Association between fibrinogen/albumin ratio and severity of coronary artery calcification in patients with chronic kidney disease: a retrospective study

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ABSTRACT

Aim. Previous studies have shown that the fibrinogen to albumin ratio (FAR) is closely related to the severity and prognosis of coronary atherosclerosis. In this study, we sought to evaluate the association between FAR and the degree of coronary artery calcification (CAC) in patients with chronic kidney disease (CKD).

Methods. In this retrospective study, 218 patients with CKD were stratified into low, medium and high FAR groups according to the tertiles of the FAR values. The CAC scores, clinical information and laboratory test results of the three FAR groups were compared. To explore the relationship between FAR and CAC we conducted binary logistic regression and correlation analyses.

Results. In the low FAR group, the CAC scores were significantly lower than those in the medium and high FAR groups ($P < 0.001$). There was a significant correlation between the FAR and CAC scores ($r = 0.510$, $P < 0.001$). The FAR was an independent predictor of CAC (OR = 1.106, 95% CI [1.004–1.218], $P = 0.042$).

Conclusion. In patients with CKD, the FAR can be considered as an effective predictor of CAC.

INTRODUCTION

Chronic kidney disease (CKD) is a widespread disease among the many chronic diseases that inflict great harm upon the world population. The incidence of CKD in China has reached 10.8% and is still on the rise (Sun et al., 2020), and has become a critical public health concern. Most CKD patients eventually die from cardiovascular-related complications due to the high mortality rate that is often related to coronary artery calcification (CAC) (Turakhia et al., 2018; Bundy et al., 2019). Vascular calcification (VC) occurs in the early stages of CKD and gradually worsens as the disease progresses. VC results in thickening and stiffness of the muscularis layer of the arterial wall, and is primarily caused by calcification of the medial layer. Unlike atherosclerosis, medial calcification is similar to osteogenesis and is mainly regulated by vascular smooth muscle cells (VSMCs) (Ottolini & Sonkusare,
One of the main mechanisms of VC is the accelerated rate of VSMC synthesis and senescence, decreased contractile protein expression, and gradual transdifferentiation into an osteoblastic/chondrocyte phenotype that releases matrix vesicles (Chen, Zhou & Yang, 2021). When high phosphate levels are present, differentiation of VSMCs into a bone/chondrogenic phenotype can occur (Voelkl et al., 2018). In the clinical course of CKD patients, in addition to high levels of phosphate and parathyroid hormone, other factors that promote VC include oxidative stress and inflammation.

Coagulopathy is a common symptom of CKD patients. Clot formation is delayed, but at the same time there is a slower rate of clot decomposition and increased clot strength. Fibrinogen is a glycoprotein produced and secreted by the liver that eventually distributes to the serum. CKD leads to increased fibrinogen levels in the body, which ultimately mediates the increased clot strength (Nunns et al., 2017).

Many other studies have shown that hypoalbuminemia is closely related to CKD. Several recent studies have reported the relationship between cardiovascular disease (CVD) and the fibrinogen/albumin ratio (FAR), confirming the relationship between CVD and FAR, a marker of systemic inflammation. In addition, FAR has important prognostic value in the assessment of end-stage renal disease (Zou et al., 2020) and acute coronary syndrome (Çetin et al., 2020). Among them, Zou et al. (2020) believe that FAR can be used as a key indicator to provide a predictive program for peritoneal dialysis all-cause mortality and CVD mortality in assessing the prognosis of patients with end-stage renal disease. Studies related to coronary heart disease have found that contrast-induced nephropathy after carotid angiography is generally associated with patients who have high FAR values (Ertas, Avci & Kiris, 2019). In patients with stable coronary heart disease, high FAR values are also associated with the formation of coronary artery side branch circulation (Zhao et al., 2020).

After a comprehensive consideration of the medical literature, we aimed to retrospectively study possible correlations between FAR and CAC in CKD patients.

**MATERIALS AND METHODS**

**Patients**

We obtained clinical data from 366 CKD patients who had been admitted during October 2018 to December 2020 to The Second Affiliated Hospital of Anhui Medical University (Hehei, Anhui Province, China).

The inclusion criteria for the study were: (1) ages over 18 years, (2) diagnosis of chronic nephritis, and (3) availability of complete clinical and laboratory data. The exclusion criteria for the study were presence of: (1) blood diseases, which may cause abnormal fibrinogen, (2) active infections, (3) malignant tumors or autoimmune diseases, and (4) history of taking anticoagulants during the past three months.

In this study, 274 CKD patients were screened. This study was approved in advance by the ethics committee of The Second Affiliated Hospital of Anhui Medical University (authorization number YJ-YX2017-004.) All patients signed an informed consent form before data collection. The data were kept anonymous and confidential, and the survey results were used only for scientific research.
Data collection
Venous blood samples were obtained from all patients before treatment and were sent for laboratory analysis within 3 h of collection. Levels of the following laboratory parameters were measured in the samples: fibrinogen (FIB), albumin (ALB), calcium, creatinine, phosphate, alkaline phosphatase, high-sensitivity C-reactive protein (hs-CRP), parathyroid hormone (PTH), procalcitonin (PCT), serum glucose, total cholesterol (TC), 25-dihydroxyvitamin D (25(OH)D), triglycerides, urea nitrogen, high-density lipoprotein cholesterol (HDL-C), glycated hemoglobin and low-density lipoprotein cholesterol (LDL-C). To determine other factors, the following calculations were made: calcium correction = serum calcium + 0.02 × (40-ALB); PLR = absolute platelet count/absolute lymphocyte count; NLR = absolute neutrophil count/absolute lymphocyte count and FAR = fibrinogen/albumin.

Dialysis modality
With respect to the dialysis modality, there were three subgroups of patients: (1) no dialysis, (2) hemodialysis and (3) peritoneal dialysis. Hemodialysis: regular hemodialysis, 3.5–4.5 h/time, 3 times/week, continuous hemodialysis for more than 3 months. Patients on peritoneal dialysis underwent continuous ambulatory peritoneal dialysis: peritoneal dialysate 1.5–2 L/time, 3–4 times/day, abdominal retention at night, continuous peritoneal dialysis for more than 3 months.

CAC score
Non-enhanced multislice coronary computed tomography (Philips iCT Brilliance 256, Koninklijke Philips N.V., Amsterdam, Netherlands) was performed at baseline. A radiologist read all CT scans. Next, the pseudo-continuous variable Agatston score was calculated, which is related to the area of the basal coronary artery and the plaque density. Calcification was defined as a CT value >130 HU, with calcification area >1 mm². The calcification score was calculated as the calcification area × peak calcification, with 1 point: 130–199 HU, 2 points: 200–299 HU, 3 points: 300–399 HU and 4 points: >400 HU. The total CAC score was the sum of the VC scores of the left main, left anterior descending, right main and supination branches of the coronary arteries. Patients were stratified according to their CAC scores into the calcification group (CAC score >0 HU) and non-calcification group (CAC score = 0 HU).

Statistical analysis
All anonymous data were recorded in an EpiData database (EpiData Association, Odense, Denmark). SPSS 23.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. For continuous variables, normally distributed data is represented by the mean and standard deviation, and non-normally distributed data by the median, first quartile and third quartile. ANOVA was applied for comparisons of normally distributed continuous variables among different groups, and Tukey’s test was used for the post hoc analysis. For non-parametric analysis, the Kruskal-Wallis test ($H$) was used for comparisons of non-normally distributed continuous variables among different groups and for further pairwise comparisons. Percentages and frequencies were used to characterize categorical
variables. The chi-square ($\chi^2$) test was applied for comparisons of categorical variables among different groups, and Bonferroni correction was used to further analyze the differences in each category. Correlation analysis (correlation coefficient: $r$) was performed on all continuous variables with CAC score. Pearson correlation analysis was used for normally distributed data, and Spearman correlation analysis for non-normally distributed data. Univariate regression analysis (odds ratio: OR) was used for all variables except those closely related to calcification. Those variables with $P < 0.05$ were then included in the multivariate regression model; otherwise, multivariate regression analysis was performed after screening variables by stepwise regression method. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

The total number of patients with CKD included in this study was 218, of which 127 were men. The mean age of all patients was 53.0 ± 14.6 years. We did not detect any contrast-induced nephropathy in non-hemodialysis patients.

Patients were classified into three groups according to the tertiles of the FAR value, as follows: FAR ≤ 0.079 was the low FAR group ($n = 73$ patients), 0.079 < FAR ≤ 0.102 was the medium FAR group ($n = 71$ patients) and FAR > 0.102 was the high FAR group ($n = 74$ patients). As shown in Table 1, patient characteristics and demographic variables are presented for the three FAR groups. There were no significant differences in gender proportions, body mass index, percentage of smokers, percentage of alcohol drinkers, primary disease type, dialysis modality or prevalence of hypertension among the low, middle and high FAR groups ($P > 0.05$). The percentages of patients who took different medications were not significantly different ($P > 0.05$; levocarnitine injection, recombinant human erythropoietin injection, three classes of antihypertensive agents, calcium-containing phosphate binders, non-calcium-based phosphate binders, nutritional/active vitamin D, calcimimetics). However, patients in the high FAR group had a higher prevalence of diabetes ($P = 0.008$) and were older ($P < 0.001$). The middle FAR group had the highest rate of insulin usage ($P = 0.003$).

Laboratory parameters

As shown in Table 2, higher levels of urea nitrogen ($P = 0.037$), serum glucose ($P = 0.024$), hs-CRP ($P < 0.001$), PCT ($P = 0.033$), NLR ($P < 0.001$), PLR ($P = 0.010$) and CAC score ($P < 0.001$) were found in the high FAR group. The middle FAR group had a slightly higher alkaline phosphatase level ($P < 0.001$). Analysis of the results showed that the urea nitrogen level in the low FAR group was much lower than that in the high FAR group or the medium FAR group ($P = 0.004$). In addition, the 25(OH)D level in the low FAR group was much higher than that in the high FAR group or the medium FAR group ($P < 0.001$). Levels of other parameters including hemoglobin, glycated hemoglobin, total cholesterol, triglycerides, HDL-C, LDL-C, phosphate, calcium correction, creatinine, uric acid, PTH, AST and ALT were not significantly different among the three FAR groups ($P > 0.05$).
Table 1  Relationship between patient characteristics and fibrinogen/albumin ratio.

| Characteristic                      | Low FARa | Middle FARa | High FARa   | P value |
|-------------------------------------|----------|-------------|-------------|---------|
| Age (years, mean ± SD)              | 47.38 ± 13.70 | 53.76 ± 12.57 | 58.86 ± 13.17 | <0.001  |
| Gender (male), n (%)                | 48 (65.8) | 38 (53.5)   | 41 (55.4)   | 0.274   |
| BMI (kg/m², mean ± SD)              | 22.56 ± 3.56 | 23.16 ± 3.27 | 23.85 ± 3.86 | 0.097   |
| Smokers, n (%)                      | 22 (30.1) | 21 (29.6)   | 16 (21.6)   | 0.430   |
| Drinkers (alcohol), n (%)           | 13 (17.8) | 8 (11.3)    | 13 (17.6)   | 0.472   |
| Primary disease, n (%)              |          |             |             | 0.269   |
| Chronic glomerulonephritis          | 29 (39.7) | 24 (33.8)   | 39 (52.7)   |         |
| Chronic nephrotic syndrome          | 26 (35.6) | 23 (32.4)   | 10 (13.5)   |         |
| Hypertensive nephropathy            | 4 (5.5)   | 4 (5.6)     | 8 (10.8)    |         |
| Diabetic nephropathy                | 2 (2.7)   | 11 (15.5)   | 10 (13.5)   |         |
| Otherb                             | 12 (16.4) | 9 (12.7)    | 7 (9.5)     |         |
| CKD stage, n (%)                    | 0.343     |             |             |         |
| 3                                   | 14 (19.2) | 4 (5.6)     | 4 (5.4)     |         |
| 4                                   | 2 (2.7)   | 3 (4.2)     | 2 (2.7)     |         |
| 5                                   | 11 (15.1) | 14 (19.7)   | 18 (24.3)   |         |
| 5d                                 | 16 (23.0) | 50 (70.4)   | 50 (67.6)   |         |
| Dialysis modality, n (%)            | 0.073     |             |             |         |
| No dialysis                        | 27 (37.0) | 21 (29.6)   | 24 (32.4)   |         |
| Hemodialysis                       | 42 (57.5) | 37 (52.1)   | 29 (39.2)   |         |
| Peritoneal dialysis                 | 4 (5.5)   | 13 (18.3)   | 11 (28.4)   |         |
| Hypertension, n (%)                 | 51 (69.9) | 54 (76.1)   | 54 (73.0)   | 0.705   |
| Diabetes mellitus, n (%)            | 5 (6.8)   | 15 (21.1)c  | 19 (25.7)c  | 0.008   |
| Anti-hypertensive agent, n (%)      |          |             |             |         |
| Calcium channel blocker             | 42 (57.5) | 46 (64.8)   | 44 (59.5)   | 0.654   |
| β-blocker                           | 24 (32.9) | 20 (28.2)   | 22 (29.7)   | 0.821   |
| Angiotensin-aldosterone antagonists | 21 (28.8) | 17 (23.9)   | 19 (25.7)   | 0.800   |
| Insulin, n (%)                      | 2 (2.7)   | 13 (18.3)c  | 12 (16.2)c  | 0.003   |
| Recombinant human erythropoietin injection, n (%) | 41 (56.2) | 45 (63.4) | 43 (58.1) | 0.661 |
| Levocarnitine injection, n (%)      | 37 (50.7) | 31 (43.7)   | 24 (32.4)   | 0.150   |
| Calcium-containing phosphate binders, n (%) | 23 (31.5) | 30 (42.3) | 26 (35.1) | 0.395 |
| Non-calcium-based phosphate binders, n (%) | 13 (17.8) | 13 (18.3) | 10 (13.5) | 0.691 |
| Nutritional/active vitamin D, n (%) | 21 (30.0) | 28 (40.0)   | 21 (30.0)   | 0.273   |
| Calcimimetics, n (%)                | 3 (4.1)   | 5 (7.0)     | 5 (6.8)     | 0.698   |

Notes.
BMI, body mass index; CKD, chronic kidney disease; SD, standard deviation.
aLow FAR group (n = 73): FAR ≤ 0.079; medium FAR group (n = 71): 0.079 < FAR ≤ 0.102; high FAR group (n = 74): FAR > 0.102.
bOther primary disease includes lupus nephritis, polycystic kidney disease and IgA nephropathy.
ccompared with low FAR group, P < 0.05.
dcompared with middle FAR group, P < 0.05.

Factors related to CAC
Spearman correlation analysis showed that dialysis duration (r = 0.210, P = 0.028), serum phosphate (r = 0.228, P = 0.015), glycated hemoglobin (r = 0.340, P = 0.049), hs-CRP (r = 0.398, P = 0.001), PLR (r = 0.283, P = 0.002), NLR (r = 0.256, P = 006) and FAR (r = 0.510, P < 0.001) were positively related to the severity of CAC (Table 3).
Table 2  Comparison of laboratory parameters among patients with different FAR level.

| Parameter                              | Low FAR\(^a\) | Middle FAR\(^a\) | High FAR\(^a\) | P value |
|----------------------------------------|---------------|-----------------|---------------|---------|
| Creatinine (µmol/L)                    | 677.17 ± 380.85 | 777.00 ± 373.99 | 751.42 ± 314.80 | 0.217   |
| Urea nitrogen (µmol/L)                 | 16.63 ± 7.74 | 19.64 ± 9.37 | 20.25 ± 9.62 | 0.037   |
| Uric acid (µmol/L)                     | 376.96 ± 101.49 | 394.33 ± 122.99 | 379.85 ± 138.55 | 0.673   |
| Calcium correction (mmol/L)            | 2.17 ± 0.22 | 2.20 ± 0.25 | 2.25 ± 0.32 | 0.223   |
| Phosphate (mmol/L)                     | 1.66 (1.30, 2.08) | 1.85 (1.50, 2.13) | 1.69 (1.35, 2.15) | 0.200   |
| Alkaline phosphatase (U/L)             | 83 (66, 117.5) | 112.5 (80.50, 93.25) | 104 (79.75, 163) | <0.001  |
| Serum glucose (mg/dl)                  | 4.45 (4.19, 4.99) | 4.66 (4.19, 5.60) | 4.88 (4.25, 5.90) | 0.024   |
| Glycated hemoglobin (%)                | 5.61 ± 1.64 | 6.34 ± 1.85 | 6.04 ± 1.46 | 0.331   |
| 25(OH)D (ng/dl)                        | 23.21 ± 11.43 | 18.62 ± 10.34 | 15.55 ± 9.87 | 0.001   |
| PTH (pg/mL)                            | 198 (74.1, 735) | 268 (97.5, 665) | 319 (155.75,531.25) | 0.593   |
| hs-CRP (mg/L)                          | 0.9 (0.6, 1.85) | 2.45 (1.10, 6.00) | 4.50 (1.00, 10.80) | <0.001  |
| PCT (ng/ml)                            | 0.12 (0.06, 0.39) | 0.15 (0.09, 0.27) | 0.31 (0.15, 0.91) | 0.033   |
| NLR\(^c\)                              | 2.66 (2.05, 3.49) | 3.20 (2.45, 4.77) | 3.73 (2.65, 5.09) | <0.001  |
| PLR\(^c\)                              | 113.89 (88.41, 155.62) | 136.67 (103.21, 175.21) | 137.64 (112.79, 179.66) | 0.010   |
| CAC score\(^c\)                        | 0 (0, 31.08) | 18.56 (0, 219.50) | 84.87 (0, 395.07) | <0.001  |
| CAC, n (%)                             | 29 (39.7) | 41 (57.7) | 44 (59.5) | 0.017   |

Notes.
25(OH)D, 25-dihydroxyvitamin D; CAC, coronary artery calcification; calcium correction, serum calcium + 0.02 × (40–ALB); hs-CRP, high-sensitivity C-reactive protein; FAR, fibrinogen/albumin ratio; NLR, neutrophil/lymphocyte ratio; PCT, procalcitonin; PLR, platelet/lymphocyte ratio; PTH, parathyroid hormone.

\(^a\)Low FAR group (n = 73): FAR ≤ 0.079; medium FAR group (n = 71): 0.079 < FAR ≤ 0.102; high FAR group (n = 74): FAR > 0.102.

\(^b\)Mean ± standard deviation.

\(^c\)Median (first quartile, third quartile).

*compared with low FAR group, P < 0.05.

#compared with middle FAR group, P < 0.05.

Risk factors for CAC

The dependent variable of the binary logistic regression analysis was presence or absence of CAC. Univariate analysis showed that advanced age, longer dialysis duration, as well as increased levels of 25(OH)D, PTH, hs-CRP, FAR and decreased uric acid level were significantly associated with a higher risk of CAC (P < 0.05). Moreover, multivariate analysis demonstrated that age (OR = 1.071, 95% CI [1.026–1.119], P = 0.002), dialysis duration (OR = 1.232, 95% CI [1.029–1.475], P = 0.023), and FAR (OR = 1.106, 95% CI [1.004–1.218], P = 0.042) were independent predictors for CAC (Table 4).

DISCUSSION

In our study of CKD patients we found that if the FAR value is higher, the prevalence of CAC is higher. We detected CAC in 54.8% of the total samples. We found that older age and a longer time since beginning dialysis, as well as higher levels of BMI, serum phosphate, PTH, hs-CRP, NLR and FAR were significantly positively correlated with a higher detection rate of CAC. CKD patients who smoked or had disease stage 5d were more likely to be diagnosed with CAC. Our findings are consistent with those of other researchers. Mizuiri et al. (2021) showed that many factors significantly affect the probability of CAC in patients undergoing hemodialysis treatment, such as smoking, hs-CRP, diabetes, phosphate levels, gender, time on dialysis, age and blood calcium levels. Chen, Zhou & Yang (2021) studied
Table 3: Correlations between continuous variables and coronary artery calcification severity.

| Parameter                  | r    | P value |
|----------------------------|------|---------|
| Age                        | 0.142| 0.131   |
| Age at dialysis            | 0.210| 0.028   |
| BMI                        | 0.094| 0.324   |
| Creatinine                 | −0.006| 0.951  |
| Urea nitrogen              | −0.012| 0.896  |
| Uric acid                  | −0.084| 0.375   |
| Total cholesterol          | −0.096| 0.321   |
| Triglycerides              | 0.041| 0.672   |
| HDL-C                      | −0.137| 0.229   |
| LDL-C                      | −0.122| 0.284   |
| Calcium correction         | 0.139| 0.142   |
| Phosphate                  | 0.228| 0.015   |
| Serum glucose              | 0.117| 0.229   |
| Glycated hemoglobin        | 0.340| 0.049   |
| Alkaline phosphatase       | 0.160| 0.088   |
| 25(OH)D                    | −0.099| 0.340   |
| PTH                        | 0.017| 0.865   |
| hs-CRP                     | 0.398| 0.001   |
| PLR                        | 0.283| 0.002   |
| NLR                        | 0.256| 0.006   |
| FAR                        | 0.510| <0.001  |

Notes.

25(OH)D, 25-dihydroxyvitamin D; BMI, body mass index; FAR, fibrinogen/albumin ratio; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PTH, parathyroid hormone; r, Spearman correlation coefficient.

The sample size for this analysis was 218.

The factors that affect radial artery calcification in patients with end-stage renal disease and found that calcium levels, HbA1c levels, duration of diabetes and duration of dialysis treatment are positively correlated with the degree of radial artery calcification.

Several studies have recently explored the relationship between FAR and CVD. Whether patients have ST-elevation myocardial infarction (STEMI) or non STEMI (NSTEMI), FAR can predict SYNTAX scores, and assess severity of cardiovascular diseases and prognosis (Erdoğan et al., 2021; Karahan et al., 2016a). In addition, an elevated FAR was significantly associated with no-reflow and short-term mortality in STEMI patients who had primary percutaneous coronary intervention (Xiao et al., 2019; Zhao et al., 2019). The FAR levels were significantly higher in patients with slow coronary blood flow and definitive coronary artery disease (CAD). It is evident that the FAR is very useful for predicting the course of the CAD process (Kayapinar, Ozde & Kaya, 2019). Zou et al. (2020) illustrated that the baseline FAR was a superior predictor of all-cause and CVD mortality in patients with continuous ambulatory peritoneal dialysis, compared to the established inflammatory markers.
Table 4  Binary logistic regression analysis of risk factors for coronary artery calcification.

| Factor                        | Univariate analysis |       | Multivariate analysis |       |
|-------------------------------|--------------------|-------|-----------------------|-------|
|                               | OR                 | 95% CI| P value               | OR    |
| Age                           | 1.052              | 1.029–1.076 | <0.001               | 1.071 |
| Gender (ref: female)          | 1.127              | 0.658–1.933 | 0.663         |       |
| Smoker (ref: non-smoker)      | 1.625              | 0.884–2.987 | 0.118         |       |
| BMI                           | 1.076              | 0.996–1.162 | 0.063         |       |
| CKD stage (ref: stage 3)      |                    |       |                       |       |
| 4                             | 3.375              | 0.532–21.419 | 0.197       |       |
| 5                             | 2.667              | 0.766–9.284 | 0.123         |       |
| 5d                            | 7.445              | 2.396–23.140 | 0.001       |       |
| Dialysis modality (ref: no dialysis) |                 |       |                       |       |
| Hemodialysis                  | 4.088              | 2.166–7.715 | <0.001   |       |
| Peritoneal dialysis           | 2.367              | 1.056–5.304 | 0.036       |       |
| Age at dialysis               | 1.234              | 1.138–1.339 | <0.001   | 1.232 |
| Uric acid                     | 0.997              | 0.995–0.999 | 0.017       | 1.029 |
| Creatinine                    | 1.001              | 1.000–1.002 | 0.052       | 1.475 |
| Alkaline phosphatase          | 1.001              | 1.000–1.002 | 0.106       |       |
| 25(OH)D                       | 1.030              | 1.001–1.060 | 0.040       |       |
| Phosphate                     | 1.010              | 0.637–1.602 | 0.966       |       |
| PTH                           | 1.001              | 1.000–1.010 | 0.010       |       |
| hs-CRP                        | 1.073              | 1.006–1.145 | 0.032       |       |
| FAR                           | 1.161              | 1.058–1.274 | 0.002       | 1.106 |

Notes.
25(OH)D, 25-dihydroxyvitamin D; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; FAR, fibrinogen/albumin ratio; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; PTH, parathyroid hormone.
Statistically significant results are in bold.

Fibrinogen can be viewed as a reactive protein that reflects the acute phase of systemic inflammation, and at the same time it plays an important role in the normal operation of blood coagulation (Karahan et al., 2016b). During coagulation, thrombin converts fibrinogen to fibrin, which polymerizes and forms the protein meshwork of the growing blood clot. The coagulation-fibrinolytic cascades and the inflammatory response are closely interconnected, and there is evidence that fibrinolysis is a marker for the onset of systemic inflammation (Cvachovec, Horácek & Vislocky, 2000). In the development of inflammation, fibrinogen is conducive to the production of pro-inflammatory cytokines and promotes the development of inflammation (Gobel et al., 2018). The systemic inflammatory response and coagulation are closely related to CKD (Gäckler et al., 2019). At the same time, lymphocytes, monocytes, platelets and endothelial cells will be affected by fibrinogen and its degradation products resulting in changes to the inflammatory response, thereby changing blood flow, causing vascular endothelial damage and thrombosis (Abdul & Sultan, 2019). Enia et al. (2005) found that death from CVD in peritoneal dialysis patients is independently related to fibrinogen.

Albumin is synthesized and secreted by liver cells, which can maintain nutrition and osmotic pressure of the body, transport many insoluble small molecules of organic matter
and inorganic ions, and participate in the inflammation process. Inflammatory response can induce barrier dysfunction, resulting in endothelial cell and albumin hyperpermeability and increased tissue oedema (Chen et al., 2019). Serum albumin, as an anti-inflammatory protein, has a protective anti-inflammatory effect during acute inflammation (China et al., 2018). CKD patients lose a large amount of protein in the urine due to renal failure that is often accompanied by hypoalbuminemia. An inflammatory state could give rise to hypoalbuminemia, which is an independent risk factor for heart failure and acute coronary syndrome. Moreover, the severity of CAD and hospital mortality are higher in patients with lower serum albumin (Kumar & Banerjee, 2017).

The occurrence of CAC is closely related to the inflammatory response. Fibrinogen and albumin as inflammatory markers may reflect the process of CAC through the following mechanisms. First, pro-inflammatory cytokines such as interleukin-1 will accelerate the synthesis of tumor necrosis factors under the action of fibrinogen. Then, these cytokines act to promote the transformation of VSMCs from the contractile to the bone/chondrogenic phenotype and they eventually become chondrocytes or adulterants (Voelkl et al., 2018). Second, under the action of fibrinogen and metabolites, endothelial function may become damaged, ultimately affecting endothelial cell permeability. Previous studies have shown that the production and progression of CAC are critically affected by vascular endothelial cells. Vascular endothelial cell abnormalities (i.e., abnormal function of morphological changes) due to any cause will promote CAC (Yung et al., 2015). Third, when hypoproteinemia occurs, patients may experience increased oxidative damage and inflammation. At the same time, the presence of cytokines makes it difficult to eliminate oxygen free radicals. For example, interleukin-6 can block the albumin synthesis pathway and elevated TNF-α selectively inhibits albumin gene expression and ultimately reduces the albumin level (Xiao et al., 2019). Finally, when the serum albumin level decreases, the blood becomes more viscous, promoting LDL-C modification to oxidized LDL-C, thereby aggravating VC (Milan et al., 2016; Ding & Manson, 2021).

The FAR predicts CAC, which may be primarily related to inflammation. Microinflammation is widespread in CKD patients, and is closely related to the increased mortality in dialysis patients (Amdur et al., 2019). The biological incompatibility of the dialysate, abnormal intestinal function, continuous accumulation of toxins produced by uremia and abnormal renal function are closely related to microinflammation. The three factors of VC, oxidative stress and microinflammation influence each other and ultimately increase cardiovascular morbidity and mortality (Schley et al., 2019). Other studies have focused on ratios or evaluation systems to study the relationship between these markers or between the markers and the mortality of CKD patients, such as FAR (Zou et al., 2020), platelet to lymphocyte ratio (PLR) (Duan et al., 2021), neutrophil to lymphocyte ratio (NLR) (Zhang et al., 2021) and Glasgow Outcome Score (GPS) (Cai et al., 2018).

In our study we found that inflammation markers such as NLR and hs-CRP were related to CAC, which is consistent with the results of previous studies. Li et al. (2020) found that the hs-CRP value was positively correlated with VC and believed that the cause was inflammation. Previous studies have shown that excessive CRP causes abnormal endothelial dysfunction. The influence of CRP weakens the activity and expression of
endothelial nitric oxide synthase, and the production of nitric oxide is inhibited. In terms of CAC and angiogenesis, nitric oxide plays a key role (Batko et al., 2020). Therefore, when CKD patients have high hs-CRP values, it may be due to a sharp decrease in the amount of nitric oxide and abnormal endothelial function (CRP-mediated). Chandra et al. (2020) also concluded that NLR could be used when predicting VC in end-stage renal disease patients. Nam, Kang & Song (2017) studied Behcet disease patients and believed that CAC and NLR were independently correlated, while CRP, carotid artery intima-media thickness, and NLR were positively correlated (moderate).

LIMITATIONS
This study has several limitations. It was conducted at a single center and included a relatively small number of patients. In addition, FAR is a dynamic index and could differ from day to day. Therefore, analyses based on a single FAR measurement may not reflect the long-term relationship between FAR and CAC score. Another limitation is that the retrospective study design makes it difficult to explain the underlying cause of the relationship between CAC and FAR.

CONCLUSION
Our study shows that the FAR is positively correlated with CAC score. In CKD patients, higher levels of FAR are independently associated with CAC. FAR may serve as an easily measurable laboratory index for the prevalence of CAC in patients with CKD.

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ADDITIONAL INFORMATION AND DECLARATIONS

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Competing Interests
The authors declare there are no competing interests.
Author Contributions

• Yuyu Zhu conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
• Shuman Tao performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
• Danfeng Zhang performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
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• Liang Yuan performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
• Haifeng Pan performed the experiments, analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
• Deguang Wang conceived and designed the experiments, performed the experiments, analyzed the data, authored or reviewed drafts of the article, and approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

The Second Affiliated Hospital of Anhui Medical University granted Ethical approval to carry out the study within its facilities (Ethical Application Ref: YJ-YX2017-004).

Data Availability

The following information was supplied regarding data availability:

The raw measurements are available in the Supplementary File.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.13550#supplemental-information.

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