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MAIN TEXT ARTICLE

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Association of mineral content outside of bone with coronary artery calcium and 1-year cardiovascular prognosis in maintenance hemodialysis patients

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Abstract

Coronary artery calcifications (CACs) are common among maintenance hemodialysis (MHD) patients and associated with increased morbidity and mortality due to cardiovascular events. The insight into chronic kidney disease-mineral and bone disorder (CKD-MBD) established a correlation between dysregulated mineral metabolism and CACs. This study aimed to identify the association of mineral content outside of bone (MCOB) with CACs and cardiovascular events in MHD patients. In the pilot prospective study with no intervention, patients underwent body composition assessment by body composition monitor after hemodialysis and computed tomography examination using the Agatston scoring method simultaneously within a week. The primary end point included cardiovascular events and cardiovascular death. Correlations and receiver operating characteristic analysis elucidated the associations of MCOB with CACs; multivariate analysis assessed the cardiovascular risk for groups with different MCOB. One hundred three eligible patients with an average age of 48 (35-63) years old were enrolled and followed up to 12 (11-12.5) months, among which 52.4% had detectable CACs at baseline. MCOB showed an inverse correlation with Agatston score and significantly discriminated the patients with Agatston score >0 (AUC = 0.737; $P < 0.001$) and 400 (AUC = 0.733; $P < 0.001$). MCOB ≤ 9.2657 mg/kg was an independent risk factor for CACs (OR = 4.853; $P = 0.044$) and strong predictor for cardiovascular morbidity and mortality (HR = 10.108; $P = 0.042$), as well as rehospitalization (HR = 2.689; $P = 0.004$). MCOB inversely correlated with the presence and extent of CACs, and could discriminate Agatston score >0 and 400, which also presented as an independent indicator for CKD-MBD and 1-year cardiovascular prognosis in adult MHD patients. Additional studies are required for identifying this issue.

Yuqin Xiong and Jiameng Li contributed equally to this work.

KEYWORDS
body composition monitor, cardiovascular outcome, chronic kidney disease-mineral and bone disorder, coronary artery calcifications, maintenance hemodialysis, mineral content outside of bone

1 | INTRODUCTION

Coronary artery calcifications (CACs) are commonly seen in patients with chronic kidney disease (CKD) undergoing hemodialysis and have been found to be a robust predictor of cardiovascular disease (CVD).[1] The mortality among maintenance hemodialysis (MHD) patients is approximately sevenfold more than similar individuals in the general population,[2] and 60%-70% of the deaths are caused by cardiovascular causes.[3]

CKD coexisting with CACs is also diagnosed as one of the entity known as chronic kidney disease-mineral and bone disorder (CKD-MBD).[4] It has become a worldwide health issue in recent years. CKD patients not only exhibit a variety of risk factors, such as abnormal mineral metabolism, anemia, malnutrition, increased oxidative stress, inflammation, and volume overload[5] which will contribute to the CVDs, but also exhibit an acquired dialytic milieu, which would accelerate calcification.[6–8] Thus, the prevalence and progression of vascular calcification increase dramatically when the patient undergoes dialysis.[9,10]

Understanding the association of mineral metabolism inside or outside of bone with CACs might be helpful in detecting CKD-MBD at an early stage, thereby providing clinicians with potential treatment targets and strategies. However, early accurate diagnosis of CKD-MBD in patients on hemodialysis is greatly hindered by unstable serum calcium, phosphate, and parathyroid hormone (PTH) concentrations due to constantly altered circulating blood volume, irregular dietary intake, or drug treatment.

Despite inevitable imperfection in serum biomarkers, several molecular mechanisms have been suggested as a potential link between cardiovascular calcification and bone metabolism[11,12]; vascular calcification and bone remodeling may share several signaling pathways and genes.[13] Previous studies showed that low bone volume or turnover determined by bone biopsies is a critical risk factor for CACs assessed by computed tomography using the Agatston scoring method in dialysis patients.[14–16] However, there is yet a gap in the association of mineral content outside of bone (MCOB) with CACs (or CKD-MBD) and cardiovascular outcomes in CKD patients on hemodialysis.

Bioelectrical impedance analysis (BIA) is a simple and noninvasive method which indirectly measures body composition by sending a weak electric current throughout the body.[17,18] Prior studies have examined the accuracy of BIA and established it as a valid tool for evaluating body composition.[19] BIA parameters, such as phase angle, lean body mass, visceral fat area, and dry weight have been previously used in nutritional assessment, volume management, and prognosis evaluation.[20–22] To date, few studies addressed the effect of mineral content or bone mineral content listed in BIA parameters on CKD patients. The present pilot prospective study was designed to evaluate the association of MCOB assessed by body composition monitor (BCM) with CACs and cardiovascular prognosis in asymptomatic MHD patients.

2 | PATIENTS AND METHODS

2.1 | Study population

Patients with CKD as the primary diagnosis were recruited from the Hemodialysis Center of West Hospital from May 2017 to January 2018. The subjects were eligible for participation in the study if the following criteria were met: (i) age 18-90 years and (ii) chronic maintenance hemodialysis was at least 90 days. The exclusion criteria were as follows: (i) peritoneal dialysis, pregnancy, known cancer, systemic illnesses, or organ diseases that may affect bone (except diabetes mellitus); (ii) a known coronary artery disease or related symptom such as chest pain; (iii) clinical conditions that may limit the study participation (eg, respiratory distress and infections), chronic alcoholism, and/or drug addiction; (iv) received medication that might affect bone metabolism (except for treatment with calcitriol, vitamin D analogs, and/or calcimimetics) within 6 months before enrollment (zoledronic acid); and (v) a history of cardiac and coronary artery surgery, a pacemaker, implanted cardiac defibrillator, or amputee.

The investigators adhered to the Declaration of Helsinki while conducting the study which was approved by the ethics committee, and written informed consent was obtained from all patients. The nephrologist determined all the treatments based on the standardized practice according to Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes (KDIGO) recommendations.[4] There were no interventions by the investigators.

2.2 | Mineral content measurement

Each patient was identified with a unique number, body composition assessment (BCA) was performed after hemodialysis using Body Composition Monitor (InbodyS720, Biospace, Seoul, South Korea) in a specific hemodialysis mode.[22] As a preparation for the measurement, patients were placed in the supine position based on the manual of the machine. Their arms were placed away from the trunk, and both legs were separated away from each other up to

30°-45°. Bioelectrical impedance analysis was performed with 8 surface electrodes placed on patient's thumbs and middle fingers and 2 sides of the ankles. The Inbody S120 device calculates the variable reactance and resistance values for different areas and frequencies. The BIA data included the intracellular water, extracellular water, total body water, fat free mass, protein, mineral content in total (MCIT), skeletal muscle mass, body cell mass, dry weight (DW), and mineral content inside of bone (MCIB). The MCOB was calculated by the following equation, MCOB (mg/kg) = [MCIT (g) − MCIB (g)] × 1000/DW (kg).

2.3 | Data collection

Data with respect to demographic characteristics, general condition, coexisting conditions, and maintenance medication were collected. Serum biochemical parameters were also recorded based on the blood samples from a routine check-up, which were collected close to the day that BCA was carried out and measured in a central laboratory. The level of urine albumin to creatinine ratio was not recorded as a majority of the MHD patients did not pass urine.

2.4 | Calcification assessment and CKD-MBD definition

The calcium scoring on a dual-source computed tomography (CT) scanner (Syngo CaScore, Siemens, Forchheim, Germany) was assessed and images reconstructed with 0.6 and 3.0 mm slice thickness for each patient within a week around the day when BCA was carried out. The Agatston scoring method[23] was applied on the reconstructed image sets by the commercially available software (Syngo CaScore) as follows: A calcified lesion was defined as an area of ≥3 connected pixels with CT attenuation of ≥130 Hounsfield Units (HU), with the use of 3-dimensional connectivity criteria (6 points). For each, the Agatston score was calculated by multiplying the area of each calcified lesion by a density factor, dependent on the maximal attenuation (HU) within the lesion and summing each of these values for a total calcification score. The density factor (0-4) was determined as follows: 1 = 130 to 199 HU, 2 = 200 to 299 HU, 3 = 300 to 399 HU, and 4 > 400 HU.

Calcification was defined as the Agatston score > 0 and CKD-MBD was diagnosed when MHD patients had detectable calcification.

2.5 | Follow-up procedure and outcome definitions

All subjects were followed-up every 1 month from study entry in the dialysis center or a designated outpatient clinic or by phone until death or censored for receiving transplants or switching to peritoneal dialysis. Death status and date of death were obtained through initiating phone calls to patients' homes, searching the local Death Index, and reviewing the hospital records.

The primary outcome was cardiovascular events and cardiovascular death, including congestive heart failure, a new onset of myocardial infarction, frequent angina, coronary revascularization, stroke, and amputation/revascularization for peripheral artery disease, and abdominal aortic aneurysm. The secondary outcome included all-cause rehospitalization and the cumulative length of stay.

2.6 | Statistical analysis

Study participants were divided into 3 groups according to the Agatston score: patients who did not show any sign of coronary calcification (Agatston score = 0), patients with Agatston score > 0 and ≤400, and patients with score > 400. The continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range), and categorical variables were presented as percentages. One-way analysis of variance (one-way ANOVA) or the Kruskal–Wallis H test was used for continuous variables according to the distribution, while chi-square test was applied to assess the categorical data. For univariate correlations, the Spearman Rho test was utilized as the Agatston score values did not show a normal distribution. Receiver operating characteristic (ROC) curves with the area under the curves (AUC) were generated to elucidate the associations of MCOB with groups of patients with different CAC scores. Kaplan–Meier curve was conducted to demonstrate the cumulative incidence of cardiovascular events and deaths in groups with different MCOB; Log Rank and Breslow tests were applied to examine the difference between curves. Variables at $P < 0.05$ in the univariate analysis and those considered clinically important were entered into multiple-variable logistic regression and Cox proportional hazard regression models, respective odds ratios (OR)/ hazard rates (HR) and 95% confidence interval (CI) were summarized. The Hosmer–Lemeshow test was employed to determine the goodness-of-fit of the model, $P > 0.05$ was regarded as an acceptable model. Data were analyzed using SPSS version 22.0 and $P < 0.05$ was considered significant.

3 | RESULTS

3.1 | Demographic and clinical characteristics of the study cohort

A total of 109 eligible patients (all Chinese) were enrolled in the present study of which 6 were excluded for switching to peritoneal dialysis (1 patient), measurement error (2 patients), poor compliance (2 patients), or new-onset cancer (1 patient). Finally, 103 subjects were included in the statistical analyses with the baseline characteristics summarized in Table 1.

TABLE 1 Demographic and clinical characteristics in groups with or without CKD-MBD

Characteristic	Total	No CKD-MBD	CKD-MBD	P^a
Patients, *n*	103	49	54	
Age (years), median (IQR)	48 (35-63)	36 (29-48)	60 (48-67)	<0.001
Male, *n* (%)	65 (63.1)	35 (71.4)	30 (55.6)	0.095
Han Chinese, *n* (%)	94 (91.3)	43 (87.8)	51 (94.4)	0.230
Middle school and above, *n* (%)	73 (70.9)	38 (77.6)	35 (64.8)	0.155
Dialysis vintage (days), median (IQR)	210 (97-1803)	104 (97-130)	1207.5 (444-2464)	<0.001
Cardiovascular risk factors				
Smoker or ever smoked, *n* (%)	36 (35)	16 (32.7)	20 (37)	0.641
Diabetes mellitus, *n* (%)	22 (21.4)	4 (8.2)	18 (33.3)	0.002
Hypertension, *n* (%)	95 (92.2)	46 (93.9)	49 (90.7)	0.553
Ejection fraction, median (IQR)	65 (59-69)	64.0 (58-69)	65 (60-69)	0.560
Peripheral vascular disease, *n* (%)	13 (12.6)	2 (4.1)	11 (20.4)	0.013
SBP (mm Hg), mean (SD)	136.47 (18.0)	138.61 (17.4)	134.54 (18.4)	0.252
DBP (mm Hg), mean (SD)	80.64 (13.0)	85.22 (12.1)	76.48 (12.5)	<0.001
Albumin (g/L), mean (SD)	36.94 (6.5)	34.36 (6.3)	39.28 (5.8)	<0.001
Hemoglobin (g/L), mean (SD)	89.92 (24.5)	81.27 (20.5)	97.78 (25.4)	<0.001
Creatinine (μmol/L), mean (SD)	808.36 (347.4)	842.55 (379.3)	777.33 (316.1)	0.344
LDL (mmol/L), median (IQR)	2.0 (0.4-5.3)	2.2 (1.7-2.9)	1.9 (1.4-2.3)	0.021
HDL (mmol/L), median (IQR)	1.1 (0.8-1.3)	1.1 (0.9-1.4)	1.0 (0.8-1.2)	0.476
TG (mmol/L), median (IQR)	1.4 (1.0-1.9)	1.5 (0.9-1.9)	1.4 (1.1-2.0)	0.440
Ca[b] (mmol/L), mean (SD)	2.4 (0.5)	2.5 (0.5)	2.3 (0.5)	0.1
P (mmol/L), mean (SD)	1.8 (0.6)	1.8 (0.6)	1.8 (0.6)	0.656
Ca × P (mg/dL), median (IQR)	51.3 (38.0-61.5)	52.5 (40.0-65.3)	49.6 (36.5-56.4)	0.219
Na (mmol/L), mean (SD)	139.3 (3.2)	139.3 (3.3)	139.2 (3.2)	0.904
K (mmol/L), median (IQR)	4.5 (4.1-5.0)	4.4 (3.9-4.8)	4.7 (4.2-5.4)	0.038
PTH (pmol/L), median (IQR)	38.7 (19.6-74.0)	39.2 (22.1-54.7)	37.4 (16.3-102.7)	0.606
ALP (IU/L), median (IQR)	75.0 (57.0-107.0)	66.0 (54.0-78.0)	90.0 (64.0-159.0)	<0.001
Maintenance medication[c]				
Phosphorus binders, *n* (%)	30 (29.1)	8 (16.3)	22 (40.7)	0.006
Calcium supplementation, *n* (%)	33 (32.0)	18 (36.7)	15 (27.8)	0.331
Vitamin D analogs, *n* (%)	61 (59.2)	25 (51.0)	36 (66.7)	0.107
Calcimimetics (cinacalcet), *n* (%)	7 (6.8)	1 (2)	6 (11.1)	0.068
Body composition parameters				
MCIT[d] (mg/Kg), mean (SD)	54.28 (8.46)	57.36 (8.12)	51.48 (7.83)	<0.001
MCIB[d] (mg/Kg), median (IQR)	44.3 (39.8-49.9)	47.4 (43.5-51.7)	41.7 (38.8-45.6)	<0.001
MCOB[d] (mg/Kg), mean (SD)	9.3 (1.6)	9.9 (1.4)	8.6 (1.5)	<0.001
Dry weight (Kg), mean (SD)	58.9 (11.3)	59.2 (11.9)	58.7 (10.9)	0.912
FFW (Kg), mean (SD)	45.2 (9.4)	48.3 (8.4)	42.3 (9.3)	0.001
MM (Kg), mean (SD)	42.5 (8.9)	45.5 (7.9)	39.8 (8.9)	0.001
BMI[e] (Kg/m^2), mean (SD)	22.2 (3.7)	21.8 (4.1)	22.6 (3.2)	0.517

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; Ca, calcium; CKD-MBD, chronic kidney disease-mineral and bone disorder; DBP, diastolic pressure; FFW, fat free weight; HDL, high density lipoprotein; IQR: interquartile range; K, potassium; LDL, low density lipoprotein; MCIB, mineral content in bone; MCIT, mineral content in total; MCOB, mineral content outside of bone; MM, muscle mass; Na, sodium; P, phosphorus; PTH, parathyroid hormone; SBP, systolic pressure; TG, triglycerides.

[a]*P* value for comparison among 2 groups excluding the total group.

[b]Ca was adjusted with formula: serum total Ca+0.8 × (4−Alb[g/dL]).

[c]Maintenance medication was defined as receiving the drugs for more than 4 weeks before admission.

[d]The unit of MCIT, MCIB, and MCOB represent mineral content in per kilogram of dry weight.

[e]BMI was calculated with actual weight.

The cohort consisted of 65 (63.1%) males with median age of 48 (35-63) years and dialysis vintage 210 (97-1803) days. Which of 21.4% suffered from diabetes mellitus. The cause of CKD were glomerulonephritis (12 cases confirmed by histology and 23 cases diagnosed by medical history and previous clinical data), hypertensive nephropathy (26 cases), diabetic nephropathy (16 cases), polycystic (9 cases), and others (17 cases).

All individuals underwent 2-3 periods of hemodialysis per week with autogenous arteriovenous fistula (53.4%) or tunneled cuffed central venous catheters (46.6%), 2000-5000 AxaIU of low molecular weight heparin for anticoagulant during 3.5-4 hours of treatment. Blood flow was 200-350 mL/min and dialysate flow was 500-700 mL/min (dialysate: Na 135-140 mmol/L, K 2-3 mmol/L, Ca 1.25 mmol/L, Mg 0.5-1.0 mmol/L, acetate 2-3 mmol/L, Cl 100-116 mmol/L, $HCO3^-$ 32-36 mmol/L, and glucose 1 g/L), ultrafiltration volume was determined on interdialysis weight gain.

3.2 | Characteristics of patients with CACs

The prevalence of CACs was 52.4% (54 cases), and the median CAC score was 1429 (ranging 0-40464). The mean MCIT, median MCIB, mean MCOB, were 54.28 ± 8.46, 44.29 (39.80-49.91), and 9.25 ± 1.58 mg/kg, respectively (Table 1).

As presented in Table 2, the group with high score value was older and exhibited a prolonged dialysis days, a higher percentage of diabetes, a lower diastolic pressure (DBP), a higher level of serum potassium (K), hemoglobin (Hb), and alkaline phosphatase (ALP), a lower muscle mass (MM), fat free mass (FFW), and the level of albumin (Alb) were significantly different among the 3 groups but did not present a linear trend.

3.3 | Comparisons of mineral content among groups with different Agatston scores

The values of MCOB ([mg/kg], 9.92 ± 1.37, 8.94 ± 1.68, 8.39 ± 1.33; $P < 0.001$), MCIB, and MCIT differed significantly among the 3 groups, and only MCOB in each group conformed to a normal distribution. As demonstrated in Figure 1, MCOB decreased numerically with increasing Agatston score, and then was selected to generate ROC-AUC based on the statistical distribution.

3.4 | Univariable correlation models evaluated the association of variables with Agatston score

The Agatston score showed a significantly inverse correlation with MCOB ($r = -0.459$, $P < 0.001$) as well as patients' FFW, MM, and DBP. However, a significantly positive correlation was established with patients' age, dialysis vintage, ALP, Hb, Alb, and K. No significant correlations were found between Agatston score and Ca, P, Ca × P, or PTH (Supp. Table S1).

Additionally, Pearson's correlation and partial correlation/multivariable linear regression analyses were not conducted due to the nonnormal distribution for Agatston scores even after transformation.

3.5 | Discrimination of biomarkers for groups with different Agatston scores

As demonstrated in Figures 2A,B, MCOB discriminated the Agatston score > 0 assessed by coronary CT (AUC = 0.737, $P < 0.001$) and showed a greater prediction efficiency than ALP or FFW. Other biomarkers such as Ca, P, PTH, MM, Alb, Hb, and K showed insignificant or inferior discrimination (curves not shown).

In the group with Agatston score > 0 and ≤ 400, the evaluated biomarkers including MCOB, FFW, ALP, and Hb failed to show significant discrimination ($P > 0.05$, data not shown). Therefore, the regression analysis for this group was not conducted.

For a group with Agatston score > 400 (Figure 3A,B), MCOB (AUC = 0.733, $P < 0.001$) and ALP (AUC = 0.803, $P < 0.001$) presented superior discrimination efficiency than biomarkers that mentioned above.

3.6 | Risk factors for MHD patients with Agatston score > 0 and 400 in univariate and multivariate logistic regression analysis

As presented in Table 3, the independent risk factors for the Agatston score > 0 were MCOB ≤ 9.2657 mg/kg (OR 4.853, $P = 0.044$), age > 60 year (OR 17.449, $P = 0.007$) and Alb (per 1 g/L increased; OR 1.193, $P = 0.006$) after adjustment for the factors which represented statistically significant in univariate analysis.

In another model that added clinical or traditional risk factors (Table 4), the independent indicators for the Agatston score > 0 included MCOB ≤ 9.2657 mg/kg (OR 4.355, $P = 0.035$), age > 60 years, dialysis vintage and Alb.

For the Agatston score > 400 (Supp. Table S2), the regression analysis that entered significant variables in inter-group comparision, showed age > 60 and dialysis vintage were the independent risk factors.

3.7 | Clinical characteristics and outcomes in MHD patients with or without MCOB ≤ 9.2657 mg/kg

One hundred three patients were followed for 12 (11-12.5) months (until November 2018), of which 2 patients dropped out for personal reasons, 8 had received allogeneic kidney

TABLE 2 Demographic and clinical characteristics according to Agatston score

Characteristic	0	0.1-400	>400	P[a]
Patients, *n*	49	25	29	
Age (years), median (IQR)	36 (29-48)	55 (46-67.5)	62.0 (55-66.5)	<0.001
Dialysis vintage (days), median (IQR)	104 (97-130)	548 (120-1185)	1946 (1020-3130)	<0.001
Cardiovascular risk factors				
Smoker or ever smoked, *n* (%)	16 (32.7)	8 (32)	12 (41.4)	0.692
Diabetes mellitus, *n* (%)	4 (8.2)	7 (28)	11 (37.9)	0.005
Hypertension, *n* (%)	46 (93.9)	23 (92)	26 (89.7)	0.973
Ejection fraction, median (IQR)	64 (58-69)	66 (62-69)	63 (59-69)	0.644
Peripheral vascular disease, *n* (%)	2 (4.1)	6 (24)	5 (17.2)	0.034
SBP (mm Hg), mean (SD)	138.6 (17.4)	135.2 (17.3)	134.0 (19.6)	0.504
DBP (mm Hg), mean (SD)	85.2 (12.1)	77.9 (15.0)	75.3 (10.0)	0.002
Albumin (g/L), mean (SD)	34.4 (6.3)	39.5 (6.6)	39.1 (5.0)	<0.001
Hemoglobin (g/L), mean (SD)	81.3 (20.5)	91.2 (21.4)	103.5 (27.5)	<0.001
Creatinine (μmol/L), mean (SD)	842.6 (379.3)	738.2 (318.6)	811.1 (315.5)	0.478
LDL (mmol/L), median (IQR)	2.2 (1.7-2.9)	2.0 (1.4-2.3)	1.8 (1.4-2.2)	0.049
HDL (mmol/L), median (IQR)	1.1 (0.9-1.4)	1.1 (0.8-1.3)	1.0 (0.8-1.2)	0.526
TG (mmol/L), median (IQR)	1.5 (0.9-1.9)	1.4 (1.1-2.1)	1.4 (1.2-1.8)	0.711
Ca[b] (mmol/L), mean (SD)	2.5 (0.5)	2.2 (0.6)	2.4 (0.4)	0.08
P (mmol/L), mean (SD)	1.8 (0.6)	1.8 (0.6)	1.8 (0.6)	0.906
Ca × P (mg/dL)^2, mean (SD)	55.7 (21.6)	47.2 (19.4)	52.6 (18.2)	0.234
Na (mmol/L), mean (SD)	139.3 (3.3)	139.0 (2.6)	139.4 (3.7)	0.864
K (mmol/L), mean (SD)	4.4 (0.6)	4.6 (0.7)	5.0 (1.2)	0.011
PTH (pmol/L), median (IQR)	39.2 (22.1-54.7)	29.2 (17.5-46.2)	59.8 (16.3-206.3)	0.132
ALP (IU/L), median (IQR)	66 (54-78)	73 (56-90)	108 (86-370)	<0.001
Maintenance medication[c]				
Phosphorus binders, *n* (%)	8 (16.3)	8 (32)	14 (48.3)	0.01
Calcium supplementation, *n* (%)	18 (36.7)	9 (36)	6 (20.7)	0.302
Vitamin D analogs, *n* (%)	25 (51)	16 (64)	20 (69)	0.254
Calcimimetics (cinacalcet), *n* (%)	1 (2)	0 (0)	6 (20.7)	0.002
Body composition parameters				
MCIT[d] (mg/Kg), median (IQR)	57.1 (53.2-62.8)	52.4 (47.8-58.0)	49.6 (46.3-53.9)	0.001
MCIB[d] (mg/Kg), median (IQR)	47.4 (43.5-51.7)	43.6 (39.6-47.8)	41.5 (38.2-44.3)	0.001
MCOB[d] (mg/Kg), mean (SD)	9.9 (1.4)	8.9 (1.7)	8.4 (1.3)	<0.001
Dry weight (Kg), mean (SD)	59.2 (11.9)	59.3 (11.5)	58.2 (10.5)	0.915
FFW (Kg), mean (SD)	48.3 (8.4)	43.8 (10.1)	41.0 (8.6)	0.002
MM (Kg), mean (SD)	45.5 (7.9)	41.3 (9.6)	38.6 (8.2)	0.002
BMI[e] (Kg/m^2), mean (SD)	21.8 (4.1)	22.8 (3.8)	22.5 (2.7)	0.256

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; Ca, calcium; DBP, diastolic pressure; FFW, fat free weight; HDL, high density lipoprotein; IQR, interquartile range; K, potassium; LDL, low density lipoprotein; MCIB, mineral content in bone; MCIT, mineral content in total; MCOB, mineral content outside of bone; MM, muscle mass; Na, sodium; SBP, systolic pressure; P, phosphorus; PTH, parathyroid hormone; TG, triglycerides.

[a]*P* value for comparison among 3 groups.

[b]Ca was adjusted with formula: serum total Ca+0.8 × (4−Alb[g/dL]).

[c]Maintenance medication was defined as receiving the drugs for more than 4 weeks before admission.

[d]The unit of MCIT, MCIB, and MCOB represent mineral content in per kilogram of dry weight.

[e]BMI was calculated with actual weight.

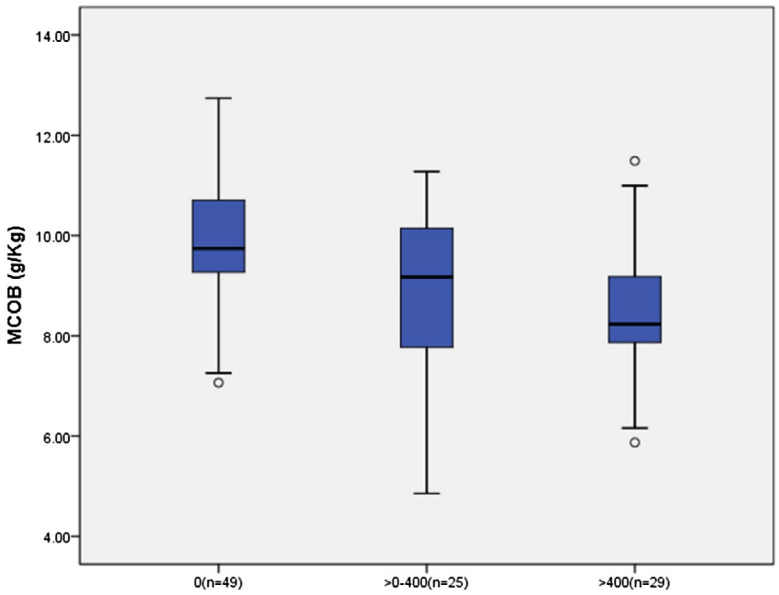

FIGURE 1 Boxplots illustrating the value of mineral content outside of bone (MCOB) in the following group: Agatston score = 0, from 0.1 to 400, and greater than 400 [Color figure can be viewed at wileyonlinelibrary.com]

transplants in Urology of West China Hospital, and 3 switched to peritoneal dialysis. 7 cardiovascular deaths and 1 died of esophageal cancer while 14 patients received parathyroidectomy during follow-up (Table 5).

The overall incidence of cardiovascular event was 12.6%, and 12 (11.7%) patients occurred positive primary outcomes. Cumulative incidence curves (Figure 4) showed a significant difference in AUC between groups ($P = 0.002$). Patients with MCOB $\leq$9.2657 mg/kg, had a greater incidence of cardiovascular events and deaths (22.4% vs. 1.9%, $P = 0.001$), higher rates of rehospitalization and prolonged cumulative rehospitalization stay compared to those with MCOB > 9.2657 mg/kg (Table 5).

3.8 | Predictors for primary and secondary end points in Cox proportional hazard regression analysis

As presented in Tables 6 and 7, only MCOB $\leq$9.2657 mg/kg independently predicted cardiovascular outcomes (HR = 10.108; $P = 0.042$) and rehospitalization (HR = 2.689; $P = 0.004$) as well after adjustment for conventional clinical factors. Age and parathyroidectomy showed significant prediction for rehospitalization but not for cardiovascular outcome. Because of few deaths, these models were not additionally analyzed for cardiovascular or all-cause deaths.

4 | DISCUSSION

4.1 | Potential mechanism and association of mineral content with CACs and cardiovascular events in MHD patients

The mechanism of vascular calcification includes mineral composition deposition and crystallization evolving over time and space, which is a sophisticatedly regulated process that involves a complex interplay between promoters and inhibitors of calcification with several similarities to bone ossification.[24] The current study showed an inverse correlation between MCIB (assumed parallel to bone volume or bone mineral density) and the Agatston score, which was in an agreement with the previous studies.[25,26] Interestingly, MCOB had a stronger correlation than MCIB. Given that the Agatston scores are increasing with the amount of atherosclerotic burden,[28,29] the decreasing levels of MCOB, as ascertained in the present study, might be explained for the rising probability of mineral deposition in the coronary artery, leading to a decrease in extracellular fluid or blood circulation correspondingly.

Since the discrimination performance of MCOB was proved in ROC curves multivariate analysis, the cohort was reassigned in 2 group according to the optimal cut-off value to address the association of MCOB with cardiovascular events, the baseline characteristics presenting in Table 5. Until 12 (11-12.5) months of follow-up, patients with MCOB $\leq$9.2657 mg/kg were more vulnerable to cardiovascular events and cardiovascular death than those without, and the significant difference of cumulative incidence between the 2 groups was demonstrated in Figure 4. Notablely, MCOB $\leq$9.2657 mg/kg was the only independent predictor for cardiovascular outcomes holding a powerful hazard rate of 10.108 (Table 6). Owing to the advantages of noninvasiveness, cost-efficiency, and convenience, body composition assessment might be applicable in the clinical setting as a tool for cardiovascular prognosis assessment. As for all-cause rehospitalization, the prediction performance of MCOB was not merely correlating local CACs, but also based on the ability of evaluating nutrition status for the whole body. Poorer MCOB correlated with poorer MCIB or

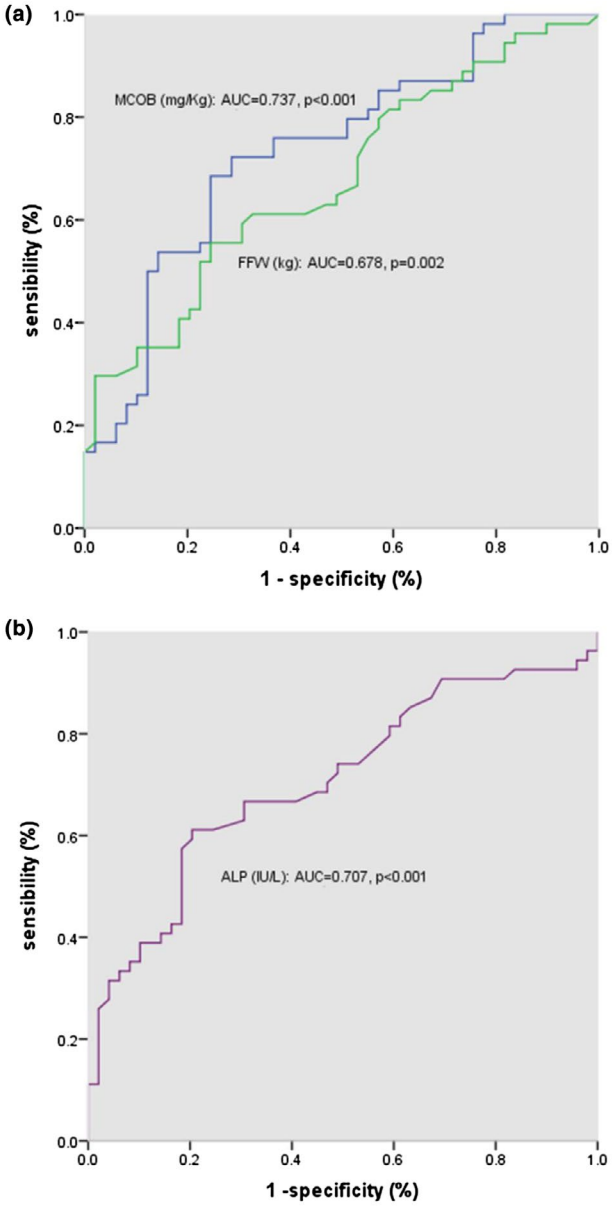

FIGURE 2 ROC curve for CACs (Agatston score > 0) in MHD patients. A, Curves illustrating smaller value of MCOB (blue line) or FFW (green line) indicates more positive test for CACs. B, Purple line illustrating larger value of ALP indicates more positive test for CACs. According to AUC, the significant discrimination of MCOB for CACs outperforms FFW or ALP. Abbreviations: ALP, alkaline phosphatase; AUC, area under the curves; CACs, coronary artery calcifications; FFW, fat free weight; MCOB, mineral content outside of bone; MHD, maintenance hemodialysis [Color figure can be viewed at wileyonlinelibrary.com]

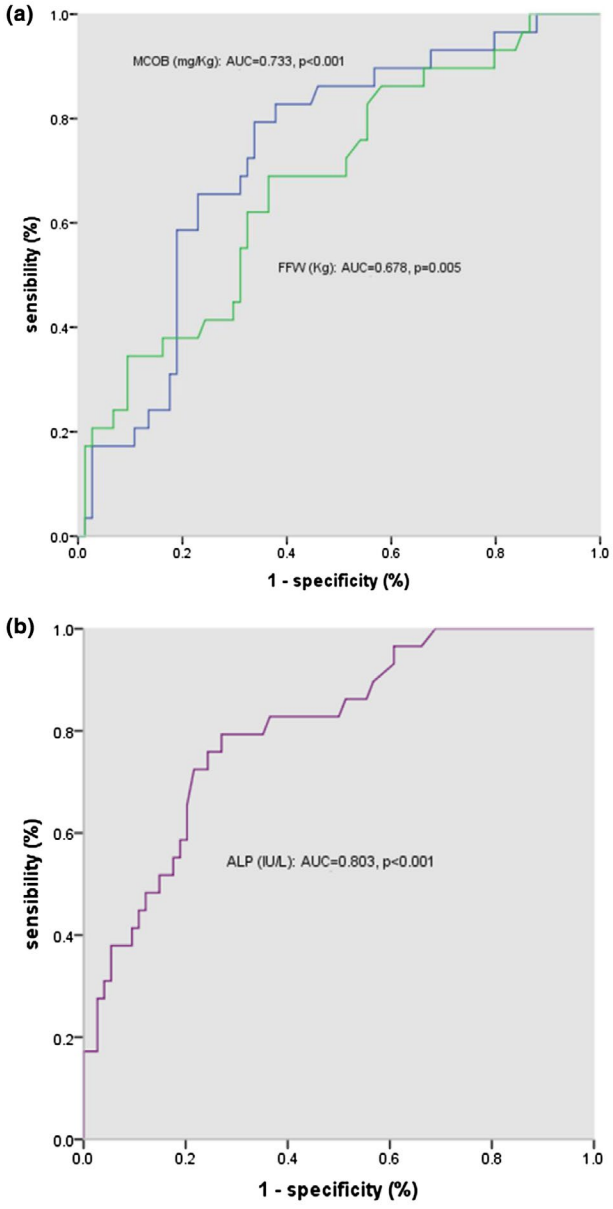

FIGURE 3 ROC curve for Agatston score > 400. A, Curves illustrating smaller value of MCOB (blue line) or FFW (green line) indicates more positive test for Agatston score > 400. B, Purple line illustrating larger value of ALP indicates more positive test for Agatston score > 400. According to AUC, the significant discrimination of MCOB for Agatston score > 400 is superior to FFW while inferior to ALP. Abbreviations: ALP, alkaline phosphatase; AUC, area under the curves; FFW, fat free weight; MCOB, mineral content outside of bone [Color figure can be viewed at wileyonlinelibrary.com]

MCIT, which was warning insufficient mineral and might causing readmission. Besides, it's not hard to imagine that older patients are prone to rehospitalization due to organ aging, and in the present study, 14 patients rehospitalized for parathyroidectomy made it become the strongest predictor for rehospitalization (Table 7).

4.2 | Conventional risk factors and assessment tool for CACs in MHD patients

Vascular calcification occurs when hydroxyapatite crystals deposit in the intimal or medial layer of the arteries. It is an actively regulated process[31] involving various signaling

TABLE 3 Risk factors for Agatston score > 0 (CKD-MBD) in univariate and multivariate logistic regression analysis

Variable	Unadjusted OR	95%CI	*P*	Adjusted OR	95%CI	*P*
MCOB ≤ 9.2657 mg/kg (yes vs. no)	6.711	2.817-15.989	< 0.001	4.853	1.047-22.491	0.044
Age > 60 years (yes vs. no)	9.000	2.836-28.564	< 0.001	17.449	2.181-139.587	0.007
Dialysis vintage (per 1 day increased)	1.458	1.195-1.779	0.002	1.001	1.000-1.001	0.121
Diabetes mellitus (yes vs. no)	2.372	1.332-4.254	0.004	1.392	0.537-3.605	0.496
PVD (yes vs. no)	4.381	1.156-16.606	0.030	2.031	0.305-13.516	0.464
DBP (per 1 mm Hg increased)	0.942	0.908-0.977	0.001	0.972	0.919-1.029	0.330
ALP ≥ 80.5 IU/L (yes vs. no)	6.129	2.531-14.839	< 0.001	2.334	0.513-10.628	0.273
Albumin (per 1 g/L increased)	1.149	1.065-1.238	< 0.001	1.193	1.052-1.352	0.006
Hemoglobin (per 1 g/L increased)	1.032	1.013-1.052	0.001	0.986	0.955-1.018	0.395
LDL (per 1 mmol/L increased)	0.580	0.361-0.932	0.024	0.594	0.273-1.290	0.188
K (per 1 mmol/L increased)	1.818	1.105-2.992	0.019	2.124	0.849-5.314	0.108
Phosphorus binders (yes vs. no)	3.523	1.387-8.948	0.008	1.849	0.407-8.391	0.426
FFW (per 1 kg increased)	0.928	0.885-0.973	0.002	3.671	0.221-61.075	0.365
MM (per 1 kg increased)	0.924	0.880-0.971	0.002	0.254	0.013-4.904	0.364
Constant				< 0.001		0.057

Hosmer-Lemeshow $\chi^2 = 6.078$, $P = 0.638$, percentage correct 88.3%.
Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; DBP, diastolic pressure; FFW, fat free weight; K, potassium; LDL, low density lipoprotein; MCOB, mineral content outside of bone; MM, muscle mass; PVD, peripheral vascular disease; OR, odd ratio.

TABLE 4 Predictors for Agatston score > 0 (CKD-MBD) in univariate and multivariate logistic regression analysis added conventional variables

Variable	Unadjusted OR	95%CI	*P*	Adjusted OR	95%CI	*P*
MCOB ≤ 9.2657 mg/kg (yes vs. no)	6.711	2.817-15.989	< 0.001	4.355	1.107-17.132	0.035
Age > 60 years (yes vs. no)	9.000	2.836-28.564	< 0.001	24.328	3.532-167.573	0.001
Dialysis vintage (per 1 day increased)	1.458	1.195-1.779	0.002	1.001	1.000-1.001	0.032
Diabetes mellitus (yes vs. no)	2.372	1.332-4.254	0.004	1.420	0.532-3.792	0.484
ALP ≥ 80.5 IU/L (yes vs. no)	6.129	2.531-14.839	< 0.001	2.160	0.466-10.011	0.325
Albumin (per 1 g/L increased)	1.149	1.065-1.238	< 0.001	1.194	1.064-1.339	0.003
Hemoglobin (per 1 g/L increased)	1.032	1.013-1.052	0.001	0.985	0.956-1.015	0.327
LDL (per 1 mmol/L increased)	0.580	0.361-0.932	0.024	0.645	0.273-1.290	0.188
P (per 1 mmol/L increased)	0.863	0.998-1.003	0.652	1.286	0.458-3.608	0.633
PTH (per 1 pmol/L increased)	1.000	0.453-1.641	0.729	1.001	0.998-1.005	0.535
Constant				0.001		0.005

Hosmer–Lemeshow $\chi^2 = 14.619$, $P = 0.067$, percentage correct 81.6%.
Abbreviations: ALP, alkaline phosphatase; CI, confidence interval; LDL, low density lipoprotein; MCOB, mineral content outside of bone; OR, odd ratio; P, phosphorus; PTH, parathyroid hormone.

pathways and influenced by several clinical factors, such as advancing age, diabetes, kidney function decline, inflammatory states, and rare genetic conditions. Consistent with the previous studies, our study showed that in asymptomatic MHD patients, CACs correlated positively with age, dialysis vintage,[32] and diabetes.[33,34] Three multivariate regression models showed old age, higher level of Alb, and longer dialysis vintage were the independent risk factors for CKD-MBD (Tables 3 and 4, Supp. Table S2).

CT with Agatston scoring method is mostly used in screening and quantifying the CACs in CKD patients, as well as, evaluating the risk of obstructive coronary artery disease (CAD) and aiding clinical decision-making.[1,35,36] In a large and prospective multi-ethnic study of atherosclerosis (MESA) cohort including patients free of known CAD at baseline, a majority of the coronary heart events, such as myocardial infarction or death from CAD, occurred in patients with an Agatston score > 100.[36] Ca scores > 400

TABLE 5 Outcomes and characteristics according to MCOB

Characteristic	Total	MCOB[a] > 9.2657 mg/kg	MCOB ≤ 9.2657 mg/kg	*P*[b]
Patients, *n*	103	54	49	–
Kidney transplantation received, *n* (%)	8 (7.8)	8 (14.8)	0 (0)	0.005
Peritoneal dialysis switched, *n* (%)	3 (2.9)	2 (3.7)	1 (2.0)	0.616
Parathyroidectomy, *n* (%)	14 (13.6)	5 (9.3)	9 (18.4)	0.178
Loss to follow-up, *n* (%)	2 (1.9)	0 (0)	2 (4.1)	0.134
Length of follow-up (months)[c], median (IQR)	12 (11-12.5)	11.5 (10.5-12.5)	12 (11-13)	0.073
Cardiovascular events, *n*[d] (%)	13 (12.6)	1 (1.9)	12 (24.5)	0.001
Cardiovascular deaths, *n* (%)	7 (6.8)	1 (1.9)	6 (12.2)	0.036
All-cause deaths, *n* (%)	8[e] (7.8)	2 (3.7)	6 (12.2)	0.106
Positive composite outcomes, *n*[f] (%)	12 (11.7)	1 (1.9)	11 (22.4)	0.001
Secondary outcomes (rehospitalization), *n* (%)	47 (45.6)	16 (29.6)	31 (63.3)	0.001
Rehospitalization occurrence, *n*[g] (%)	73 (70.9)	24 (44.4)	52 (106.1)	–
Cumulative rehospitalization days[h], median (IQR)	0 (0-20)	0 (0-12)	10 (0-23)	0.004

Abbreviations: FFW, fat free weight; MCOB, mineral content outside of bone.
[a]The unit of MCOB represents mineral content in per kilogram of dry weight.
[b]*P* value for comparison among 2 groups excluding the total group.
[c]Each patient was followed for the outcome of interest until death or censoring for transplantation or peritoneal dialysis.
[d]One of the patients suffered 2 vascular events (1 stroke and 1 amputation).
[e]One died of esophageal cancer and 7 of cardiovascular events.
[f]Composite outcomes included cardiovascular events and cardiovascular death.
[g]Note that 1 patient could have several rehospitalizations.
[h]Sum of the length of each rehospitalization for each patient during follow-up period.

indicated CAD at an advanced stage, thereby implying the invasive coronary angiography as the next diagnostic step in recent studies.[37,38] Our study excluded MCOB as an independent indicators for Agatston score > 400 (Supp. Table S2), which might be attributed to the small sample size. There must be more accurate methods with contrast agent used for evaluating CACs even its effect on cardiac function of MHD patients, which might, however, worsen the residual renal function. For asymptomatic MHD patients with fragile conditions. It seems unlikely to consent with any expensive examination at the risk of contrast agent exposure. Therefore, we applied noncontrast contained CT in detecting coronary artery disease.

4.3 | The role of serum biomarker for CACs in MHD patients

In CKD, the inflammatory cytokines and abnormal mineral metabolism, especially hyperphosphatemia, induce vascular calcification.[41] Clinical studies suggested that predialysis CKD patients have preserved levels of the mineralization inhibitors to protect themselves from exposure to high Ca × P levels, which could be rapidly broken as dialysis initiates.[42,43] The calcium load in dialysis vessels was approximately twofold as that in predialysis vessels and strongly correlated with the time on dialysis.[45,46] This phenomenon might account for the high morbidity and mortality of CKD-MBD in MHD patients.

In the present study, ALP showed the strongest correlation with calcification scores among serum biomarkers, and also, a preferred discrimination for CACs in MHD patients without known liver disease or obvious abnormal liver function index. However, the multivariate analysis definitely weakened its practical role (Tables 3 and 4). The ability of removing phosphate (dephosphorylation) needed in multiple metabolic processes (such as proteins and nucleotides) made ALP crucial for bone mineralization, but paradoxically, it could be deleterious in other processes, such as vascular calcification and increasing cross-talk between bone and vessels. Consistently, Bover et al.[47] emphasized the diagnostic and prognostic potential of ALP for CKD-MBD, while not recommended as an isolated assessment indicator due to the further complicated balance between beneficial and harmful activities in the context of CKD.

In theory, CKD confers modifiable risk factors including dysregulated mineral metabolism with high circulating levels of Ca and phosphate.[48] However, the present study showed an irrelevant correlation of Ca, P, Ca × P, PTH with Agatston score ($P > 0.05$), which presented neither statistical difference among 3 groups (Table 2) nor the independent risk factors for CKD-MBD (Tables 3 and 4). This differed from the results presented by Adeney et al.[49] that demonstrated an association of high serum phosphate concentrations with the prevalence of cardiovascular calcification in individuals with moderate CKD and no clinical cardiovascular disease, or that

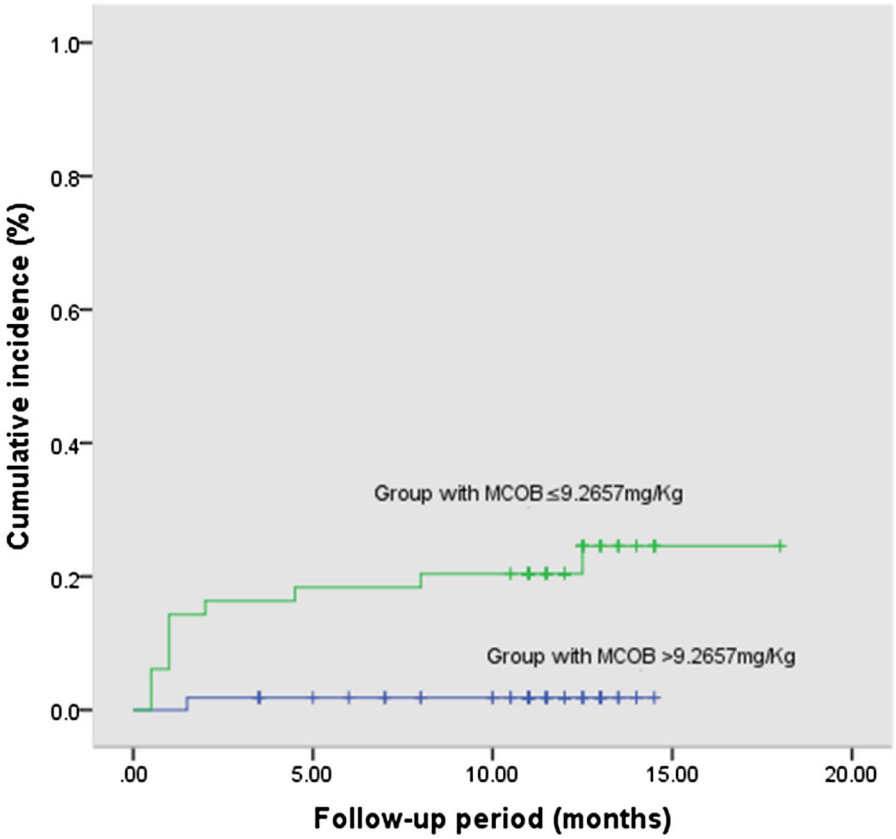

FIGURE 4 Curves respectively illustrating the cumulative incidence of cardiovascular event and cardiovascular deaths in two groups during follow-up (Log Rank $\chi^2 = 9.865$, $P = 0.002$; Breslow $\chi^2 = 9.584$, $P = 0.002$); green line represents group with MCOB ≤ 9.2657 mg/kg, blue line represents group with MCOB > 9.2657 mg/kg. Abbreviation: MCOB, mineral content outside of bone [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 6 Cox proportional hazard regression models for cardiovascular events and cardiovascular death

Variable	Unadjusted HR	95%CI	*P*	Adjusted HR	95%CI	*P*
MCOB ≤9.2657 mg/kg (yes vs. no)	12.554	1.619-97.326	0.015	10.108	1.090-93.737	0.042
Age > 60 years (yes vs. no)	5.733	1.725-19.052	0.004	3.745	0.847-16.556	0.082
Dialysis vintage (per 1 day increased)	1.000	1.000-1.000	0.733	1.000	0.999-1.001	0.901
Diabetes mellitus (yes vs. no)	1.996	1.133-3.515	0.017	0.992	0.488-2.017	0.982
Albumin (per 1 g/L increased)	1.022	0.934-1.118	0.637	0.993	0.897-1.099	0.889
FFW (per 1 kg increased)	0.958	0.899-1.021	0.188	1.004	0.934-1.080	0.906
Parathyroidectomy (yes vs. no)	0.562	0.072-4.355	0.581	0.734	0.074-7.310	0.792

Overall (score) $\chi^2 = 16.573$, $P = 0.02$.
Abbreviations: CI, confidence interval; FFW, fat free weight; HR, hazard rate; MCOB, mineral content outside of bone.

reported by Hartmut et al.[50] considering PTH level as an independent risk factor for CACs as assessed by CT calcification score in patients with CKD on dialysis.

The negative results might be attributed to the number of patients, who were administered calcium-phosphorus-regulated agents, such as calcium tablets (32%), calcitriol (59.2%), and sevelamer/lanthanum carbonate/calcium acetate (29.1%). This might indirectly influence the PTH release, and a few patients (6.5%) used cinacalcet to inhibit the level of serum PTH directly.[32] In addition, the concentration of all serum biomarkers frequently suffered from rapid fluctuation with the alteration of circulating blood volume during intermittent hemodialysis, which greatly limited the prediction of these biomarkers for CKD-MBD.

The measurement of minerals intracellularly and extracellularly based on segmental bioelectrical impedance principle, without confounders from circulating blood volume, may be used as a surrogate marker for CACs as

TABLE 7 Cox proportional hazard regression models for rehospitalization

Variable	Unadjusted HR	95%CI	*P*	Adjusted HR	95%CI	*P*
MCOB ≤ 9.2657 mg/kg (yes vs. no)	2.473	1.351-4.529	0.003	2.689	1.365-5.297	0.004
Age > 60 years (yes vs. no)	2.157	1.200-3.878	0.010	2.463	1.192-5.089	0.015
Dialysis vintage (per 1 day increased)	1.000	1.000-1.001	< 0.001	1.000	1.000-1.000	0.964
Diabetes mellitus (yes vs. no)	1.155	0.831-1.604	0.391	0.861	0.565-1.313	0.487
Albumin (per 1 g/L increased)	1.020	0.974-1.068	0.401	0.984	0.937-1.034	0.522
FFW (per 1 kg increased)	0.971	0.941-1.002	0.066	1.000	0.965-1.036	0.983
Parathyroidectomy (yes vs. no)	4.877	2.467-9.642	< 0.001	6.916	2.551-18.754	< 0.001

Overall (score) $\chi^2 = 39.760$, $P < 0.001$.
Abbreviations: CI, confidence interval; FFW, fat free weight; HR, hazard rate; MCOB, mineral content outside of bone.

well as cardiovascular events, especially suitable for MHD patients.

5 | LIMITATION

The present study had some limitations. Firstly, the occasional measurements of hormone levels, body composition, or CACs scoring aggravated the potential for laboratory measurement or technical error. Secondly, coronary calcification by CT scan might not distinguish between intimal and medial calcification so that it was not clear whether MCOB correlated with medial or intimal calcifications or both. Thirdly, the study population consisting of Chinese individuals did not reflect a multiethnic cohort, hence the results cannot be generalized to other ethnic groups or a common population. Fourthly, findings are limited by small sample size and heterogeneous population, and as a result, subgroup analysis could not be conducted. Furthermore, the relatively short follow-up period for asymptomatic patients presented fewer deaths, limiting a Cox hazard regression analysis for cardiovascular mortality than the composite end point, which necessitated further investigation for the current cohort.

6 | CONCLUSION

The pilot prospective observational study showed that in 103 Chinese patients with CKD undergoing hemodialysis, MCOB assessed by BCM had a stronger correlation with CACs compared to conventional serum biomarkers, including Ca, P, or PTH. MCOB could discriminate patients with CKD-MBD and Agatston score > 400, and also presented as an independent risk factor for CKD-MBD and a significant predictor for cardiovascular outcomes. Since the change in circulating blood volume during intermittent hemodialysis and the usage of medication in CKD standard management leads to instability in the level of serum biomarkers, MCOB could be used as a surrogate marker for the presence of CKD-MBD and the extent of CACs in asymptomatic MHD patients as well as for predicting cardiovascular morbidity and mortality. Thus, additional studies are required for further validation.

STATEMENT OF ETHICS

The investigators adhered to the Declaration of Helsinki while conducting the study and written informed consent was obtained from all patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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