Original Paper

Analysis of Factors Influencing Vascular Calcification in Chronic Kidney Disease Patients Based on Oxidative Stress Response and Establishment of a Predictive Model

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Keywords. Chronic kidney disease; Vascular calcification; Oxidative stress; Risk model

Introduction. In this study, we compared the oxidative stress responses of patients with chronic kidney disease (CKD) and those with CKD-associated vascular calcification (CKD-VC), and established a risk predictive model for CKD-VC based on this comparison, providing a new approach for the clinical prevention and treatment of CKD-VC.

Methods. We conducted several cross-sectional surveys involving 173 patients with chronic kidney disease (CKD) who were admitted between September 2023 and October 2024 admitted to Affiliated Hospital of Hebei University. Sixty-two patients had VC (CKD-VC group), while the 111 patients did not have VC (CKD group). The levels of superoxide dismutase (SOD), malondialdehyde (MDA), glutathione peroxidase (GSH-Px), and catalase (CAT) of the two groups were measured. Additionally, factors influencing CKD-VC were analyzed using Logistic regression, and a risk predictive model was established accordingly.

Results. The levels of SOD and GSH-Px were lower in the CKD-VC group than the CKD group, whereas the CAT and MDA level was higher ($P < .05$). Logistic regression analysis indicated that SOD, GSH-Px, CAT, MDA, serum calcium, serum phosphorus, age, hypersensitive C-reactive protein (hs-CRP), albumin (ALB), and urine acid (UA) were all independent factors affecting CKD-VC ($P < .05$). The risk predictive model established based on these factors had high diagnostic sensitivity and specificity for CKD-VC, reaching 100.00% and 87.39%, respectively, with an area under the curve (AUC) of 0.980.

Conclusion. This study established a risk predictive model for CKD-VC based on oxidative stress response, which has high diagnostic efficacy. This model provides a new approach for the clinical prevention and treatment of CKD-VC in the future, helping to more accurately identify high-risk patients and take corresponding intervention measures to effectively ensure patient safety.

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INTRODUCTION

Chronic kidney disease (CKD) is a global public health concern, affecting approximately 10–13% of the general population,[1] with cardiovascular disease (CVD) as its most common and fatal complication.[2] Vascular calcification (VC)—the ectopic deposition of calcium-phosphate crystals in the vascular wall, particularly in the coronary

arteries—is the primary pathological mechanism linking CKD to CVD, even in early CKD stages with no overt calcium-phosphorus metabolism disorder.[3] Statistically, 30–50% of CKD patients develop varying degrees of VC, and no effective clinical treatment regimen for CKD-associated VC (CKD-VC) currently exists.[4] Thus, identifying reliable predictors and establishing a risk model for CKD-VC is critical to improving patient prognosis.

Recently, emerging evidence highlights the critical role of oxidative stress in CKD-VC pathogenesis. For the purpose of this study, oxidative stress response is defined as the imbalance between the production of reactive oxygen species (ROS) and the capacity of the antioxidant defense system to neutralize ROS, leading to oxidative damage of cellular components.[5] Key antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) play pivotal roles in neutralizing reactive oxygen species (ROS); second, they represent both the primary enzymatic antioxidant defense (SOD, GSH-Px, CAT) and a key lipid peroxidation product (MDA) that directly reflects ROS-induced cellular damage, providing a comprehensive assessment of antioxidant capacity and oxidative injury;[6] third, these markers are cost-effective and readily translatable to routine clinical practice, in contrast to more specialized biomarkers (e.g., advanced oxidation protein products [AOPP], advanced glycation end products [AGE], total antioxidant status [TAS]) that require specialized detection equipment and are not widely available in clinical settings. Mechanistically, SOD catalyzes the dismutation of superoxide anions to hydrogen peroxide and oxygen, GSH-Px and CAT further scavenge hydrogen peroxide to prevent the formation of highly toxic hydroxyl radicals, and the depletion of these antioxidant enzymes impairs ROS clearance.[7] Elevated MDA levels, as a byproduct of lipid peroxidation, indicate excessive ROS-induced damage to vascular smooth muscle cell (VSMC) membranes, which directly promotes VSMC osteogenic differentiation—the key cellular process underlying VC. Recent studies, including Wu S. *et al.*'s work, have demonstrated that this imbalance (reduced SOD/GSH-Px activity and elevated MDA levels) directly accelerates ectopic calcification in CKD.[8] We speculate that analyzing the relevant factors influencing the occurrence of VC in CKD patients based on this well-characterized oxidative stress response and establishing a risk predictive model accordingly may represent a novel and clinically applicable approach for assessing the CKD-VC risk.

Given the critical role of oxidative stress in CKD-VC and the clinical applicability of SOD, GSH-Px, CAT and MDA, we conducted a cross-sectional survey to: (1) compare the oxidative stress responses between CKD patients with and without VC; (2) identify independent factors (including oxidative stress markers) associated with CKD-VC; and (3) establish a clinically applicable risk predictive model for CKD-VC based on these factors. This study aims to provide a novel, practical approach for the early identification and prevention of CKD-VC in clinical practice.

MATERIALS AND METHODS

Research design and research subjects

We conducted a cross-sectional survey of patients with chronic kidney disease (CKD) admitted to Affiliated Hospital of Hebei University from September 2023 to October 2024. First, the required sample size for this study was computed using G-Power software. After being screened through the inclusion and exclusion criteria, 173 subjects were included in the study. Among them, 62 patients were found to have VC and designated as the CKD-VC group, while the remaining 111 patients did not have VC and were designated as the CKD group. Rationale for inclusion and exclusion criteria: (1) CKD patients with complete medical records and G1–G4 stage were included to ensure homogeneity of the study population and exclude end-stage kidney disease (ESRD, G5) patients, as ESKD is associated with extreme oxidative stress and severe VC that would confound the analysis of early-to-moderate CKD-VC (defined as eGFR < 60 mL/min/1.73m^2 for ≥3 months or persistent kidney damage with normal or reduced eGFR for ≥3 months), with complete medical records and classified into CKD stages G1–G4 (G1: eGFR ≥90; G2: 60≤eGFR < 90; G3: 30≤eGFR < 60; G4: 15≤eGFR < 30 mL/min/1.73m^2); (2) Patients with malignant tumors, infectious diseases, or immunodeficiency disorders were excluded because these conditions independently induce systemic oxidative stress and inflammation, which would mask the oxidative stress response specific to CKD and VC; (3) Patients with liver dysfunction were

excluded because the liver is the primary organ for synthesizing antioxidant enzymes (SOD, GSH-Px, CAT) and albumin, and liver dysfunction would alter oxidative stress and nutritional markers independent of CKD; (4) Patients with heart failure or coronary heart disease (CHD) were excluded because CHD is both a cause and consequence of VC, and heart dysfunction is associated with increased ROS production, which would introduce bidirectional confounding between cardiac disease and CKD-VC; (5) Patients receiving dialysis, renal transplantation, or drugs affecting oxidation reactions (statins, phosphate binders) in the past three months were excluded to eliminate the direct impact of these interventions on oxidative stress, calcium-phosphorus metabolism, and VC. Figure 1 illustrates the complete case selection and research design. This study has been approved by the ethics committee of Affiliated Hospital of Hebei University (NO. 20210424). and will be carried out strictly in strict adherence to the Declaration of Helsinki.

This is a retrospective cross-sectional study. All oxidative stress biomarkers (SOD, MDA, GSH-Px, CAT) were assayed retrospectively from stored fasting venous blood samples (collected at admission and stored at -80°C in the hospital's biobank for routine clinical research) using standardized ELISA kits. The blood samples were collected for fasting blood sugar, serum calcium, serum phosphorus, hypersensitive C-reactive protein (hs-CRP), albumin (ALB), and urine acid (UA) levels from the study subjects on admission. After standing at room temperature for 30 minutes, the serum was separated by centrifugation and detected according to the instructions of the kit. Coronary vascular calcification was assessed using dedicated unenhanced spiral chest computed tomography (CT) imaging protocols performed for the specific purpose of CKD-VC evaluation (not for other clinical indications), and all included patients underwent this identical imaging modality. Biomarker measurement was completed within 72 hours of the CT imaging for all patients, ensuring temporal alignment between exposure (oxidative stress) and outcome (VC) assessment.

VC determination

All patients underwent standardized dedicated unenhanced spiral computed tomography (CT) scanning of the chest using a 64-slice CT scanner (Siemens Somatom Definition AS, Germany) with the following protocol: 120 kV, 200 mAs, slice thickness 1 mm, reconstruction interval 0.5 mm. Coronary vascular calcification was quantified using the Agatston scoring system via dedicated calcification scoring software (Syngo.via, Siemens), with a trained and board-certified radiologist (blinded to the patients' clinical and oxidative stress biomarker data) performing all image interpretations and score calculations. A single Agatston score > 0 was defined as the presence of coronary VC, and a score = 0 as the absence of VC.[9] All scoring procedures were conducted in accordance with the standard operating procedures for coronary calcification assessment recommended by the American Heart Association (AHA).

Oxidative stress measurement

Three milliliters of fasting venous blood was collected from patients upon admission into a coagulation-promoting tube. After standing at room temperature for 30 minutes, the serum was separated by centrifugation to quantify SOD, MDA, GSH-Px, and CAT levels using enzyme-linked immunosorbent assay (ELISA) kits.

Data collection

Age, sex, Body mass index (BMI), duration, type and stage of CKD, blood pressure [systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)], lipids [triglyceride (TG), total cholesterol (TC), low/high-density lipoprotein cholesterol (LDL-C/HDL-C)], renal function [glomerular filtration rate (GFR), serum creatinine (Scr), uric acid (UA), blood urea nitrogen (BUN), serum calcium, serum phosphorus], nutrient proteins [albumin (ALB), hemoglobin (GBH), total protein (TP)] and (hs-CRP).

Statistical analysis

Statistical analyses were performed using SPSS 25.0 software. Categorical data (normal distribution was confirmed by Shapiro-Wilk test) were recorded as [n (%)] and compared using the chi-square test. Continuous data was recorded as (c ± s), and the independent samples t-test was used for comparison. Multivariate logistic regression analysis was performed to identify independent predictors of CKD-VC, with variables selected via a two-step approach: first, variables with $P < .10$

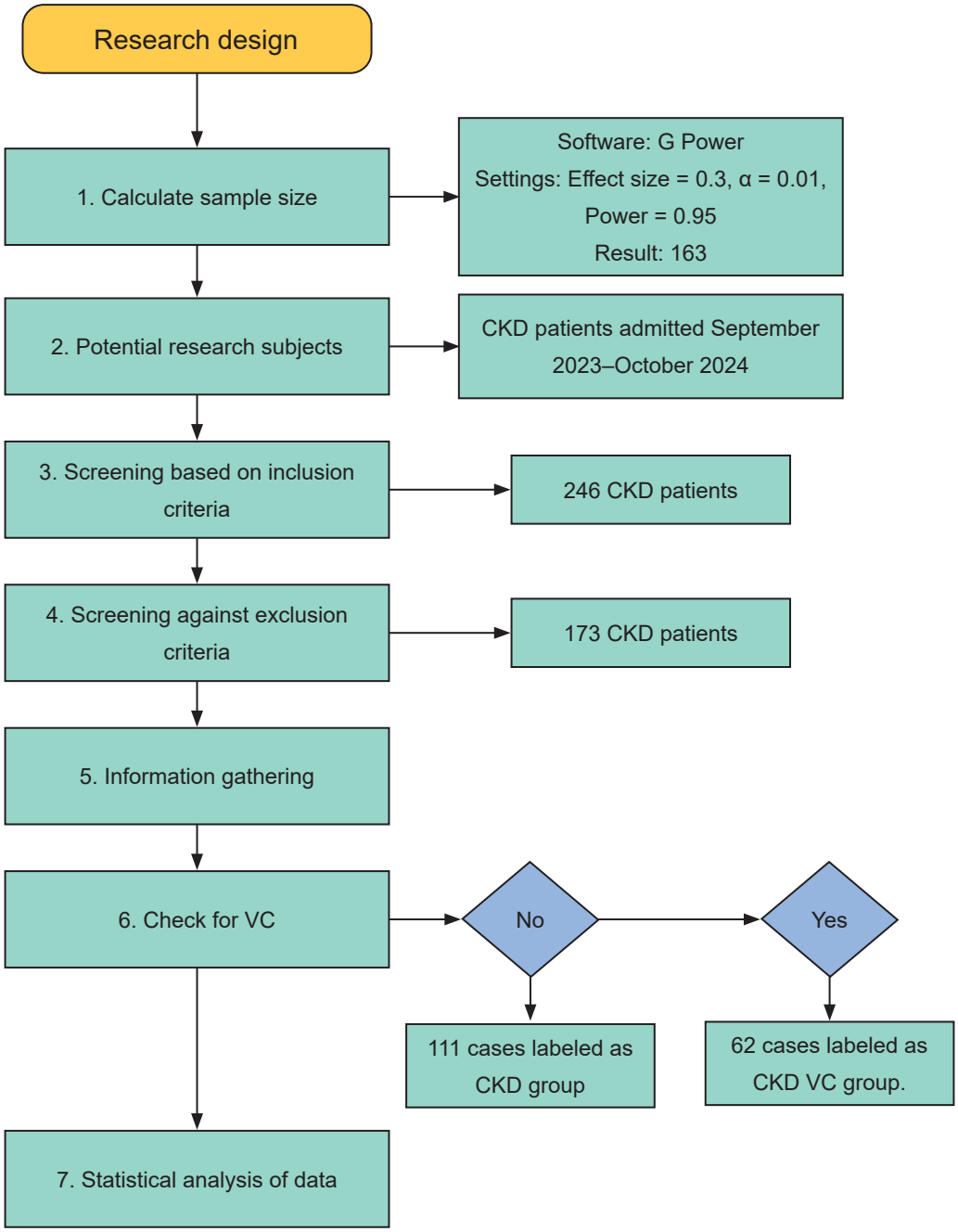

Figure 1. The design of this study and the main processes. This flowchart illustrates the complete study design, including patient recruitment (September 2023–October 2024), screening via inclusion/exclusion criteria, and group allocation (CKD group: no VC, n = 111; CKD-VC group: with VC, n = 62). All patients underwent dedicated chest CT for VC assessment and oxidative stress biomarker measurement within 72 hours of imaging. The study was approved by the Ethics Committee of Affiliated Hospital of Hebei University and conducted in accordance with the Declaration of Helsinki.

in univariate analysis (including oxidative stress markers, age, serum calcium, serum phosphorus, UA, ALB, hs-CRP, and CKD stage) were included as candidate covariates; second, a stepwise backward elimination method was applied (entry threshold $P < .10$, exit threshold $P < .05$) to retain only independent predictors with a statistically significant association with CKD-VC. The dependent variable was the presence/absence of VC (0 = no VC, 1 = VC; revised for consistent binary coding). A risk predictive model for CKD-VC was constructed using the regression coefficients (β) from the final

multivariate logistic regression model. Internal validation of the model was performed using the bootstrapping method (1000 bootstrap resamples) to assess model stability and reduce overfitting risk, with the area under the curve (AUC) of the bootstrap-corrected ROC curve used to verify diagnostic performance. The diagnostic value of the model was analyzed using receiver operating characteristic (ROC) curves, with the optimal cut-off value determined by the Youden index (sensitivity + specificity -1). Model performance was evaluated by AUC (an AUC closer to 1 indicates better diagnostic performance), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Overfitting was further assessed by comparing the observed AUC (in the study population) with the bootstrap-corrected AUC; a small difference (< 0.05) indicated no significant overfitting. A *P*-value less than .05 was considered statistically significant.

RESULTS

Comparison of oxidative stress responses

First and foremost, we compared the oxidative stress response indicators of the two groups. The results indicated lower levels of SOD and GSH-Px, as well as higher levels of CAT and MDA, in the CKD-VC group compared with the CKD group ($P < .05$). It suggests that the CKD-VC group exhibited a more pronounced oxidative stress response (Table 1).

Univariate analysis of factors influencing VC

Comparative analysis of the data of patients in the CKD and CKD-VC groups, showed that there was no difference in BMI, sex, CKD type, blood pressure, and blood lipids between the two groups ($P > .05$), suggesting that these factors are not associated with CKD-VC. While age, serum calcium, serum phosphorus, hs-CPR were higher, ALB was lower in the CKD-VC group than in the CKD group ($P < .05$), suggesting that these indices might be involved in the progression of CKD-VC. UA, a key endogenous antioxidant that scavenges ROS in physiological conditions, was significantly higher in the CKD-VC group than in the CKD group ($P < .001$). This abnormal elevation of UA in CKD patients is a well-recognized marker of impaired antioxidant capacity and increased oxidative stress, as UA can convert to an oxidant precursor state in the pathological CKD microenvironment, leading to enhanced ROS production and vascular damage (Table 2).

Multivariate analysis of factors influencing VC

Subsequently, we performed logistic regression analysis with indicators of the presence of differences in the univariate analysis as well as indicators of oxidative stress as covariates, and whether or not VC occurred in the patient as the dependent variable (CKD was assigned a value of 1 and CKD-VC was assigned a value of 2). The results showed that SOD and CAT were not independent factors affecting CKD-VC, while Age, UA, serum calcium, serum phosphorus, UA, hs-CPR, and MDA were independent risk factors affecting CKD-VC ($P < .05$), and ALB and GSH-Px were protective factors against CKD-VC ($P < .05$) (Table 3).

Risk model for CKD-VC

Based on the results of the multifactorial analysis, we established a risk prediction model for CKD-VC with the model equation: log(P) = -40.198+(Age×0.196)+(0.012×UA)+(3.256 ×serum calcium)+(9.501×serum phosphorus)+(-0.269×ALB) + (0.283 × hs-CRP) + (-0.057 × GSH-Px) + (0.670 × MDA). The ROC curve analysis showed that the model had a diagnostic sensitivity of 100.00% and a specificity of 87.39% for CKD-VC (AUC = 0.980, 95%CI = 0.965-0.995, $P < .001$) (Figure 2). Internal validation via 1000 bootstrap resamples confirmed the model's stability, with a bootstrap-corrected AUC of 0.976 (95%CI = 0.958-0.994), which was only 0.004 lower than the observed

Table 1. Comparison of oxidative stress responses

	CKD group (n = 111)	CKD-VC group (n = 62)	t	*P*
SOD (U/mL)	63.89 ± 11.93	58.61 ± 7.06	3.186	.002
GSH-Px (U/mL)	85.35 ± 11.28	77.43 ± 15.97	3.796	< .001
CAT (U/L)	5.53 ± 1.58	6.67 ± 2.93	3.342	.001
MDA (mmol/L)	8.87 ± 1.75	9.71 ± 2.59	2.541	.012

Note: chronic kidney disease, CKD; vascular calcification, VC; superoxide dismutase, SOD; malondialdehyde, MDA; glutathione peroxidase, GSH-Px; catalase, CAT.

Table 2. Univariate analysis of factors influencing VC

Factors	CKD group (n = 111)	CKD-VC group (n = 62)	*t*	*P*
Age	59.44 ± 4.28	65.48 ± 6.70	7.233	< .001
BMI (kg/m^2)	23.31 ± 1.52	23.50 ± 1.70	0.760	.448
Sex, male/female	84/27	49/13	χ^2 = 0.252	.616
Duration of CKD (years)	3.49 ± 0.55	3.60 ± 0.93	0.977	.330
Types of CKD			χ^2 = 1.731	.421
Hypertensive nephropathy	31 (27.93)	20 (32.26)		
Diabetic nephropathy	63 (56.76)	29 (46.77)		
Chronic glomerulonephritis	17 (15.32)	13 (20.97)		
Stage of CKD			χ^2 = 0.954	.812
G1	24 (21.62)	13 (20.97)		
G2	42 (37.84)	26 (41.94)		
G3	30 (27.03)	13 (20.97)		
G4	15 (13.51	10 (16.13)		
Smoking			χ^2 = 0.289	.591
Yes	49 (44.14)	30 (48.39)		
No	62 (55.86)	32 (51.61)		
SBP (mmHg)	127.01 ± 18.96	128.98 ± 16.39	0.689	.492
DBP (mmHg)	81.34 ± 9.13	80.42 ± 7.68	0.674	.501
MAP (mmHg)	97.74 ± 9.83	96.48 ± 8.03	0.858	.392
Lipids (mmol/L)				
TC	4.23 ± 0.73	4.36 ± 0.69	1.153	.250
TG	1.92 ± 0.61	1.98 ± 0.77	0.557	.578
LDL-C	2.81 ± 0.76	2.86 ± 0.73	0.394	.694
HDL-C	1.10 ± 0.31	1.14 ± 0.30	0.818	.414
Renal function				
Scr (μmol/L)	86.02 ± 18.64	89.53 ± 20.37	1.148	.252
UA (μmol/L)	333.31 ± 50.69	401.15 ± 81.70	6.737	< .001
BUN (mmol/L)	15.75 ± 3.43	16.28 ± 3.02	1.012	.313
GFR (mL/min/1.73 m^2)	69.04 ± 11.78	66.58 ± 14.57	1.209	.228
Serum calcium (mmol/L)	1.64 ± 0.31	1.90 ± 0.36	4.990	< .001
Serum phosphorus (mmol/L)	2.04 ± 0.28	2.46 ± 0.30	9.117	< .001
Nutritional proteins				
ALB (g/L)	38.18 ± 6.70	33.01 ± 6.26	4.985	< .001
GBH (%)	8.18 ± 1.66	8.31 ± 1.85	0.481	.631
TP (g/L)	48.11 ± 6.02	46.18 ± 7.93	1.806	.073
hs-CPR (mg/L)	10.22 ± 2.56	15.21 ± 4.53	9.263	< .001

Note: body mass index, BMI; chronic kidney disease, CKD; vascular calcification, VC; systolic blood pressure, SBP; diastolic blood pressure, DBP; mean arterial pressure, MAP; total cholesterol, TC; triglycerides, TG; low-density lipoprotein cholesterol, LDL-C; high-density lipoprotein cholesterol, HDL-C; serum creatinine, Scr; uric acid, UA; blood urea nitrogen, BUN; albumin, ALB; globe protein, GBH; total protein, TP; high-sensitivity c-reactive protein, hs-CPR; glomerular filtration rate, GFR. CKD stages were defined according to the 2021 KDIGO Guideline: G1 (eGFR ≥ 90 mL/min/1.73m^2), G2 (60 ≤ eGFR < 90), G3 (30 ≤ eGFR < 60), G4 (15 ≤ eGFR < 30).

Table 3. Multivariate analysis of factors influencing VC

Factors	B	S.E.	Wald χ^2	*P*	OR	95%CI
Age	0.196	0.081	5.857	.016	1.216	1.038, 1.425
UA	0.012	0.006	4.538	.033	1.012	1.001, 1.024
Serum calcium	3.256	1.184	7.568	.006	5.947	2.551, 26.956
Serum phosphorus	9.501	2.477	14.716	< .001	13.050	10.274, 26.560
ALB	-0.269	0.083	10.550	.001	0.764	0.650, 0.899
hs-CRP	0.283	0.101	7.776	.005	1.327	1.088, 1.618
SOD	-0.028	0.034	0.690	.406	0.972	0.909, 1.039
GSH-Px	-0.057	0.028	4.187	.041	0.944	0.894, 0.998
CAT	0.313	0.187	2.805	.094	1.368	0.948, 1.973
MDA	0.670	0.255	6.881	.009	1.954	1.184, 3.223

Note: regression coefficient, β; standard error, S.E.; odds ratio, OR; 95% confidence interval, 95%CI; uric acid, UA; albumin, ALB; high-sensitivity c-reactive protein, hs-CPR; superoxide dismutase, SOD; malondialdehyde, MDA; glutathione peroxidase, GSH-Px; catalase, CAT.

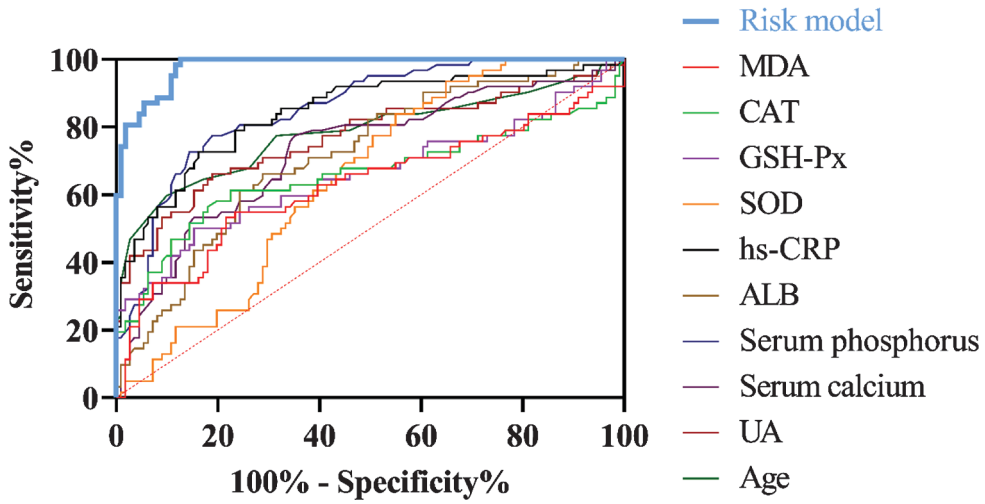

Figure 2. Risk model for CKD-VC. This ROC curve evaluates the diagnostic performance of the CKD-VC risk predictive model established from multivariate logistic regression analysis (including age, UA, serum calcium, serum phosphorus, ALB, hs-CRP, GSH-Px, and MDA as independent variables). The model's diagnostic performance metrics are reported as: area under the curve (AUC) = 0.980 (95%CI = 0.965-0.995, $P < .001$), sensitivity = 100.00%, specificity = 87.39%, optimal cut-off value = 0.52 (Youden index), positive predictive value (PPV) = 89.13%, negative predictive value (NPV) = 100.00%. Internal validation via 1000 bootstrap resamples yielded a bootstrap-corrected AUC = 0.976, indicating no significant overfitting. The diagonal line represents the reference line (AUC = 0.5, no diagnostic value).

AUC (0.980), indicating no significant overfitting of the model. The optimal cut-off value for the model (determined by the Youden index) was 0.52, with a positive predictive value (PPV) of 89.13% and a negative predictive value (NPV) of 100.00%.

DISCUSSION

CKD patients are at a high risk of developing vascular calcification (VC). VC can occur insidiously even in the early stages of CKD when calcium and phosphorus metabolism has not yet become deranged. In advanced stages of CKD, where the calcium-phosphorus product is significantly elevated, the progression of VC becomes even more aggressive.[10] VC poses a serious threat to the function of arteriovenous fistulas and the effectiveness of dialysis in hemodialysis patients, and is a significant contributor of increases prevalence of CVD and mortality.[11] Therefore, in-depth research into the influencing factors and preventive measures for VC is crucial for delaying CKD progression and mitigating associated complications in these patients.

Previously, it was widely believed that CKD-VC was primarily due to the excessive deposition of calcium and phosphorus on the damaged vascular wall.[12] However, more recent perspectives tend to view VC as a highly regulated active process of the differentiation of vascular smooth muscle cells (VSMCs) into osteoblasts.[13] Although the exact mechanisms of this process have not yet been fully elucidated, multiple studies have implicated oxidative stress as one of the crucial links.[5,14] In our current study, we similarly found significant oxidative stress in the CKD-VC group, reaffirming this viewpoint. As is well-known, reactive oxygen species (ROS) is inevitable byproducts of organ activities, which can be eliminated by the body under normal circumstances. While our study included patients across all CKD stages (G1-G4), the majority were in early stages (G1-G2: 66/173, 38.2%). This aligns with Zhang R. *et al.*'s findings that showed oxidative stress markers (e.g., plasma MDA) were elevated even in non-dialysis-dependent CKD patients,[15] suggesting that oxidative stress precedes overt VC. An animal experiment by Muñoz M. *et al.* demonstrated increased expression of ROS-generating enzyme NADPH oxidase subunits and decreased antioxidant enzymes in CKD rats, which induced vascular media calcification and ultimately resulted in VC in these rats.[16] These results all highlight the important role of oxidative stress in CKD-VC. Furthermore, our study also showed that GSH-Px and MDA are independent factors associated with CKD-VC, underscoring the importance of antioxidant stress treatment in the future treatment of CKD. However, multifactorial analysis showed that SOD, CAT and CKD-VC

were not related, which we believe may be due to the fact that the effects of SOD and CAT on the oxidative stress response were indirect, and thus both did not show independent effects on CKD-VC with the intervention of other factors. It is important to note that this retrospective cross-sectional study cannot establish a causal relationship between oxidative stress and CKD-VC, and the observed associations do not preclude the possibility of bidirectional causality (e.g., VC may also induce further oxidative stress in the vascular microenvironment).

On the other hand, we discovered that serum calcium and phosphorus, age, hs-CRP, ALB, and UA are independent factors influencing the occurrence of CKD-VC. The reasons are as follows: (1) As widely recognized factors affecting VC, the roles of serum calcium and phosphorus have been verified in numerous previous studies.[17,18] An elevation in serum calcium and phosphorus levels can facilitate the formation of VC crystals and the phenotypic alteration of vascular smooth muscle cells (VSMCs), leading to abnormal bone metabolism in patients and subsequently resulting in VC. (2) As age increases, the degree of vascular aging exacerbates and vascular function deteriorates, making it more prone to calcium ion deposition. Additionally, degenerative changes take place in the elastic fibers of blood vessels in elderly patients,[19] leading to reduced vascular elasticity and increased vulnerability of the vessels. (3) hs-CRP serves as an important marker of human inflammatory responses, and an increase in the hs-CRP level indicates an aggravation of the body's inflammatory response.[20] The research by Zhao Y. *et al.* indicates that inflammation can promote atherosclerosis by influencing the LDL-C receptor pathway.[21] It is hypothesized that this is also one of the mechanisms through which hs-CRP participates in VC. Meanwhile, an increase in hs-CRP typically reflects the intensification of oxidative stress responses, corroborating the aforementioned comparison results of the oxidative stress response. (4) Malnutrition has emerged as one of the hotspots of recent research on VC. Malnutrition can not only induce inflammation and oxidative stress but also reduce the synthesis of liver albumin and augment energy consumption.[22] The research by Harada K. *et al.* found that in non-dialysis CKD patients, the Geriatric Nutritional Risk Index (GNRI), as a nutritional predictor, exhibits a significant correlation with severe VC.[23] (5) UA is a crucial antioxidant and possesses the capability of scavenging ROS. In a pathological examination report on patients with coronary heart disease by Sultana S. *et al.*, it was noted that when coronary heart disease (CHD) patients are in the late stage of atherosclerosis, highly expressed UA will convert into an oxidant precursor state, leading to the oxidation of LDL-C, facilitating the adhesion of a vast number of granulocytes to endothelial cells, releasing superoxide anions and peroxides, and thereby inducing vascular endothelial dysfunction and vascular inflammation.[24]

Finally, based on the regression analysis results, we established a CKD-VC risk model. Through ROC curve analysis, it was observed that the diagnostic sensitivity and specificity of this model for CKD-VC reached 100.00% and 87.39%, respectively (AUC = 0.980), demonstrating its outstanding evaluation performance. The minimal difference between the observed AUC (0.980) and bootstrap-corrected AUC (0.976) (< 0.05) confirms the absence of significant overfitting, further supporting the model's reliability in the study population.

Limitations

This study is a retrospective cross-sectional study, which inherently carries the risk of selection bias and cannot establish causal relationships between variables and CKD-VC; only associative relationships can be inferred. Second, the study population only included patients with coronary VC, and other types of CKD-VC (e.g., abdominal aortic calcification, heart valve calcification) were not included due to the limited sample size, which may limit the generalizability of the results to all CKD-VC subtypes. Third, oxidative stress biomarkers were measured at a single time point (at admission), and longitudinal changes in oxidative stress over time and their dynamic association with VC progression were not assessed; a prospective cohort study is required to evaluate the temporal relationship between oxidative stress and VC development. Fourth, the study did not control for all potential confounding factors (e.g., vitamin K levels, magnesium status), which are known to influence both oxidative stress and calcium-phosphorus metabolism in CKD. Fifth, the risk model established in this study only underwent

internal validation via bootstrapping and has not been externally validated in an independent CKD patient cohort; external validation is essential to confirm the model's generalizability to other clinical settings. Sixth, although CKD stage was included in the analysis and no significant difference was observed between groups, the study population was predominantly early-stage CKD (G1-G2), and the results may not be applicable to late-stage CKD (G4) or ESKD (G5) patients with more severe oxidative stress and calcium-phosphorus disorder. Finally, the study only assessed four core oxidative stress biomarkers; future studies incorporating a broader panel of markers (e.g., AOPP, AGE, TAS) may provide a more comprehensive understanding of oxidative stress in CKD-VC. Despite these limitations, this study provides valuable clinical insights into the association between oxidative stress and CKD-VC, and establishes a clinically applicable risk model with high diagnostic performance for coronary VC in early-to-moderate CKD patients.

CONCLUSION

Compared with CKD patients, CKD-VC patients exhibit obvious oxidative stress reactions. The risk predictive model established based on oxidative stress indicators can accurately assess the occurrence of VC in CKD patients. This finding provides a new approach for clinical prevention and treatment of CKD-VC in the future and can offer more reliable safeguards for the safety of CKD patients.

ETHICAL APPROVAL

The study protocol was approved by the Ethics Committee of Affiliated Hospital of Hebei University (NO. 20210424).

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FUNDING

Not applicable.

AUTHOR CONTRIBUTIONS

Jianmin Zhang and Xuan Zhou designed the study, Lei Ran and Xiaoxi Wu wrote the manuscript, Li Guo collected and analyzed data, Jing Li and Lei Wang revised the manuscript, Lei Ran and Xiaoxi Wu made equal contributions in this work as co-first authors. All authors read and approved the final submitted manuscript.

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