Research Article

De novo Cardiac Valve Calcification after Hemodialysis in End-Stage Renal Disease Patients Predicts Future Cardiovascular Events: A Longitudinal Cohort Study

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Keywords

Cardiac valve calcification · Hemodialysis · Cardiovascular events

Abstract

Background: Cardiac valve calcification (CVC) in maintenance hemodialysis patients is associated with adverse cardiovascular outcomes. However, whether de novo CVC in incident hemodialysis patients predicts future cardiovascular events is unknown. **Methods:** This study included 174 patients newly receiving hemodialysis without CVC as reflected by echocardiography between January 2005 and December 2014. De novo CVC was determined with echocardiography once every 6 months until December 2016. **Results:** The median follow-up was 66 months (range, 19–141). De novo CVC developed in 80 out of 174 (45.98%) subjects: 58 developed aortic valve calcification (AVC) alone, 42 developed mitral valve calcification (MVC) alone, and 20 developed both AVC and MVC. The median time from baseline to de novo CVC was 46 months (range, 3–120) for AVC and 50 months (range, 13–127) for MVC. Patients who developed CVC had a higher major adverse cardiovascular events (MACE) rate than those who did not (AVC: 30/58 [51.72%] vs. 23/116 [19.83%]; MVC: 25/42 [59.52%] vs. 28/132 [21.21%]). Multivariate time-dependent Cox regression showed an association between MACE with both de novo AVC and MVC (AVC: hazard ratio [HR] 3.2, 95% confidence interval [CI] 1.55–6.63; MVC: HR 5.95, 95% CI 2.90–12.20). **Conclusions:** De novo CVC is an independent risk factor for MACE in hemodialysis patients, and regular CVC screening among hemodialysis patients without preexisting CVC may be helpful to identify patients at increased risk of adverse cardiovascular outcomes.

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Introduction

Cardiac valve calcification (CVC) is an independent predictor of adverse cardiovascular outcomes in the general population [1]. Increasing with aging, CVC is a tightly regulated, active process similar to atherosclerotic cardiovascular calcification and can occur 20 years earlier in patients with chronic kidney disease (CKD) than in healthy individuals. In CKD patients, CVC progresses rapidly: the estimate of prevalence in patients with stage 3 CKD is 26% [2] and as high as 75% in patients with stage 5 CKD on dialysis (CKD5D) [3]. The rapid progression could be attributed to alterations in calcium-phosphate homeostasis, inflammation, and pathological bone remodeling, due to uremic environment.

About 42.5–70.1% of CKD patients had no preexisting CVC when dialysis was initiated [4]. The time need to develop de novo CVC in hemodialysis patients is controversial. Several studies found that 20–46% of patients on incident peritoneal dialysis or maintenance hemodialysis developed de novo CVC or coronary artery calcification within 12 months [5, 6]. In contrast, other works indicated that in incident hemodialysis patients, absence of calcification in the coronary artery or superficial femoral artery was associated with minimal or no calcification progression during follow-up of 18–30 months [7]. More importantly, whether de novo CVC has the same predictive value (as compared to preexisting CVC) for cardiovascular morbidity and mortality is unknown.

In this longitudinal cohort study, we examined the temporal pattern of de novo CVC development in patients without CVC upon the initiation of hemodialysis. A time-dependent Cox regression model was used to analyze the potential association of de novo CVC with future major adverse cardiovascular events (MACE).

Subjects and Methods

Study Population

The cohort included 203 subjects newly receiving hemodialysis for end-stage renal disease at Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine between January 2005 and December 2014. They had no evidence of CVC (as reflected by echocardiography within the 3 months of initiating hemodialysis). De novo CVC was determined with echocardiography once every 6 months until the last follow-up. Patients were excluded if they had any malignancy, autoimmune disease (e.g., systemic lupus erythematosus, rheumatic heart disease), congenital heart disease, pregnancy, or a life expectancy <6 months. Patients underwent regular hemodialysis therapy (4 h per session, 3 times per week), and the calcium concentration in dialysate was either 1.25 or 1.50 mmol/L. The last follow-up was conducted on December 31, 2016. Only the data of the 174 patients who remained on hemodialysis until the last follow-up were analyzed (the remaining 29 subjects converted to peritoneal dialysis or received transplantation). The investigators of this study had access to information that could identify individual patients during or after data collection.

Data Collection

Baseline data on demographics, comorbidities, vitamin D analogue use, and laboratory variables were collected within the first 3 months of hemodialysis initiation. As phosphate binders were included in the local medical insurance since March 2016, the use of phosphate binders in this cohort was largely limited (<5%). Body mass index (BMI) was calculated as the ratio of body weight (kg) to squared height (m²). Medical chart reviews were conducted to ascertain the background disease of renal failure and history of cardiovascular disease (CVD) (including myocardial infarction, angina pectoris, peripheral vascular disease, and cerebrovascular accident). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at a supine position three times in the arm that did not contain an arteriovenous fistula or shunt. Mean arterial pressure (MAP) was calculated as $DBP + (SBP - DBP) / 3$.

Fig. 1. Probability distribution of time from baseline to developing de novo CVC and time from baseline to MACE. **a** Probability distribution of time from baseline to developing de novo AVC. **b** Probability distribution of time from baseline to MACE in patients developing de novo AVC. **c** Probability distribution of time from baseline to developing de novo MVC. **d** Probability distribution of time from baseline to MACE in patients developing de novo MVC. AVC, aortic valve calcification; CVC, cardiac valve calcification; MACE, major adverse cardiovascular events; MVC, mitral valve calcification.

Biochemical Analysis

Fasting venous blood was collected for routine blood chemistry and determination of serum concentrations of albumin, calcium, phosphorus, intact parathyroid hormone (iPTH), triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein (hsCRP). Serum calcium was adjusted for serum albumin concentration using the formula corrected calcium = [total measured calcium + $0.8 \times (4.0 - \text{albumin in g/dL})$]. Blood was routinely assessed monthly and the remaining above variables were assessed at baseline and every 3 months (required by the local HD Quality Control Committee) until the end of follow-up. A time-averaged (TA) value was given as values averaged over the follow-up period.

Echocardiography

Comprehensive echocardiography (Vivid 7; GE-VingMed Sound AB, Horten, Norway) was performed within the first 3 months of hemodialysis initiation (baseline) using a 3.3-MHz multiphase array probe. Images were acquired with the patients in a left decubitus position under the two-dimensional M-mode as recommended by the American Society of Echocardiography guidelines [8]. De novo CVC was defined as the presence of bright echoes >1 mm on one or more cusps of aortic valve, mitral valve, or mitral annulus [9, 10].

Table 1. Clinical parameters of patients with or without de novo CVC at baseline

Characteristic	Without de novo AVC (n = 116)	De novo AVC (n = 58)	Without de novo MVC (n = 132)	De novo MVC (n = 42)
Age, years	51.70±12.40	60.64±12.13 ^a	53.25±13.27	59.19±11.03 ^a
Women	42 (36.21%)	23 (39.66%)	44 (33.33%)	21 (50.00%)
Body mass index	25.65±3.87	25.62±3.95	25.51±3.81	26.04±4.15
Smoking history	41 (35.34%)	20 (34.48%)	50 (37.88%)	17 (26.19%)
Previous history of CVD	8 (6.90%)	6 (10.34%)	11 (8.33%)	3 (7.14%)
DM as primary cause of renal failure	15 (12.93%)	13 (22.41%)	18 (13.64%)	10 (23.81%)
MAP, mm Hg	104.77±6.83	103.09±8.34	104.68±7.19	102.71±7.87
Vitamin D analog at study entry	80 (68.96%)	38 (65.52%)	91 (68.94%)	28 (69.05%)
Laboratory measurements				
Hemoglobin, g/dL	80.67±19.34	84.67±16.05	81.06±19.19	84.98±15.28
hsCRP >3 mg/L	31 (27.93%)	26 (45.61%) ^a	43 (33.86%)	14 (34.15%)
Albumin, g/L	36.29±7.29	37.89±7.88	36.68±7.78	37.25±6.55
TC, mmol/L	4.13±1.07	4.46±1.26	4.19±1.12	4.44±1.47
TG, mmol/L	1.31 [0.92–1.92]	1.34 [0.91–2.20]	1.25 [0.92–1.83]	1.59 [0.98–2.38]
HDL-C, mmol/L	1.21±0.34	1.17±0.30	1.19±0.30	1.22±0.41
LDL-C, mmol/L	2.41±0.77	2.64±0.98	2.42±0.68	2.66±1.22
iPTH, pg/mL	247.6 [133.7–381.0]	256.6 [100.0–409.0]	247.6 [123.2–377.5]	252.0 [96.22–491.20]
Phosphorus, mmol/L	2.23±0.71	2.04±0.51	2.18±0.66	2.14±0.64
Corrected calcium, mmol/L	1.97±0.33	2.11±0.35 ^a	2.01±0.35	2.03±0.33
Ca × P, mg ² /dL ²	54.50±16.83	54.19±18.17	54.04±16.25	55.50±20.18
EF, %	66.01±5.17	66.12±5.97	66.13±5.50	65.78±5.29

Values are presented as mean ± standard deviation, *n* (%), or median [interquartile range]. AVC, aortic valve calcification; CVC, cardiac valve calcification; CVD, cardiovascular disease; DM, diabetes mellitus; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; MVC, mitral valve calcification; TC, total cholesterol; TG, triglyceride. ^a Intergroup differences between with or without de novo AVC or MVC at baseline in each group, *p* < 0.05.

Left ventricular ejection fraction (EF) was assessed by two-dimensional echocardiography using the modified Simpson method [11]. Echocardiography was performed every 6 months to screen for the development and extent of CVC. All images were analyzed independently by two experienced sonographers who were blinded to the clinical details.

Study Outcome

The primary outcome was composite MACE, defined as cardiovascular death, nonfatal myocardial infarction, coronary revascularization procedure, and nonfatal hemorrhagic or unspecified stroke. Only the first event during the observation period was considered.

Statistical Analysis

For statistical analysis, frequencies were reported for categorical data, mean and standard deviation for normally distributed continuous data, and median and range or interquartile range for skewed continuous data. Continuous data were compared using the Student *t* test or the Mann-Whitney test, as appropriate. Categorical data were compared using the χ^2 test.

Patients were stratified according to the presence or absence of de novo CVC: (1) those without de novo aortic valve calcification (AVC) or mitral valve calcification (MVC); (2) those with de novo AVC; and (3) those with de novo MVC. Kaplan-Meier survival curves were used to describe the cumulative incidence of MACE-free survival and the results were assessed using the log-rank test. Multivariate time-dependent Cox regression models were constructed to assess the association of de novo AVC and de novo MVC with future MACE after adjusting for (1) age and sex, (2) age, sex, BMI, smoking status, diabetes mellitus as primary cause of renal failure, and history of CVD, and (3) age, sex, BMI, smoking status, diabetes mellitus as primary cause of renal failure, history of CVD, and baseline levels of EF, LDL-C, hsCRP, albumin, and hemoglobin. Multivariate Cox regression analysis was performed to select inde-

Table 2. Baseline and TA clinical parameters of patients with and without de novo CVC

Variables	Without de novo AVC (n = 116)		De novo AVC (n = 58)		Without de novo MVC (n = 132)		De novo MVC (n = 42)	
	baseline value	TA value	baseline value	TA value	baseline value	TA value	baseline value	TA value
hsCRP >3 mg/L	31 (27.93%)	27 (23.28%)	26 (45.61%)	32 (55.17%) ^a	43 (33.86%)	38 (28.79%)	14 (34.15%)	21 (50.0%) ^a
Albumin, g/L	36.29±7.29	38.55±3.18 ^b	37.89±7.88	37.07±3.47 ^a	36.68±7.78	38.38±3.12 ^b	37.25±6.55	37.03±3.82 ^a
TC, mmol/L	4.13±1.07	4.12±0.93	4.46±1.26	4.48±1.26 ^a	4.19±1.12	4.19±0.98	4.44±1.47	4.39±1.31 ^a
TG, mmol/L	1.31 [0.92–1.92]	1.56 [0.96–1.92] ^b	1.34 [0.91–2.20]	1.59 [1.17–2.74]	1.25 [0.92–1.83]	1.63 [1.09–2.72] ^b	1.59 [0.98–2.38]	1.34 [0.82–2.08]
HDL-C, mmol/L	1.21±0.34	1.08±0.33	1.17±0.30	1.10±0.36	1.19±0.30	1.07±0.32	1.22±0.41	1.13±0.38
LDL-C, mmol/L	2.41±0.77	2.29±0.68	2.64±0.98	2.55±0.82 ^a	2.42±0.68	2.33±0.69	2.51±0.86	2.66±1.22
iPTH, pg/mL	247.6 [133.7–381.0]	300.0 [150.0–400.0]	256.6 [100.0–409.0]	239.6 [150.0–409.0]	247.6 [123.2–377.5]	291.5 [150.0–400.0]	252.0 [96.22–491.20]	300 [150.0–540.8]
Phosphorus, mmol/L	2.23±0.71	1.95±0.54 ^b	2.04±0.51	2.22±0.65 ^a	2.18±0.66	2.00±0.58 ^b	2.14±0.64	2.19±0.61
Corrected calcium, mmol/L	1.97±0.33	2.32±0.41 ^b	2.11±0.35	2.49±0.37 ^{a, b}	2.01±0.35	2.34±0.41 ^b	2.03±0.33	2.47±0.39 ^b
Ca × P, mg ² /dL ²	54.50±16.83	54.44±16.94	54.19±18.17	65.92±19.48 ^{a, b}	54.04±16.25	56.29±17.62 ^b	55.50±20.18	64.53±20.30 ^{a, b}
Kt/V	–	1.34±0.32	–	1.31±0.22	–	1.36±0.28	–	1.29±0.18
EF, %	66.01±5.17	65.12±6.39	66.12±5.97	63.97±6.43 ^b	66.13±5.50	65.80±5.05	65.78±5.29	61.41±8.76 ^{a, b}
Vitamin D analog	80 (68.96%)	82 (70.69%)	38 (65.52%)	39 (67.24%)	91 (68.94%)	93 (70.45%)	28 (69.05%)	30 (71.43%)

Values are presented as mean ± standard deviation, n (%), or median [interquartile range]. AVC, aortic valve calcification; CVC, cardiac valve calcification; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; Kt/V, marker of dialysis adequacy; LDL-C, low-density lipoprotein cholesterol; MVC, mitral valve calcification; TA, time-averaged; TC, total cholesterol; TG, triglyceride. ^a Differences of TA values between patients with or without de novo AVC or MVC, $p < 0.05$. ^b Inter-group differences between baseline and TA values in each group, $p < 0.05$.

pendent determinants of de novo AVC or de novo MVC among variables with p values < 0.1 in univariate analysis. Modeling results are reported as hazard ratio (HR) and 95% confidence interval (CI). All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set as $p < 0.05$.

Results

Patient Characteristics

A total of 174 patients (109 males and 65 females) were followed up for a median of 66 months (range, 19–141). AVC developed in 58 (33.33%) patients and MVC in 42 (24.14%) patients; overlapping (both AVC and MVC) was observed in 20 (11.49%) patients. The median time to de novo AVC was 46 months (range, 3–120; Fig. 1a) and 50 months (range, 13–127; Fig. 1c) for de novo MVC.

Patients who developed de novo AVC or de novo MVC were significantly older at baseline than those who did not (Table 1). The percentage of subjects with elevated hsCRP at baseline (> 3 mg/L) was significantly higher in patients with de novo AVC in comparison to those who did not develop AVC. Corrected calcium at baseline was also significantly higher in patients with de novo AVC.

Table 2 shows the TA values of clinical parameters in patients with versus without de novo CVC. Compared with patients without de novo AVC, there were significant differences in TA levels of albumin, TC, LDL-C, phosphorus, corrected calcium, Ca × P, and EF as well as the proportion of hsCRP > 3 mg/L in patients with de novo AVC. Compared with patients without de novo MVC, there were significant differences in TA levels of albumin, Ca × P, TC, EF as well as the proportion of hsCRP > 3 mg/L in patients with de novo MVC. Multivariate Cox regression analysis identified baseline LDL-C as an independent determinant for both de novo AVC and MVC development (Table 3).

Table 3. Multivariate Cox regression analysis for independent determinants of de novo CVC

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
<i>Determinants of de novo AVC</i>						
Baseline albumin, g/L	0.95	0.91–0.98	0.004	–	–	–
Baseline TC, mmol/L	1.29	1.01–1.66	0.01	–	–	–
TA TC, mmol/L	1.22	0.98–1.52	0.07	–	–	–
Baseline LDL-C, mmol/L	2.02	1.16–3.52	0.02	2.00	1.10–3.62	0.02
Baseline phosphorus, mmol/L	1.77	1.08–2.90	0.02	–	–	–
Baseline Ca × P, mg ² /dL ²	1.02	1.01–1.04	0.01	–	–	–
<i>Determinants of de novo MVC</i>						
Baseline albumin, g/L	0.91	0.85–0.99	0.02	–	–	–
Baseline TG, mmol/L	1.42	0.97–2.08	0.07	–	–	–
Baseline LDL-C, mmol/L	4.40	1.33–14.55	0.01	5.34	1.40–20.32	0.01
Baseline Ca × P, mg ² /dL ²	1.03	1.01–1.06	0.02	–	–	–

AVC, aortic valve calcification; CI, confidence interval; CVC, cardiac valve calcification; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MVC, mitral valve calcification; TA, time-averaged; TC, total cholesterol; TG, triglyceride.

Table 4. Subgroups of MACE occurring in patients with and without de novo CVC

Characteristic	Without de novo AVC (n = 116)	De novo AVC (n = 58)	Without de novo MVC (n = 132)	De novo MVC (n = 42)
Cardiac death	4	14	9	9
Nonfatal MI/coronary revascularization	11	8	9	10
Nonfatal hemorrhagic/unspecified stroke	8	8	10	6
Total MACE	23	30	28	25

AVC, aortic valve calcification; CVC, cardiac valve calcification; MACE, major adverse cardiovascular events; MI, myocardial infarction; MVC, mitral valve calcification.

De novo CVC and MACE

A total of 53 MACE occurred during the follow-up period. Patients who developed de novo AVC or de novo MVC had a higher MACE rate than those who did not (AVC: 30/58 [51.72%] vs. 23/116 [19.83%], $p < 0.0001$; MVC: 25/42 [59.52%] vs. 28/132 [21.21%], $p < 0.0001$). Subgroups of MACE and number of events in each group are listed in Table 4.

The median time to MACE was 73 months (range, 15–141; Fig. 1b) in patients developing AVC and 71 months (range, 15–141; Fig. 1d) in patients developing MVC. Kaplan-Meier survival analysis showed a higher risk of MACE in patients with de novo CVC versus those without ($p = 0.004$ for de novo AVC, $p = 0.003$ for de novo MVC) (Fig. 2a, b).

Multivariate time-dependent Cox regression showed an association between MACE with both de novo AVC (HR 3.20, 95% CI 1.55–6.63, $p = 0.002$) and MVC (HR 5.95, CI 2.90–12.20, $p < 0.0001$) (Fig. 2c).

Fig. 2. Kaplan-Meier survival curves and multivariable-adjusted HRs for MACE occurrence in patients with or without de novo CVC. **a** Kaplan-Meier survival curves for MACE in patients with or without de novo AVC. **b** Kaplan-Meier survival curves for MACE in patients with or without de novo MVC. **c** Multivariable-adjusted HRs for MACE associated with de novo AVC or MVC. AVC, aortic valve calcification; CVC, cardiac valve calcification; HR, hazard ratio; LCL, lower confidence limit; MACE, major adverse cardiovascular events; MVC, mitral valve calcification; UCL, upper confidence limit.

Discussion

Presence of CVC, a marker of systemic atherosclerotic vascular disease, increases the risk of cardiovascular mortality up to 5.4-fold in patients on dialysis [10]. The KDIGO clinical practice guidelines classify patients with known valvular calcification as having the highest rank of cardiovascular risk [12] and recommend checking for CVC in patients with CKD stages 3–5D using echocardiography.

In this longitudinal study with a median follow-up of >5 years, we showed that one-third of incident hemodialysis patients developed de novo AVC within a median time of 46 months, whereas the proportion of de novo development of MVC was 22.4% within a median time of

50 months. We also confirmed the association between de novo CVC and cardiovascular outcomes: (1) patients with de novo AVC and de novo MVC had a 3-fold and 6-fold higher risk, respectively, of MACE after adjustment for known cardiovascular risk factors; (2) the median time from de novo CVC to MACE was 2 years.

It is noteworthy that only patients with no detectable CVC at baseline were included in the data analysis of the current study, whereas previous studies included patient populations with varying degrees of baseline calcification and dialysis vintage [13, 14], both of which are independent predictors of mortality and calcification progression. Consistent with the reported rate of 57.8 versus 26.3% for AVC and MVC in a previous study in patients on incident peritoneal dialysis [5], we observed a higher proportion of patients who developed de novo AVC compared with de novo MVC (33.3% for AVC vs. 22.4% for MVC). Also consistent with previous studies conducted in both general and hemodialysis patients [15], we noticed an association between de novo development of AVC and MVC with baseline LDL-C in the multivariate Cox regression model. We failed to find an association between de novo CVC with indicators of alterations in calcium-phosphate homeostasis (hyperphosphatemia, high corrected calcium levels, elevated levels of iPTH, and $\text{Ca} \times \text{P}$) and inflammation (elevated levels of hsCRP and hypoalbuminemia), which have been proposed as predictors of calcification development or progression in dialysis patients [6, 7, 16]. This result might be related to the study population, study period, and modest sample size. In addition, since we did not measure the levels of CVC-associated molecular factors such as fibroblast growth factor-23, klotho, and fetuin-A [15], which is one limitation of this study, it cannot be excluded that the levels of these calcification mediators might be associated with CVC development in this study.

Another notable difference from previous studies is that we performed subgroup analyses to determine what type of de novo CVC influenced MACE risk. This is an important question, since the differences in calcification patterns of mitral and aortic valves might be associated with different cardiovascular complications. AVC is a leading driver of aortic valve stenosis, which is closely associated with left ventricular hypertrophy [17], and left ventricular hypertrophy is recognized as a strong predictor of cardiovascular mortality in hemodialysis patients [18]. AVC is also associated in hemodialysis patients with higher risk of atrial fibrillation [19] and restenosis after placement of drug-eluting stents [20]. In two previous studies conducted in maintenance hemodialysis and peritoneal dialysis patients, presence of AVC was associated with increased risk of all-cause and CVD mortality [9]. Of note, as a further complication, the risk of cardiovascular mortality was significantly higher in patients with both MAC and AVC than in those with only one valve affected [8, 16]. In contrast, the independent predictive power of AVC for all-cause and CVD mortality was absent after adjustment for confounders such as left ventricular hypertrophy, inflammatory markers, and preexisting cardiovascular complications [4]. In addition, another study found that MAC, but not AVC, predicts mortality in dialysis patients, especially those with diabetes [21]. The Framingham Heart Study [22] also identified the combination of CKD and MVC, rather than AVC or aortic stenosis, to be associated with a 3-fold increased risk for mortality. MVC has been noted to be closely related to cardiac arrhythmia, atrial fibrillation, thromboembolic events, mitral valve stenosis or regurgitation, and stroke, each one being able to influence the cardiovascular outcome. The results of our study confirmed and extended the above findings as both de novo AVC and de novo MVC were independently associated with adverse cardiovascular outcome and the risk of MACE occurrence in de novo MVC was nearly double that in de novo AVC. However, the risk of MACE in the 20 patients with both de novo AVC and MAC was not significantly increased compare with those patients with only de novo AVC or de novo MAC.

Evidence from studies both in the general population [23] and the dialysis population [9] suggest that CVC, rather than a chronic degenerative process, involves active inflammation fueled by atherosclerotic risk factors and is considered a marker of atherosclerosis. Previous studies demonstrated a significant correlation between AVC/MVC and the presence and

greater extent of coronary artery or carotid atherosclerosis or calcification, and CVC predicts coronary ischemic events [9, 24]. Coexistence of CVC and vascular calcification indicates more advanced stage of atherosclerosis and worse prognosis. Therefore, presence of CVC can alert the clinician to the possibility of severe atherosclerosis and may be useful in stratifying the severity of CVD and the prediction of future MACE.

The results of our study should be interpreted with caution given the following limitations. First, echocardiography may detect microcalcification in the cardiac valve with lower sensitivity than cardiac computed tomography, which can determine a CVC score in Agatston units. We chose echocardiography because cardiac computed tomography was not routinely used at our hospital when this study was initiated. Second, our cohort came from a single medical center with limited sample size, so the preliminary results of this study may not be representative of the general population of patients new to hemodialysis. The study results of the ongoing China Dialysis Calcification Study [25], which is a nationwide, multicenter, prospective cohort study planning to enroll 1,520 dialysis patients, will help further elucidate the correlation between CVC and adverse cardiovascular outcomes in the hemodialysis population. In addition, phosphate binders were not routinely prescribed in our cohort, and therefore the time to development or the intensity of CVC may differ in other hemodialysis populations treated with these medications, since hyperphosphatemia and elevated $\text{Ca} \times \text{P}$ have previously been implicated as a potential causal factor for CVC.

Conclusion

Despite these limitations, this study provides preliminary evidence that de novo CVC could predict long-term mortality in patients new to dialysis. This may be clinically useful in light of the fact that a substantial proportion of patients on dialysis who do not have CVC at baseline will go on to develop it, and regular CVC screening among hemodialysis patients without preexisting CVC will be helpful to identify patients at increased risk of adverse cardiovascular outcomes.

Statement of Ethics

The study protocol was approved by the Institutional Review Board of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-D-2004-006). All study-related procedures were performed in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to enrollment.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.-J. Lin, G.-R. Jiang, and W. Lu designed the study. F.-J. Lin, L.-S. Huang, G. Ji, G.-R. Jiang, and W. Lu conducted the study. X. Zhang, X. Zhou, and R. Luo analyzed the data. F.-J. Lin, G.-R. Jiang, and W. Lu wrote the paper. All authors read and approved the final manuscript.

References

- 1 Lu ML, Gupta S, Romero-Corral A, Matejková M, De Venecia T, Obasare E, et al. Cardiac calcifications on echocardiography are associated with mortality and stroke. *J Am Soc Echocardiogr*. 2016 Dec;29(12):1171–8.
- 2 Guerraty MA, Chai B, Hsu JY, Ojo AO, Gao Y, Yang W, et al.; CRIC Study Investigators. Relation of aortic valve calcium to chronic kidney disease (from the Chronic Renal Insufficiency Cohort Study). *Am J Cardiol*. 2015 May;115(9):1281–6.
- 3 Ikee R, Honda K, Ishioka K, Oka M, Maesato K, Moriya H, et al. Differences in associated factors between aortic and mitral valve calcification in hemodialysis. *Hypertens Res*. 2010 Jun;33(6):622–6.
- 4 Takahashi H, Ishii H, Aoyama T, Kamoi D, Kasuga H, Ito Y, et al. Association of cardiac valvular calcifications and C-reactive protein with cardiovascular mortality in incident hemodialysis patients: a Japanese cohort study. *Am J Kidney Dis*. 2013 Feb;61(2):254–61.
- 5 Avila-Díaz M, Mora-Villalpando C, Prado-Urbe Mdel C, Orihuela-Rodriguez O, Villegas-Antelo E, Gómez-Noriega AM, et al. De novo development of heart valve calcification in incident peritoneal dialysis patients. *Arch Med Res*. 2013 Nov;44(8):638–44.
- 6 Di Iorio B, Nargi O, Cucciniello E, Bellizzi V, Torracca S, Russo D, et al.; INDEPENDENT study investigators. Coronary artery calcification progression is associated with arterial stiffness and cardiac repolarization deterioration in hemodialysis patients. *Kidney Blood Press Res*. 2011;34(3):180–7.
- 7 Bellasi A, Kooienga L, Block GA, Veledar E, Spiegel DM, Raggi P. How long is the warranty period for nil or low coronary artery calcium in patients new to hemodialysis? *J Nephrol*. 2009 Mar–Apr;22(2):255–62.
- 8 Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989 Sep–Oct;2(5):358–67.
- 9 Wang AY, Ho SS, Wang M, Liu EK, Ho S, Li PK, et al. Cardiac valvular calcification as a marker of atherosclerosis and arterial calcification in end-stage renal disease. *Arch Intern Med*. 2005 Feb;165(3):327–32.
- 10 Wang AY, Wang M, Woo J, Lam CW, Li PK, Lui SF, et al. Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. *J Am Soc Nephrol*. 2003 Jan;14(1):159–68.
- 11 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al.; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006 Mar;7(2):79–108.
- 12 Kidney Disease: improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2009 Aug;113:S1–130.
- 13 Jung HH, Kim SW, Han H. Inflammation, mineral metabolism and progressive coronary artery calcification in patients on haemodialysis. *Nephrol Dial Transplant*. 2006 Jul;21(7):1915–20.
- 14 Noordzij M, Cranenburg EM, Engelsman LF, Hermans MM, Boeschoten EW, Brandenburg VM, et al.; NECOSAD Study Group. Progression of aortic calcification is associated with disorders of mineral metabolism and mortality in chronic dialysis patients. *Nephrol Dial Transplant*. 2011 May;26(5):1662–9.
- 15 Rattazzi M, Bertacco E, Del Vecchio A, Puato M, Faggini E, Pauletto P. Aortic valve calcification in chronic kidney disease. *Nephrol Dial Transplant*. 2013 Dec;28(12):2968–76.
- 16 Sigrist MK, Taal MW, Bungay P, McIntyre CW. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. *Clin J Am Soc Nephrol*. 2007 Nov;2(6):1241–8.
- 17 Turkmen F, Emre A, Ozdemir A, Sevinc C, Erisken E, Yesilcimen K. Relationship between aortic valve sclerosis and left ventricular hypertrophy in chronic haemodialysis patients. *Int Urol Nephrol*. 2008;40(2):497–502.
- 18 Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giaccone G, Cataliotti A, et al.; CREED Investigators. Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. *J Am Soc Nephrol*. 2001 Dec;12(12):2768–74.
- 19 Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, Stefani F, et al. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. *Am J Kidney Dis*. 2005 Nov;46(5):897–902.
- 20 Ishii H, Kumada Y, Toriyama T, Aoyama T, Takahashi H, Amano T, et al. Aortic valvular calcification predicts restenosis after implantation of drug-eluting stents in patients on chronic haemodialysis. *Nephrol Dial Transplant*. 2009 May;24(5):1562–7.
- 21 Raggi P, Bellasi A, Gamboa C, Ferramosca E, Ratti C, Block GA, et al. All-cause mortality in hemodialysis patients with heart valve calcification. *Clin J Am Soc Nephrol*. 2011 Aug;6(8):1990–5.
- 22 Fox CS, Larson MG, Vasan RS, Guo CY, Parise H, Levy D, et al. Cross-sectional association of kidney function with valvular and annular calcification: the Framingham heart study. *J Am Soc Nephrol*. 2006 Feb;17(2):521–7.

- 23 Mohler ER 3rd. Are atherosclerotic processes involved in aortic-valve calcification? [Lancet](#). 2000 Aug; 356(9229):524–5.
- 24 Ho J, FitzGerald S, Cannaday J, Stolfus L, Weilbacher D, Henderson Y, et al. Relation of aortic valve calcium to myocardial ischemic perfusion in individuals with a low coronary artery calcium score. [Am J Cardiol](#). 2007 Jun;99(11):1535–7.
- 25 Liu ZH; China Dialysis Calcification Study (CDCS) Group. Vascular calcification burden of Chinese patients with chronic kidney disease: methodology of a cohort study. [BMC Nephrol](#). 2015 Aug;16(1):129.