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Risk factors for heart valve calcification in chronic kidney disease

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Abstract

Cardiovascular disease (CVD) is a common cause of death in patients with chronic kidney disease (CKD). Aortic and mitral valve calcification (AVC and MVC, respectively) are critical indicators of CVD and all-cause mortality in CKD patients.

We conducted a single center retrospective study of Chinese inpatients with CKD to identify risk factors associated with valve calcification (VC).

Of 288 enrolled CKD patients, 22.9% had VC, all of which exhibited AVC, while 21.2% exhibited MVC. The VC group were significantly older than the non-VC group (70.42 ± 11.83 vs 56.47 ± 15.00, $P < .001$), and contained more patients with history of coronary artery disease (12.1% vs 4.5%, $P = .025$) or stroke (18.2% vs 5.4%, $P < .001$). Subjective global assessment scoring indicated that more VC patients were mid/severely malnourished. Levels of prealbumin, cholesterol (Ch), triglycerides, low-density lipoprotein (LDL), apolipoprotein E, ejection fraction, and fraction shortening were significantly lower, and blood C reactive protein, IL-6, left ventricular internal end diastole diameter measured in end diastole, and interventricular septum thickness (IVST) levels were significantly higher in the VC group. Bone metabolism did not differ significantly between the 2 groups. Multivariable logistic regression analysis indicated that age, blood Ch, and LDL levels were significantly associated with VC.

Advanced age, increased IVST, hypocholesterolemia, and hyper-LDL cholesterolemia were key risk factors for VC in Han patients with CKD.

Abbreviations: Alb = albumin, APO = apolipoprotein, Ca = calcium, Ch = cholesterol, CKD = chronic kidney disease, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, IVST = interventricular septum thickness, KDIGO = Kidney Disease: Improving Global Outcomes, LDL = low-density lipoprotein, LVDd = left ventricular internal end diastole diameter, LVH = left ventricular hypertrophy, LVPWTd = left ventricular internal posterior wall thickness measured in end diastole, MBD = mineral and bone disorder, pAlb = pre-Alb, PEW = protein-energy wasting, TG = triglyceride, VC = valve calcification.

Keywords: cholesterol, chronic kidney disease, heart valve calcification, inflammation, malnutrition

1. Introduction

Cardiovascular disease (CVD) is the most common cause of death in patients with chronic kidney disease (CKD). In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) CKD–Mineral and Bone Disorder (MBD) Work Group suggested that patients with CKD and heart valve calcification (VC) should be considered at the highest risk of CVD.[1] Approximately 120 million patients have CKD in China, representing a prevalence of 10.8%,[2] which does not differ significantly from the rate of CKD reported in the United States of America (13.1%) or Norway (10.2%).[3,4] Nevertheless, a national survey conducted in 2013 found that awareness of CKD (10.04%) remains low in China.[3–5]

VC is a common complication of CKD and is a critical indicator of CVD and all-cause mortality in patients with CKD[6–8] and in patients with end-stage renal disease (ESRD).[9] The incidence of VC increases with CKD progression, from around 40% in stage 3 CKD to 80% to 99% in stage 5 CKD.[10–14] Typical manifestations include calcification of the vessel wall, myocardium, and heart valves, which cannot only impair cardiac conduction and cause arrhythmia, but also serve as an indicator of coronary artery disease progression.

Many risk factors have been associated with VC in patients with CKD, including canonical factors such as age, hypertension, diabetes, and dyslipidemia as well as noncanonical factors such as MBDs, inflammation, and malnutrition. Nevertheless, the exact contributions of these factors have not been well characterized in

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Asian populations. The incidence and severity of heart VC have been observed to increase with age,[15] and the onset of VC has been reported to occur several decades earlier in patients with CKD than in other populations.[16] A Chinese study indicated that the relative risk of heart VC increased by 2.22 to 2.66-fold with each decade of life, while the rate of VC remains higher in patients with CKD.[17] Vascular calcification is reported to increase left ventricular after load and is the most important contributor to the development of left ventricular hypertrophy (LVH) in ESRD patients.[18] Atherosclerosis and vascular calcification were previously reported to be independent predictors of LVH in hemodialysis patients.[19] Serum phosphorus can be cardiotoxic, leading to LVH, but this effect can be successfully reversed with adequate control of serum phosphorus.[20] Furthermore, the level of fibroblast growth factor-23, a hormone associated with vascular calcification, increases very early in CKD and is strongly associated with CVD, including LVH, and mortality.[21] Therefore, strategies to address cardiovascular risk in early CKD are imperative and vascular calcification is a potential therapeutic target.

Here, we describe a single center retrospective study of Han Chinese inpatients with CKD designed to examine the risk factors associated with VC.

2. Methods

2.1. Subjects

The study consecutively enrolled and retrospectively analyzed 288 Han Chinese inpatients with CKD admitted to the Department of Nephrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine for the first time between January 1 and June 1, 2015. CKD was staged according to the estimated glomerular filtration rate (eGFR), as reported by the Kidney Disease Outcomes Quality Initiative.[22] The eGFR was calculated using the CKD-Epidemiology Collaboration Equation (CKD-EPI).[23]

The inclusion criteria were as follows: patients ≥18 years of age diagnosed with CKD according to the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD (defined as abnormalities of kidney structure or function present for >3 months impacting the health).[24,25] CKD was staged according to eGFR (mL/min/1.73 m^2) as follows, GFR ≥ 90, G1; GFR = 60–89, G2; GFR = 45–59, G3a; GFR = 30–44, G3b; GFR = 15–29, G4; and GFR ≤ 15, G5. Patients with acute kidney injury, active inflammatory diseases, parathyroidectomy, or evident malignancies; concomitant diseases that affect calcium (Ca) status and soft tissue calcifications such as sarcoidosis, multiple myeloma, HIV, and amyloidosis; conditions prohibiting arterial calcification measurements; or pregnancy or lactation were excluded. Written informed consent was obtained from all patients included in the study and the ethics committee of Shanghai General Hospital approved the study.

2.2. Echocardiography

Color ultrasound (Philips-ie33, Philips North America Corporation, Andover, MA) was used to examine VC in patients with CKD. If bright, dense echoes exceeding 1 mm were observed on one or more leaflets of the mitral and/or aortic valves, the patient was diagnosed with VC.[26] Ultrasound images were evaluated by an experienced ultrasound physician. Based on echocardiography, the patients were divided into 2 groups: VC and non-VC. All echocardiography examinations were performed according to the recommendations of the American Society of Echocardiography (ASE).[27,28] Left ventricular mass was calculated according to the Devereux formula 26: LVM (g) = $0.8 \times 1.04([LVDd + IVST + LVPWTd]^3 - LVDd^3) + 0.6$ (left ventricular internal end diastole diameter [LVDd], interventricular septum thickness [IVST], left ventricular internal posterior wall thickness measured in end diastole [LVPWTd]). Left ventricular mass index was calculated by dividing LVM by the body surface area.[29] LVH was diagnosed when LVMI was ≥125 g/m^2 in males or ≥110 g/m^2 in females, according to the recommendations of the ASE.3 clinical indices.

2.3. Data collection

History of primary disease, hypertension, diabetes, coronary artery disease, and stroke was scored using the subjective global assessment by 2 experienced physicians.[30] Subjective evaluations were validated by consistency analysis. Blood pressure and body mass index (kg/m^2) were recorded at admission. Hemoglobin, albumin (Alb), pre-Alb (pAlb), blood urea, serum creatinine, uric acid, Ca, phosphorus (P), intact parathyroid hormone, 25-hydroxy vitamin D, N-terminal/mid-region osteocalcin, β carboxy-terminal cross-linking telopeptide of type I collagen (measured at 6 and 24 hours), total cholesterol (Ch), triglycerides (TGs), high-density lipoprotein, low-density lipoprotein (LDL), lipoprotein a, apolipoprotein (APO)-AI, APO-B, APO-E, and urine protein and Alb levels were measured routinely.

2.4. Treatments

Blood pressure, anemia, dyslipidemia, and renal osteopathy were treated by the nephrologists according to the KDIGO guidelines (http://kdigo.org/home/). Use of antihypertensive drugs including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, Ca antagonists and β receptor blockers, statin, erythropoietin, active vitamin D3, and Ca carbonate was recorded.

2.5. Statistical analysis

All continuous data were evaluated for normality using the Kolmogorov–Smirnov test. Normally distributed continuous variables were presented as mean ± standard deviation and analyzed using the Student *t* test. Nonnormally distributed variables were presented as median (interquartile range) and analyzed using the Mann–Whitney *U* test. Categorical variables were presented as number and frequencies, and analyzed using the chi-square test or Fisher exact test. Multivariable logistic regression analysis was used to identify factors associated with heart VC. Candidate variables were included in multivariable logistic regression analysis if $P < .4$ in univariable analyses. Odds ratios and 95% confidence intervals were calculated. Forward conditioning was used for variable selection. Hence, 0.05 was set for variable inclusion and 0.10 was set for variable exclusion. SPSS 16.0 (IBM, NY) was used for statistical analysis. $P < .05$ was considered to indicate significant differences.

3. Results

3.1. Participant characteristics

Of the 288 Han inpatients with CKD (190 male and 98 female) admitted to our department, 66 (22.9%) had VC, of which all exhibited aortic valve calcification and 14 (21.2%) exhibited mitral valve calcification. The gender distribution did not differ

Table 1

Demographic and clinical characteristics of participants.

Patient information	VC group (n = 66)	Non-VC group (n = 222)	P
Gender (male/female)	48/18	142/80	.187
Age, y	70.42 ± 11.83	56.47 ± 15.00	<.001
Course of disease, mo	12 (6,48)	18 (8,72)	.351
Diabetes, %	18 (27.3)	62 (27.9)	.917
Hypertension, %	50 (75.8)	160 (72.1)	.554
Coronary disease, %	8 (12.1)	10 (4.5)	.025
Stroke, %	12 (18.2)	12 (5.4)	<.001
CKD 1 stage, %	0	19 (8.6)	.014
CKD 2 stage, %	8 (12.1)	55 (24.8)	.029
CKD 3 stage, %	26 (39.4)	70 (31.5)	.234
CKD 4 stage, %	10 (15.2)	20 (9.0)	.152
CKD 5 stage, %	2 (3.0)	16 (7.2)	.218
CKD 5D stage, %	20 (30.3)	42 (18.9)	.048
Hemodialysis, %	8 (12.1)	20 (9.0)	.453
Peritoneal dialysis, %	12 (18.2)	22 (18.9)	.067
Systolic blood pressure, mm Hg	141.88 ± 22.15	139.00 ± 21.02	.496
Diastolic blood pressure, mm Hg	81.30 ± 13.32	84.11 ± 12.27	.260
BMI	21.5 ± 6.8	22.7 ± 7.3	.350
ACEI/ARB	30 (45.5)	121 (54.5)	.19
CCB	45 (68.2)	153 (68.9)	.91
β-Blocker	18 (27.3)	72 (32.4)	.42
Statin	31 (47.0)	95 (42.8)	.55
Erythropoietin	42 (63.6)	118 (53.2)	.13
Active vitamin D3	22 (33.3)	62 (27.9)	.39
Calcium carbonate	28 (42.4)	70 (31.5)	.10

ACEI = antihypertensive drugs including angiotensin converting enzyme inhibitors, ARB = angiotensin II receptor blockers, β-blocker = β receptor blockers, BMI = body mass index, CCB = calcium antagonists, CKD = chronic kidney disease, CKD 5D stage = CKD 5 stage dialysis, VC = valve calcification.

significantly between the VC and non-VC groups, but patients in the VC group were significantly older than in the non-VC group (70.42 ± 11.83 vs 56.47 ± 15.00, $P < .001$; Table 1). The types of drugs used in the VC and non-VC group did not differ significantly (Table 1).

Chronic glomerulonephritis, diabetes, and hypertension were the most frequently reported primary diseases. The types and frequency of primary diseases, hypertension, diabetes, and blood pressure did not differ significantly between the VC and non-VC groups, but the rates of coronary artery disease and stroke were higher in the VC group than in the non-VC group (12.1% vs 4.5%, $P = .025$, and 18.2% vs 5.4%, $P < .001$, respectively). The percentage of patients with stage 1 and 2 CKD in the VC group was significantly lower than in the non-VC group, and the percentage of patients in stage 5 CKD was significantly higher in the VC group that in the non-VC group. The rate of hemo- and peritoneal dialysis was also higher in the VC group than in the non-VC group, but not statistically significantly higher.

Thirty patients in the VC group had chronic glomerulonephritis, 12 had diabetes, 10 had hypertension, 4 had obstructive nephropathy, 3 had systemic vasculitis, 2 had focal segmental glomerulosclerosis, 2 had gout, 2 had tumor-associated nephropathy, and 1 had renal artery stenosis. In the non-VC group, 114 patients had chronic glomerulonephritis, 32 had diabetes, 18 had hypertension, 14 had polycystic kidney disease, 12 had IgA nephropathy, 10 had systemic vasculitis, 6 had membranous nephropathy, 4 had obstructive nephropathy, 2 had focal segmental glomerulosclerosis, 2 had gout, 2 had hepatitis B virus-associated nephritis, 2 had systemic lupus erythematosus, 2 had purpura nephritis, 1 had multiple myeloma, and renal artery stenosis.

Table 2

Participant biochemical parameters.

	VC group (n = 66)	Non-VC group (n = 222)	P
Hb, g/L	106.72 ± 23.41	113.08 ± 23.52	.174
Alb, g/L	37.30 ± 8.20	38.18 ± 6.65	.436
pAlb, g/L	238.44 ± 91.48	281.09 ± 67.81	.005
SGA scoring mid/severe, %	9 (13.64)	13 (5.86)	.037
Bun, mmol/L	12.85 ± 6.66	13.77 ± 9.45	.599
Scr, μmol/L	181 (125.5, 535)	158 (112, 558)	.523
Ua, μmol/L	412.88 ± 101.23	422.70 ± 114.80	.659
GFR, mL/min	28.53 (7.90, 49.71)	35.37 (9.35, 57.56)	.217
Ch, mmol/L	4.00 ± 1.10	4.65 ± 1.31	.012
TG, mmol/L	1.40 ± 0.65	1.76 ± 0.90	.037
HDL, mmol/L	1.08 ± 0.34	1.15 ± 0.37	.349
LDL, mmol/L	2.58 ± 0.95	3.07 ± 1.20	.037
Lp (α), mg/L	352 (179, 622)	214 (108, 459)	.083
APO-A, g/L	1.13 (0.98, 1.41)	1.25 (1.09, 1.50)	.133
APO-B, g/L	0.86 (0.65, 1.12)	0.96 (0.77, 1.18)	.123
APO-E, mg/L	37.3 (30.2, 45.6)	44.3 (33.9, 56)	.009
Ca, mmol/L	2.23 ± 0.19	2.19 ± 0.21	.309
P, mmol/L	1.34 ± 0.24	1.37 ± 0.45	.660
PTH, pg/mL	59.12 (38.11, 82.70)	50.37 (31.68, 144.35)	.897
25 (OH)D, nmol/L	39.50 (26.21, 51.93)	40.59 (31.58, 57.54)	.519
N-MID, ng/mL	27.96 (15.70, 71.82)	24.30 (15.96, 59.23)	.833
β-CTX, pg/mL	733.00 (517.65, 1472.00)	780.45 (480.13, 1406.75)	.815
CT, pg/mL	3.55 (2.00, 10.36)	2.00 (2.00, 4.31)	.076
CRP, mg/L	5.5 (0.5, 16.35)	0.5 (0.5, 3.5)	.004
IL-6, pg/mL	18.76 (5.95, 46.9)	10.32 (2.5, 14.59)	.005
24 h urine protein, g	0.83 (0.27, 2.86)	0.81 (0.25, 2.00)	.913
24 h urine albumin, g	617.85 (104.33, 2319.13)	434.95 (85.92, 1455.34)	.761
Left ventricular internal end diastole diameter measured in end diastole (LVDd), mm	48.12 ± 10.10	42.19 ± 18.04	.018
Interventricular septum thickness (IVST), mm	9.88 ± 2.61	8.44 ± 3.83	.015
Left ventricular posterior wall thickness measured in end diastole (LVPWTd), mm	9.58 ± 2.46	8.25 ± 3.74	.057
Ejection fraction, %	58.3 ± 19.2	62.4 ± 4.8	.037
Fraction shortening, %	30.9 ± 12.4	33.8 ± 3.3	.044
Left ventricular hypertrophy, %	12 (18.2)	42 (18.9)	.924
Left ventricular mass index (LVMI)	99.80 ± 27.94	96.96 ± 32.41	.659
Aortic valve calcification	66 (100%)		
Mitral valve calcification	14 (21.2%)		

Alb = albumin, APO-A = apolipoprotein A, APO-B = apolipoprotein B, APO-E = apolipoprotein E, Bu = blood urea, Ca = calcium, Ch = cholesterol, CRP = C reactive protein, CT = calcitonin, β-CTX = β-carboxy-terminal cross-linking telopeptide of type I collagen, GFR = glomerular filtration rate, Hb = hemoglobin, HDL = high-density lipoprotein, IL-6 = interleukin-6, LDL = low-density lipoprotein, Lp (α) = lipoprotein (α), N-MID = N-terminal/mid-region osteocalcin, 25 (OH)D = 25-hydroxy vitamin D, P = phosphorus, pAlb = pre-Alb, PTH = intact parathyroid hormone, Scr = serum creatinine, SGA = subjective global assessment, TG = triglyceride, Ua = uric acid, VC = valve calcification.

3.2. Biochemical parameters

Patients in the VC group had significantly lower pAlb levels than those of the non-VC group, and levels of Ch, TG, LDL, and APOE were significantly lower in the VC group than in the non-VC group. According to subjective global assessment scoring, the percentage of patients with mid/severe malnutrition in the VC group was significantly higher than in the non-VC group. Serum levels of inflammatory markers serum CRP and IL-6 were significantly higher in the VC group than in the non-VC group. Moreover, hemoglobin levels were lower in the VC group but not statistically significantly lower, and bone metabolism did not differ significantly between the 2 groups (Table 2).

LVDd, LVPWTd, and IVST were significantly greater in the VC group than in the non-VC group ($P < .05$). Ejection fraction was significantly lower in the VC group ($P < .05$), but the rates of LVH and left ventricular mass index did not differ significantly between these groups (Table 2).

Table 3

Risk factors significantly correlated with VC.

Variable	*P*	OR (95%CI)
Age	<.001	1.091 (1.048, 1.136)
Ch	.003	0.488 (0.306, 0.780)
LDL	.008	163.028 (3.796, 7002.467)
IVST	.067	1.550 (0.970, 2.476)

Ch = cholesterol, CI = confidence interval, IVST = interventricular septum thickness, LDL = low-density lipoprotein, OR = odds ratio, VC = valve calcification.

3.3. Multivariable logistic regression analysis

Factors which univariable analysis indicated to be significantly associated with VC were assessed via multivariable logistic regression analysis. As indicated in Table 3, higher age (OR 1.091, 95%CI 1.048, 1.136), higher LDL levels (OR 163.028, 95%CI 3.796, 7002.467), thicker IVST (OR 1.550, 95%CI 0.970, 2.476), and lower total Ch levels (OR 0.488, 95% CI 0.306, 0.780) were associated with vascular calcification ($P < .05$).

4. Discussion

To analyze risk factors for VC in patients with CKD, we retrospectively analyzed 288 CKD patients. Over one-fifth of patients had VC, of which all exhibited aortic valve calcification and roughly one-fifth of which exhibited mitral valve calcification. The patients in the VC group were significantly older than those in the non-VC group and had higher rates of coronary artery disease and stroke. Significantly more VC patients were malnourished, and levels of pAlb, Ch, TGs, LDL, and APO E were significantly lower in VC patients than in non-VC patients. EF and fraction shortening were also lower in VC patients. Markers of inflammation, CRP, and IL-6 levels were elevated in VC patients, and left ventricular internal end diastole diameter measured in end diastole and IVST were significantly higher in the VC group.

The risk of death from CVD and non-CVD is reported to be higher in patients with ESRD.[31] Oxidative stress, anemia, inflammation, protein-energy wasting (PEW), Ca, P, and lipoprotein disorders may also contribute to this increased risk.[31] Nevertheless, some risk factors for CVD defined in the general population appear to have the opposite effect in this patient population.[32–35] For example low Ch levels have been reported to be associated with poor prognosis of patients with ESRD; and Ch levels appear protective.[32–35] This "reverse epidemiology" phenomenon could be explained by the fact that inflammation, PEW, and other complications associated with severe ESRD can reduce Ch levels.[36] Both short- and long-term[37] factors can influence mortality. In the general population, hypercholesterolemia is a long-term risk factor for progression of atherosclerosis and death, acting over several decades whereas inflammation and PEW are associated with mortality within several months to years. As the mortality of patients with ESRD was far higher than that of the general population, most patients do not live long enough to reveal the impact of long-term risk factors such as high Ch level.[38] In addition, some studies have suggested that higher lipid concentrations directly improve survival of patients with chronic diseases including ESRD.[39] Thorough investigation of APOE polymorphisms may reveal the mechanisms responsible for poor prognosis in ESRD patients with low Ch levels.[40]

The reverse epidemiology phenomenon has been reported not only in patients with CKD,[41] but also in chronic heart[42] and respiratory[43] failure, and rheumatoid arthritis.[44] Chronic microinflammation was also commonly seen in these patients, which typically have a long disease course. Although some studies have only observed the Ch reverse epidemiology phenomenon in inflammatory disorders complicated with malnutrition,[34] other studies did not show the same results.[35,45]

Serum CRP and IL-6 levels reflect chronic systemic microinflammation and have been associated with the risk of VC in CKD. This pathway may be affected by multiple factors including oxidative stress, hyperglycemia, and hyperlipidemia.[46] Inflammation may accelerate VC in patients with ESRD by interfering with LDL receptor-mediated signaling pathways, as observed in atherosclerosis.[47] Krasniak et al[48] examined the average carotid intima-media thickness, coronary artery calcification score, and VC associated factors in 73 patients under maintenance HD and found that both CRP and IL-6 were positively correlated, indicating that inflammation may contribute to VC. Nuclear factor-κB is a key factor in many inflammatory responses,[49] and nuclear factor-κB activation promotes secretion of many cytokines (including tumor necrosis factor-α, IL-6, and CRP) that are positive regulators of VC that may promote calcification of vascular membranes and soft tissues.

Low or normal serum Ch level and inflammation are associated with CVD and all-cause mortality in HD patients. Not only are levels of the acute inflammatory factor CRP increased, but also levels of the antiinflammatory cytokine IL-10 are decreased. Moreover, the increased incidence of hospitalization seemed to more strongly indicate upregulation of inflammatory markers.[50] The release of IL-6 and its soluble receptors by peripheral blood mononuclear cells was elevated in HD patients with low Ch levels.[51] Increased serum IL-6 and depressed sgp130 (inhibitor of IL-6 soluble receptor) are independent indicators of CVD and all-cause hospitalization. In addition, mortality was strongly influenced by malnutrition (cachexia) and Ch levels, which are good indicators of nutrition status.[52]

Furthermore, MBDs were specific risk factors for VC in patients with CKD. VC in patients with CKD is reported to be similar to osteogenesis, but it has also been reported that VC was not correlated with Ca, P, or PTH levels.[53] We observed no correlation between VC and blood Ca, P, and intact parathyroid hormone, or with indicators of bone metabolism including 25-hydroxy vitamin D, N-terminal/mid-region osteocalcin, β-CTX, and CT. Whether these factors are associated with advanced age, malnutrition, and drug intervention in the VC group requires further investigation.

This research is limited by the scope of this single center study of inpatients. A study with a larger sample size and a wider range of patients (including outpatients with less severe disease) may allow stratified multivariable logistic regression analysis of factors including age, and whether or not patients achieved ESRD or dialysis. Crucially, although we observed higher rates of coronary artery disease, hypertension, stroke, and late stage CKD in the VC group, whether VC increased IVST, hypocholesterolemia, and hyper-LDL cholesterolemia, or vice versa cannot be determined by this retrospective study. A longitudinal study may be able to further probe the causative relationship between these factors.

5. Conclusion

Taken together, our results suggest that advanced age, increased IVST, hypocholesterolemia, and hyper-LDL cholesterolemia

were key risk factors for VC in patients with CKD, and were closely associated with inflammation and malnutrition. Heart VC screening should be regularly performed in elderly patients with CKD, especially those aged over 60.

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