

Prognosis and risk factors of cardiac valve calcification in Chinese end-stage renal disease patients

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Research article

Keywords: end-stage renal disease, hemodialysis, cardiac valve calcification, vascular calcification

Posted Date: August 31st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-64057/v1>

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Abstract

Background

Cardiac valve calcification (CVC) was an important risk factor for cardiovascular complication. But the prevalence, clinical features and risk factors for CVC in ESRD patients were not fully clear at present. In this study, we explored the possible risk factors and clinical characteristics of CVC happened in Chinese ESRD patients.

Methods

We conducted a retrospective case-control study on 433 cases of ESRD patients who received maintenance dialysis (MHD) for at least 3 months in the First Affiliated Hospital of Chongqing Medical University from October 2014 to December 2015. 93 patients were confirmed to happen cardiac valve calcification (CVC) by echocardiography, and 200 patients without CVC in the same period as control, matched with age and gender. The demographic data, clinical characteristics, and laboratory parameters of the two groups were analyzed.

Results

Of 433 cases of ESRD patients, the average annual incidence of CVC was 30.3%. The most common calcification was in aortic valve, followed by mitral valve. Dialysis age ($P=0.006$, OR = 2.25), serum calcium ($P=0.046$, OR = 2.04), diabetes ($P=0.037$, OR = 1.81), and pulse pressure ($P<0.001$, OR = 3.22) were the risk factors of CVC, but serum albumin ($P=0.047$, OR = 0.54) was a protective factor for CVC. The ESRD patients with CVC were also more likely to suffer from arrhythmia, heart failure and coronary heart disease (CHD), and the all-cause mortality also increased significantly.

Conclusions

High prevalence of CVC happened in Chinese ESRD patients, which was a risk signal for severe atherosclerosis, more morbidity and mortality of cardiovascular events in ESRD patients. Dialysis age, serum calcium, diabetes, and pulse pressure were the independent risk factors of CVC in ESRD patients, while serum albumin was a protective factor.

Introduction

Epidemiological and clinical studies demonstrated that calcification in vascular or tissue was common, and cardiovascular complication was the leading cause of mortality in patients with end-stage renal disease (ESRD). Braun et al [1] reported that over one half adult hemodialysis patients had evidence of cardiac valve calcification (CVC), which happened more early and accelerated more dramatically[2].

Growing studies showed CVC was tightly associated with cardiovascular complication in ESRD patients. Moreover, cardiovascular complication significantly shorten the life span of the patients with ESRD[3], which was an important predictor for all-cause mortality and cardiovascular mortality[4].

The pathophysiology of CVC, though not entirely determined, is definitely multifactorial. In addition to conventional risk factors including age, gender, smoking, and primary disease such as hypertension or diabetes mellitus, ESRD patients have some unique risk factors for accelerated soft tissue calcification. In ESRD patients, metabolic disorders characterized by abnormal calcium and phosphorus levels may play a key role[4], CVC and vascular calcification are associated with clinical syndromes because of chronic kidney disease-mineral bone metabolic disorders (CKD-MBD). However, other factors which conduce to CVC formation are not fully determined.

The aim of the study was to investigate the epidemiological characteristics of CVC, the risk factors of CVC, the relationship between CVC and prognosis in Chinese ESRD patients.

Materials And Methods

Study Subjects

We conducted a retrospective cohort study and cross-sectional study that included 433 ESRD patients who had received more than 3 months of MHD in the dialysis center of the First Affiliated Hospital of Chongqing Medical University between October 2014 and December 2015. Exclusion criteria for the study included ESRD patients with hemodialysis vintage less than 3 month, aging more than 75 year-old, combination with congenital heart disease, infective endocarditis, rheumatic heart disease and these without complete data. 293 patients were rolled in this study in the end, including 160 male and 133 female, aged from 43 to 74, the average age was 64.0 ± 7.2 year-old. 93 ESRD patients confirmed CVC by echocardiography as CVC group. 200 ESRD patients without CVC, matching age and gender, were choosed as control group in the same period (Figure 1). The etiology of ESRD were shown in Figure 2, including 99 cases of primary gomerulonephritis, 96 cases of diabetes mellitus, 56 cases of primary hypertension, 13 cases of polycystic kidney, 12 cases of obstructive nephropathy, and 11 cases of interstitial nephritis (Figure 2). All patients underwent hemodialysis twice or three times a week. Conventional drug treatment covered antihypertensive agents including calcium channel blockers(CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and so on, anemiadrug including ferrous sulfate, and recombinant human erythropoietin (EPO) and phosphatebinders or alfacalcidol tablets.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and written informed consent was obtained from all the patients.

Clinical Data Collection

General information including age, gender, cigarette smoking, duration of hemodialysis, diabetes, hypertension and clinical manifestations including cardiovascular complication and cerebrovascular diseases (CVD) were collected. Systolic, diastolic and pulse pressures were measured before hemodialysis at 2-wk intervals were averaged for 3 months.

Pre-dialysis laboratory variables including hemoglobin, albumin, calcium, phosphorus, intact parathyroid hormone (iPTH), serum lipid and high sensitivity C-reactive protein (hs-CRP) were collected when the patients were rolled in the study. Calculating corrected serum calcium according to the serum calcium level. Calcium was corrected for serum albumin levels <40g/L as follows: Corrected calcium (mmol/L) = calcium (mmol/L) + 0.2 × [4 - serum albumin (g/dl)] [5].

Echocardiography

All subjects underwent echocardiography with Philips IE33 echocardiograph equipped with a S5-1 PureWave array probe (frequency 1.7/3.3MHz) to verified the presence of CVC. CVC was defined as bright echoes of more than 1 mm on one or more cusps of the aortic valve or mitral valve or mitral annulus [6].

Computer tomography scan

To determine vascular calcification, all ESRD patients underwent a chest and abdominal computer tomography (CT) scan on a SOMATOM Perspective scanner, few patients did the coronary artery CT. A calcified plaque in coronary artery and aorta was considered present if CT value was more than 130 scores [7].

Statistical analysis

Statistical analysis were performed using SPSS 21.0 statistical software. Data distribution was tested for normality using Kolmogorov-Smirnoff test. All numeric data with normal distribution was shown as means ± SD, analyzed by Student's *t*-test. Numeric variables with skew distribution were expressed as median (interquartile range), compared by Mann-Whitney *U* test. Categorical variables were expressed as percentages, analyzed by chi-square test. The relation between CVC and its associated complication was evaluated by using Spearman's correlation analysis. The risk factors associated with CVC were identified by using Binary logistic regression analysis. *P* < 0.05 was considered statistically significant.

Results

Prevalence of cardiac valve calcification in ESRD patients

In our single-center study, of all 433 ESRD patients, there were 30.3% ESRD patients with cardiac valve calcification (CVC). Of 93 ESRD patients with CVC, the most common was aortic valve calcification with prevalence of 60.2%, followed by mitral valve calcification with prevalence of 26.9%, and 12 (12.9%) ESRD patients occurred to both mitral and aortic valve calcification.

Basic clinical characteristics in ESRD patients with CVC

Of 293 ESRD patients enrolled in this study, 93 ESRD patients with CVC included 55 male and 38 female, aged from 44 to 74, the average age was 64.0 ± 7.0 year-old. 200 ESRD patients without CVC included 105 male and 95 female, aged from 43 to 74, the average age was 64.0 ± 7.0 year-old. Age and gender matched between the two groups.

We explored the risk factors for CVC in ESRD patients, and found no difference of smoking history between the two groups (Table 1). However, we found that the prevalence of diabetes mellitus and hypertension in ESRD patients were significantly higher in CVC patients than that of non-CVC (nCVC) patients, and the same as systolic pressure, diastolic pressure, pulse pressure and dialysis vintage ($P < 0.05$) (Table 1).

Table 1
The basic clinical characteristics in ESRD patient with CVC

	CVC(n = 93)	nCVC(n = 200)	P
age(y)	64.0 ± 7.0	64.0 ± 7.0	0.869
male	55(59.1%)	105(52.5%)	0.288
smoking	37(39.8%)	78(39.0%)	0.898
diabetes mellitus	53(57.0%)	89(44.5%)	0.046
hypertension(yr)	10(6,13)	8(3,11)	0.027
SP (mmHg)	160 ± 22	142 ± 20	< 0.001
DP (mmHg)	83 ± 14	73 ± 11	< 0.001
PP(mmHg)	77 ± 14	69 ± 17	< 0.001
dialysis duration(mo)	32(8,72)	19(7,43)	0.038
<i>SP, systolic pressure; DP, diastolic pressure; PP, pulse pressure</i>			

Nutrition and inflammation related factors in ESRD patients with CVC

At the same time, we analyzed the nutrition and inflammation related biochemical indicators in ESRD patients with CVC, the results showed that the hemoglobin, albumin, and HDL were significantly lower in ESRD patients with CVC ($P < 0.05$). However, no statistical differences of TC, LDL, TG, and hs-CRP were found between the two groups (Table 2).

Table 2
The variation of nutrition and related inflammation factors in ESRD patients

	CVC(n = 93)	nCVC(n = 200)	P
hemoglobin(g/L)	95.6 ± 25.3	104.4 ± 22.7	0.005
albumin (g/L)	36.4 ± 5.5	37.9 ± 5.2	0.027
total cholesterol(mmol/L)	3.63(2.97,4.26)	3.76(3.00,4.47)	0.318
LDL cholesterol(mmol/L)	2.25 ± 0.79	2.17 ± 0.89	0.407
HDL cholesterol (mmol/L)	1.01(0.82,1.21)	1.06(0.87,1.35)	0.044
TG(mmol/L)	1.16(0.90,1.57)	1.51(0.89,2.03)	0.442
hs-CRP(mg/L)	10.89(3.41,20.00)	10.28(2.15,20.00)	0.365
<i>TC, total cholesterol; LDL, low density lipoprotein; HDL, high-density lipoprotein;</i>			
<i>TG, triglycerides; hs-CRP, high sensitivity C-reactive protein</i>			

Mineral-bone metabolism associated parameters in ESRD patients with CVC

As alterations of mineral-bone metabolism were associated with increased risk of CVC. In this study, we analyzed the changes of serum mineral-bone metabolism associated parameters in ESRD patients with CVC, and found that corrected serum calcium, and calcium-phosphorus product in CVC were higher than that in nCVC patients ($P < 0.05$). No statistical differences in serum phosphorus and iPTH were found between the two groups (Table 3).

Table 3
Disorder of calcium-phosphorus metabolism in ESRD patients with CVC

	CVC(n = 93)	nCVC(n = 200)	P
calcium(mmol/L)	2.32 ± 0.27	2.23 ± 0.24	0.005
phosphorus(mmol/L)	1.76 ± 0.55	1.71 ± 0.70	0.461
calcium × phosphorus product(mmol/L)	4.03(2.92,4.92)	3.40(2.67,4.64)	0.029
iPTH(pg/ml)	268.8(109.9,307.2)	271.4(134.7,337.5)	0.277
<i>iPTH, intact parathyroid hormone</i>			

Risk factors for CVC in ESRD patients analyzed by Binary logistic regression

All factors with $P < 0.10$ at univariate analysis were included in a binary logistic regression model with backward selection. As shown in Table 4, longer dialysis vintage ($P = 0.006$, OR = 2.25), higher corrected serum calcium ($P = 0.046$, OR = 2.04), the prevalence of diabetes ($P = 0.037$, OR = 1.81), and higher pulse pressure ($P < 0.001$, OR = 3.22) were independent risk factors for CVC in ESRD patients, while higher serum albumin ($P = 0.047$, OR = 0.54) was protective factor.

Table 4
Independent risk factors associated with CVC in ESRD patients

	OR(95% CI)	P
dialysis duration	2.25(1.26,4.02)	0.006
calcium	2.04(1.01,4.12)	0.046
DM	1.81(1.04,3.15)	0.037
PP	3.22(1.85,5.59)	< 0.001
albumin	0.54(0.29,0.99)	0.047
<i>DM, diabetes mellitus; PP, pulse pressure</i>		

Table 4 Independent risk factors associated with CVC in ESRD patients

Artery calcification in ESRD patients with CVC

Vascular calcification was a frequent complication in ESRD patients. However, the relationship between vascular calcification and CVC was still unclear. In this article, we found that there were a great number of ESRD patients with different degree calcification in aortic, and coronary artery (Fig. 3). Moreover, in CVC patients, the incidence of aortic artery calcification, coronary artery calcification, and both aortic and coronary artery calcification was higher than that in nCVC patients ($P < 0.001$) (Table 5). The incidence of aortic calcification in ESRD patients with CVC was nearly 1.44 times as much as nCVC, and the prevalence of coronary artery calcification was 1.74 times, similarly, both aortic and coronary artery calcification was 1.87 times.

Table 5
Vascular calcification of ESRD patients with and without CVC

	CVC(n = 90)	nCVC(n = 192)	P
aortic calcification	77(85.6%)	114(59.3%)	< 0.001
coronary alcification	59(65.1%)	72(37.4%)	< 0.001
both aortic and coronary calcification	50(55.6%)	57(29.7%)	< 0.001

Cardial and cerebrovascular complications in ESRD patients with CVC

We further analyzed the relationship between cardiovascular complications and CVC. We found that the prevalence of cardiac-cerebrovascular complications increased significantly in ESRD patients with CVC. The incidence of arrhythmia, heart failure, and coronary heart disease (CHD) in CVC patients was 1.8, 2.5, and 1.4 times compared with nCVC patients, respectively ($P < 0.05$), and atrial arrhythmia was the most common arrhythmia. However, no difference of cerebrovascular complications (CVD) was found between the two groups. The risk of all-cause mortality in CVC group was 3.7 times higher than that of nCVC group ($P < 0.05$). Of 16 died patients, 11 died of cardiac-cerebrovascular complications, 5 died of severe infection during the followed-up from 3 months to 10 years (Table 6).

Table 6
Cardial-cerebrovascular complications of ESRD patients with and without CVC

	CVC (n = 93)	nCVC(n = 200)	P
arrhythmia	24(25.8%)	29(14.5%)	0.019
heart failure	16(17.2%)	14(7.0%)	0.003
CHD	43(46.2%)	65(32.5%)	0.023
CVD	19(20.4%)	37(18.5%)	0.696
all-cause mortality	11(11.8%)	5(2.5%)	< 0.001
<i>CHD, coronary heart disease; CVD, cerebrovascular disease</i>			

We further used Spearman's correlation analysis to determine the relation between CVC and cardiovascular complications in ESRD patients. Our results showed that CVC in ESRD patients were obviously associated with aortic calcification, coronary artery calcification, heart failure, and all-cause mortality ($P < 0.05$). However, no relationship between CVC and arrhythmia or CHD was found (Table 7).

Table 7
The relation between CVC and cardiovascular complication

	γ	P
aortic calcification	0.261	< 0.001
aortic and coronary calcification	0.247	< 0.001
coronary alcification	0.248	< 0.001
arrhythmia	0.071	0.229
heart failure	0.157	0.007
CHD	0.019	0.748
all-cause mortality	0.191	< 0.001
<i>CHD, coronary heart disease</i>		

Discussion

CVC was common complication in ESRD patients

Vascular or tissue calcification is a highly prevalent condition at all stages of chronic kidney disease (CKD), and increasingly recognized to be a common complication in ESRD patients, which represents an important part of the CKD-MBD complex. Documents[1, 8]reported that two thirds of the adult hemodialysis patients had electron beam computed tomographic evidence of coronary artery calcification (CAC) and that over half had cardiac valve calcification. Consistent with the report of literature, in this study, the average annual incidence of CVC was 30.3% in our dialysis center, and aortic valve calcification was the most frequent site, accounting for 60.2%. This was followed by mitral valve calcification, with prevalence of 26.9%, and 12.9% ESRD patients had both mitral and aortic valve calcification.

Risk factors for CVC in ESRD patients

It has been thought that valve calcification and atherosclerotic calcification have certain common factors and a similar pathogenesis. The traditional risk factors for CVC included hypertension[11]and diabetes. In this study, firstly, we found that ESRD patients with CVC had a longer history of hypertension and a higher systolic pressure, diastolic pressure and pulse pressure, and regression analysis confirmed pulse pressure was the independent risk factor for CVC. Study[12]had found that the stability of hemodynamics was very important to maintain normal cardiac valve function. In ESRD patients, the way of hemodialysis, ultrafiltration volume, and blood flow during hemodialysis could make blood pressure fluctuation and hemodynamic abnormality, which may lead to dysfunction of endothelial cells and stromal cells of cardiac valve and inflammatory, remodeling and eventually developed CVC. Furthermore, increased pulse

pressure caused by decreased artery diastolic and compliance after vascular calcification, was an independent risk factor for CVC in turn.

Much study had reported that vascular calcification was more serious in the ESRD patients with diabetes, and impaired fasting glucose and diabetes could be used as predictors of vascular calcification in ESRD patients[13]. In this study, we also found a higher prevalence of CVC in ESRD patients with diabetes. High blood glucose and hyperinsulinemia, inflammatory state, glycosylation product accumulation, and endocrine disorders of diabetes, and so on, all could damage endothelial cells and stromal cells of cardiac valve, eventually led to CVC[14].

It was important to find that even though there were certain common factors to the pathogenesis of cardiac valve calcification and atherosclerotic calcification, however, the pathogenesis in the ESRD patients was likely different from the calcification observed in the general population. For example, the calcification score in ESRD patients was not only substantially higher than age-matched and gender-matched patients with coronary artery disease but also progressed rapidly within short period. Furthermore, When CVC was initially present, the speed, and the degree of calcification increased as age or dialysis vintage[15]. In this study, we also confirmed dialysis vintage was an independent risk factor in ESRD patients with CVC. Arjona Barrionuevo et al[16] had confirmed CVC and vascular calcification increased as dialysis vintage in ESRD patients including diabetic nephropathy. Goldsmith et al[17] observed 38 MHD patients with 10 ~ 25 years, vascular calcification prevalence increased from 39% at dialysis onset to 92% after the average dialysis vintage for 16 years, with a mean onset 9.7 years after initiating dialysis.

ESRD patients receiving MHD were shown to be a MICA syndrome including malnutrition, inflammation, atherosclerosis, and calcification, and serum albumin reflected the nutritional status in ESRD patients[18]. However, the relationship between nutritional conditions, inflammation and CVC in ESRD patients was still unclear. In this study, we also found that ESRD patients has a lower level of hemoglobin and serum albumin, with increased vascular calcification, which was consistent with the prior reports[18]. Interestingly, although serum lipid played an important role in the process of cardiac-cerebrovascular disease development, our data showed no significant difference of serum TC, LDL, and TG was found between in ESRD patients with and without CVC. In fact, in patients with ESRD, peripheral serum lipid levels did not reflect lipid deposition in the tissue, and the severity of arteriosclerosis [19]. It had been reported that lipid adjusting drugs didn't delay the process of vascular calcification effectively in ESRD patients, reduced fatality rate because of cardiac-cerebrovascular diseases[19, 20]. However, we found that much lower peripheral serum HDL in ESRD patients with CVC, indicating HDL may be a protect factor for CVC. As we all know, HDL may reduce cholesterol deposition, resist atherosclerosis, to protect artery[18, 21]. This finding was similar to the report of Japan hemodialysis population, but in contrast to the western hemodialysis population[22], the mechanism may be associated with generous background but need to be explored. Otherwise, although a state of chronic inflammation existed in ESRD patients received MHD because of biocompatibility in dialyser and dialysis fluid[22], no statistical difference in hs-CRP between the two groups, showing that Inflammation may not be a independent factor but a synergy

with malnutrition for CVC in ESRD patients [18]. Further detection of inflammatory medium may be need to confirm the role of inflammatory in CVC in ESRD patients.

Calcium-phosphate metabolic disorders were most common complication in ESRD patients, and also be thought as an unique nontraditional risk factor of cardiac-cerebrovascular calcification. Hypocalcemia and/or hyperphosphatemia could stimulate excessive PTH secretion, caused secondary hyperparathyroidism, metabolic bone disease, artery, and other tissue metastatic calcification, eventually formed a vicious circle, increased the mortality in ESRD patients[23]. Studies had found that high phosphorus, and calcium-phosphorus product were the independent risk factors of deaths in ESRD patients[24]. But the relationship between calcium, phosphorus metabolism disorders and CVC in Chinese ESRD patients was still to be further study. In this study, we found that adjusted serum calcium and the calcium-phosphorus product in CVC patients were significantly elevated compared with nCVC group, while PTH significantly decreased, and further logistic regression analysis showed that high adjusted serum calcium was an independent risk factor for CVC. Long-term exposure to high calcium-phosphorus environment could lead to cell phenotypic change, osteogenesis cell form, osteogenesis transcription factors mediate osteogenesis, which was similar to the formation of bone [25, 26], eventually lead to cardiac valve, artery and the whole body metastatic calcification. In ESRD patients, low PTH secondary from hypercalcemia, caused decreased bone calcification because of the reduced osteoblast activity and more serious metastatic calcification resulting from excess serum calcium. Oddly, this study didn't find CVC was directly related with serum phosphorus, which needed to expand the sample size to further confirmed.

The predicted value of CVC in cardiac-cerebrovascular complications in ESRD patients

Cardiac-cerebrovascular events were the most important cause of death in ESRD patients, which was due to the early-onset and progressive vascular calcification in ESRD patients. Research had found that any part of the artery wall calcification increased 3 ~ 4 times risk of death, and cardiovascular event[9]. However, in ESRD patients, the relation between CVC and artery calcification remained undetermined. In this study, ESRD patients with CVC had more overt vascular calcification, reached 90.1%, and the prevalence of aortic or coronary artery calcification in CVC group was 1.44 ~ 1.87 times more than that of nCVC group. Furthermore, our data showed that ESRD patients with CVC had a higher prevalence of arrhythmia, heart failure, CHD, i.e. 1.4–2.5 times compared with nCVC group, and the risk of all-cause mortality was 3.7 times higher than that of nCVC. Spearman's correlation analysis further demonstrated that CVC was relevant for the aortic calcification, coronary artery calcification, heart failure, and all-cause mortality. Therefore, CVC may be a marker of vascular calcification and, cardiovascular events. Calcified cardiac valve reduced itself compliance, led to sclerosis or stenosis, decreased ventricular outflow, finally contributed to ventricular hypertrophy, resulting in myocardial ischemia, arrhythmia, heart failure, and even sudden death, which was particularly significant in those with both aortic and mitral valve calcification[10]. Similarly, some documents[3, 4] has indicated that CVC itself was a superior predictor of clinical outcomes in ESRD patients and closely associated with an increased risk of cardiovascular

events and all-cause mortality. Taken together, all of these findings indicated that CVC may reflect a poor clinical prognosis in ESRD patients.

In summary, in this retrospective case-control study, it showed that CVC was a common complication in ESRD patients, and a danger signal for severe atherosclerosis and cardiovascular events in ESRD patients. Diabetes, increased pulse pressure, longer dialysis vintage, and higher adjusted serum calcium were independent risk factors for CVC in ESRD patients, while higher serum albumin was a protective factor.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University .Written informed consent was obtained from all the patients, and all patients were identified by numbers, not their real names.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no competing interests.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

These studies were supported by grant from National Natural Science Foundation of China (No. 81370816) and grant from Natural Science Foundation of Chongqing Science and Technology Commission of China (No.cstc2012jjA10136) and Chongqing Municipal Health Bureau of China (No. 2011-1-016) to X. Du, National Natural Science Foundation of China (No. 81202318) to X. Chen.

Authors' contributions

All authors reviewed the final version and approved the content. JQX performed data collection and helped with the data interpretation and manuscript writing. XMC helped with the design of the study and

manuscript writing. CTL helped with the collection of biological samples. XGD designed the experiment, performed the literature search, and was responsible for manuscript writing and data analysis and interpretation.

Acknowledgement

The authors are very grateful to the team from Department of Nephrology and Emergency Department of the First Affiliated Hospital of Chongqing Medical University, and all those who have provided support and help for this study.

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Figures

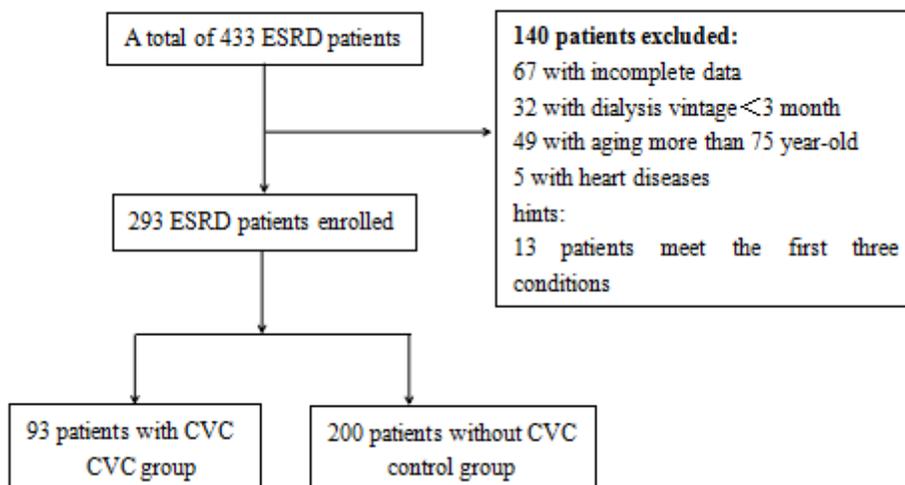


Figure 1

Flow chart of study design

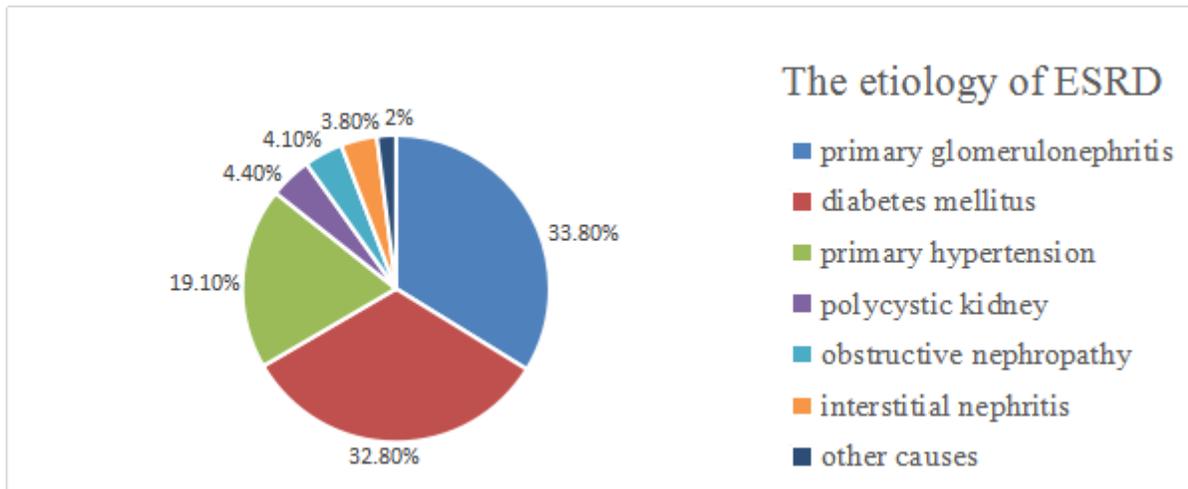


Figure 2

Etiology of end-stage kidney disease

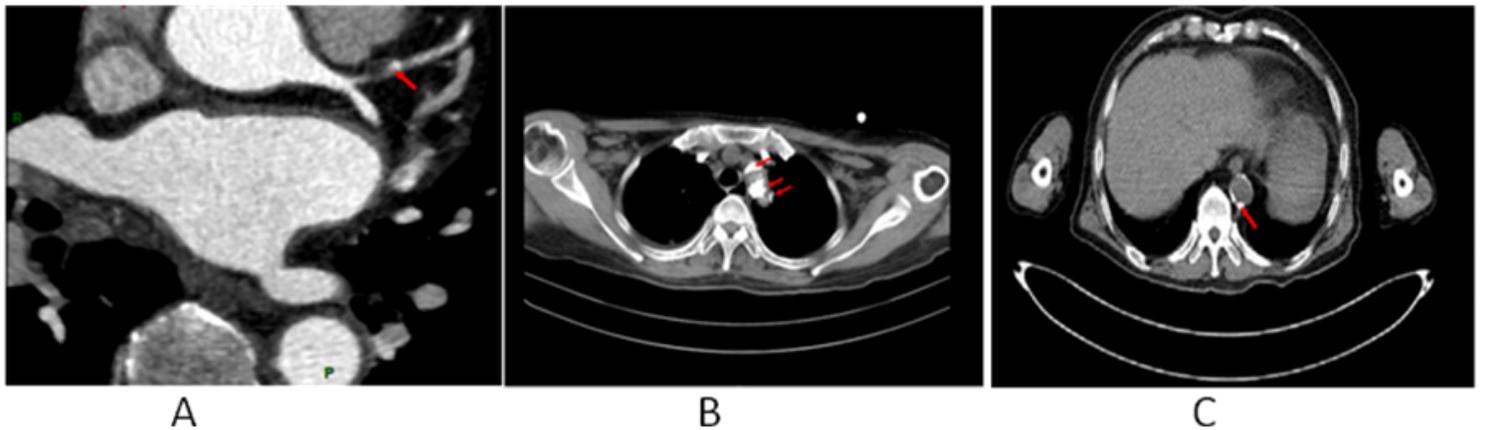


Figure 3

Calcification in the coronary artery and aorta in ESRD patients. Representative calcification in the left anterior descending branch of coronary artery (red arrow) (A), thoracic aorta (red arrow)(B)and abdominal aorta (red arrow)(C).