) were included. Two hundred and nine patients (82.6%) received their first dialysis treatment through an arteriovenous fistula. The mean body mass index was 24.8 ± 4.8. The levels of anemia-related markers were as follows: hemoglobin 8.8 ± 1.5 g/dL, transferrin saturation 0.23 ± 0.15, and ferritin 89.5 ng/mL (range 42.8–180.5 ng/mL). Renal-related markers were as follows: blood urea nitrogen level 105.8 ± 33.8 mg/dL, serum creatinine level 9.9 ± 3.1 mg/dL, and estimated glomerular filtration rate 4.8 ± 1.9 mL/min/1.73 m². Furthermore, the serum Mg level was not different between patients taking and not taking a PPI.

Compared to the middle and low Ca-Mg ratio groups, the high Ca-Mg ratio group (4.8 ± 0.7) had a significantly lower nutrition status in total protein and serum albumin levels. Additionally, this group tended to have a lower hemoglobin level and a higher serum ferritin level than the middle and low Ca-Mg ratio groups, but this was not significant. Regarding inflammatory markers, the white blood cell count and C-reactive protein level were similar among the three groups. There was no significant difference in the medical history and etiology of ESRD among the three groups (Table 1). Table 2 shows that there was no significant difference in the calcification scores among the three groups. Five patients died of an infection, 11 died of CVD, 3 died of hemorrhagic stroke, 6 died of a malignancy, and 11 died of an unknown reason or an accident.

Fig. 2. Kaplan-Meier survival curve showing the survival rate 3 years after initiating dialysis. Ca, calcium; Mg, magnesium.

Table 3. One- and 3-year all-cause and cardiovascular mortality

	1-year rate	95% CI	3-year rate	95% CI	<i>p</i> value
<i>Free survival rate</i>					
Low	0.94	0.86–0.97	0.78	0.66–0.87	<0.01*
Middle	0.99	0.91–0.99	0.92	0.78–0.97	
High	0.85	0.74–0.91	0.70	0.55–0.80	
<i>Cardiovascular mortality rate</i>					
Low	0.01	0.001–0.06	0.01	0.0001–0.06	0.02*
Middle	0	0.00–0.00	0.02	0.002–0.10	
High	0.06	0.02–0.14	0.12	0.05–0.23	

CI, confidence interval. * Statistically significant ($p < 0.05$).

Patients' Survival Rate

Kaplan-Meier curves showed that the survival rate was higher in patients with a high Ca-Mg ratio than in those with a middle and low Ca-Mg ratio (Fig. 2). The 1- and 3-year survival rates in the high Ca-Mg ratio group were 84.6% (95% confidence interval [CI] 73.8–91.2) and 69.8% (95% CI 55.4–80.3), respectively (Table 3), and these were the lowest rates among all the groups. In the Cox hazard survival models, the Ca-Mg ratio was an independent risk factor of all-cause mortality after adjusting all the models. After adjusting model 3, the hazard ratio of all-cause mortality was 3.94 (95% CI 1.37–11.33) (Table 4). The high Ca-Mg ratio group had an extremely higher rate of CVD mortality than the other two groups ($p < 0.01$; Fig. 3). The 1-year mortality rate of CVD was 6.0% (95% CI 1.9–13.6), and the 3-year rate was 12.3% (95% CI 5.2–22.6) (Table 3). After adjusting several variables similarly for all-cause mortality, the CVD mortality tended to be extremely high in those with a high Ca-Mg ratio (Table 4).

The ROC curve showed the relationship between the CVD mortality rate and the Ca-Mg ratio or the serum Mg level. The cutoff value for the Ca-Mg ratio (4.37) predicted CVD mortality

Fig. 3. Results of the Gray test of the comparison of the cumulative incidence of cardiovascular mortality among the three groups. * Statistically significant ($p < 0.05$). Ca, calcium; Mg, magnesium.

Table 4. Hazard ratio of all-cause and cardiovascular mortality according to Ca-Mg ratio after adjusting model 3

	Unadjusted			Model 1			Model 2			Model 3		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
<i>All-cause mortality</i>												
Low	2.55	0.92–7.09	0.07	4.65	1.63–13.29	<0.01*	3.95	1.38–11.28	0.01*	3.18	1.09–9.25	<0.01*
Middle	1.00	reference	–	1.00	reference	–	1.00	reference	–	1.00	reference	–
High	4.06	1.49–11.07	<0.01*	5.57	1.98–15.71	<0.01*	4.87	1.71–13.83	<0.01*	3.94	1.37–11.33	0.001*
<i>Cardiovascular mortality</i>												
Low	1.00	reference	–	1.00	reference	–	1.00	reference	–	1.00	reference	–
Middle	1.22	0.17–8.67	0.84	3.08	0.27–35.2	0.36	0.91	0.03–27.8	0.95	1.49	0.04–58.1	0.83
High	5.99	1.26–28.6	0.02*	5.57	1.69–122.6	0.01*	17.1	1.71–13.83	0.08	27.2	0.72–1,024.0	0.07

Associations are given as adjusted HR (95% CI). Model 1: demographics (age, sex, and cause of end-stage renal disease), comorbid conditions (history of heart failure, cardiovascular disease, and hemorrhagic stroke), medications (angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor, statin, Mg oxide, proton pump inhibitor, oral iron, calcium carbonate, and phosphate binder), and univariate variables with $p < 0.10$ (estimated glomerular filtration rate and chloride). Model 2: model 1 + inflammation markers (white blood cell count and C-reactive protein levels) + nutrition markers (serum albumin, hemoglobin, total cholesterol, and ferritin levels). Model 3: model 2 + secondary hyperparathyroidism (intact parathyroid hormone and serum phosphate levels). Ca, calcium; CI, confidence interval; HR, hazard ratio; Mg, magnesium. * Statistically significant ($p < 0.05$).

with a sensitivity of 78.7% and a specificity of 87.5% (Fig. 4). The area under the curve was 0.753 (95% CI 0.575–0.930). The area under the curve for the Ca-Mg ratio was significantly greater than that of the serum Mg level (Table 5). In patients with a high Ca-Mg ratio, there were no deaths due to arrhythmia; all-cause death was due to ischemic heart disease and heart failure.

Discussion

This is the first observational study of the association between the Ca-Mg ratio and all-cause and cardiovascular mortality in patients starting dialysis. We found that a higher Ca-Mg ratio was significantly associated with increased all-cause and cardiovascular mortality in patients with ESRD on dialysis. Serum Ca and Mg levels were important factors associated

Fig. 4. Receiver operating characteristic curve showing the sensitivity and specificity of the Ca-Mg ratio at dialysis initiation compared to the serum Mg level. Ca, calcium; Mg, magnesium.

Table 5. Predictive value of Ca-Mg ratio and serum Mg regarding cardiovascular mortality

	Cutoff	Sensitivity	Specificity	AUC	95% CI	p value
Mg	2.0	0.62	0.88	0.69	0.50–0.88	0.03*
Ca-Mg ratio	4.37	0.79	0.88	0.75	0.58–0.93	

AUC, area under the curve; Ca, calcium; CI, confidence interval; Mg, magnesium. * Statistically significant ($p < 0.05$).

with vessel calcification [17]. These two electrolytes had a contrary effect on each other. We devised the Ca-Mg ratio as a novel marker for evaluating the survival rate and CVD mortality.

In a previous study, the blood sample was collected just before the first dialysis session, and the authors evaluated the relationship between blood sample data and all-cause and cardiovascular mortality [6]. Thus, we collected the blood sample using a similar method. Our blood sample data were not affected by the electrolyte concentration of the dialysate, which was the same at all the dialysis facilities that participated in this study.

In the high Ca-Mg ratio group, the serum brain natriuretic peptide level was lower, and the left ventricular ejection fraction tended to be higher; however, the prevalence of a history of CVD was similar to that in the other groups. The serum brain natriuretic peptide level did not directly indicate heart failure, but it was indicative of excess body fluid. At the time of dialysis initiation, excess body fluid is severe, regardless of a history of heart failure. Therefore, there is no direct relationship between the serum brain natriuretic peptide level at dialysis initiation and CVD mortality.

The hazard ratio of all-cause mortality formed a U-shaped graph, so the middle Ca-Mg ratio group had the highest survival rate. However, regarding CVD mortality, those with a

high Ca-Mg ratio (high Ca and low Mg levels) had an extremely higher mortality rate than the other groups. The high serum Ca and low Mg concentrations were risk factors of progression of vessel calcification; thus, in the high Ca-Mg ratio group, we suppose that all-cause and CVD mortality were high [9, 10]. Next, the low Ca-Mg ratio group (low Ca and high Mg levels) had a poor outcome of all-cause mortality similar to the high Ca-Mg ratio group; however, the mortality rate of CVD was the lowest in the middle Ca-Mg ratio group. A large cohort study of patients with HD in the United States found that hypocalcemia was an independent risk factor of all-cause mortality [18]. Hypermagnesemia tended to be a risk factor of all-cause mortality, not mortality due to CVD in patients with incidental HD [9]. In consideration of these two facts, we expected that in the low Ca-Mg ratio group, all-cause mortality would be high, but CVD mortality would be low. All-cause mortality and mortality due to CVD in the middle Ca-Mg ratio group may have been the lowest among the three groups because serum Ca and Mg levels were within appropriate ranges. Therefore, this can explain why the graph for all-cause mortality was U-shaped. Similarly, serum sodium levels have been reported as examples of data that form a U-shaped graph for all-cause mortality [19].

No study has directly indicated the relationship between the Ca-Mg ratio and vessel calcification. In this study, we first evaluated the association between several types of calcification scores and the Ca-Mg ratio. There was no significant difference in the vessel calcification score among the three groups. Similarly, the prevalence of CVD and cerebrovascular stroke was not significantly different either. However, after dialysis initiation, CVD mortality was different. Considering these results in the high Ca-Mg ratio group, it can be presumed that the incidence of CVD mortality increases due to the progression of vascular calcification.

It has been reported that the duration of dialysis has a negative correlation to the serum Mg level in patients on peritoneal dialysis [20]. In Mg-deficient patients, taking an Mg supplement improved intima media thickness and endothelial function [21]. Thus, treating a serum Mg deficiency with an Mg supplement can reduce the frequency of CVD events. However, no study has been conducted on patients on HD; thus, a further study is warranted.

In the endocrine system, intragastric hydrochloric acid is involved in intestinal absorption of several electrolytes, and PPIs inhibit this endocrine process; however, the mechanism is still unknown. Hypomagnesemia and hypercalcemia are well-known phenomena in patients taking PPIs [22]. A PPI may have an effect on the Ca-Mg ratio; however, we found no difference in the serum Ca and Mg levels between patients taking and not taking PPIs.

This study has several limitations. First, this was a cross-sectional, observational, small-sample, single-center study. Thus, the number of CVD deaths was low. Second, the etiology of ESRD in all patients was based on the clinical prognosis, not results of a renal biopsy. Third, blood samples for biochemical analysis were only obtained once at the beginning of the first dialysis session, because this study was based on the health care service provided by health insurance. Thus, we could not analyze the time-varying serum Ca-Mg ratio. Finally, the serum Mg and Ca levels were affected by loop and thiazide diuretics; however, in this study, we could not investigate the effect of these drugs.

We found that the Ca-Mg ratio is a significant accurate marker of CVD mortality and all-cause mortality in patients starting dialysis. This novel marker was more useful than the serum Mg level alone. It is clinically uncertain whether an increased Mg and/or reduced Ca level, which leads to an adequately decreased Ca-Mg ratio, improves the risk of CVD mortality. Future studies on this topic are warranted.

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Statement of Ethics

This study was approved by the Ethics Committee of Ishinomaki Red Cross Hospital (approval No.: 14-20). It was conducted in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. All patients provided written informed consent.

Disclosure Statement

The authors declare no conflicts of interest.

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