

Prognosis of Heart Valve Calcification on Cardiovascular Events in Hemodialysis Patients without Central Venous Catheters

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Keywords

All-cause mortality · Aortic valve calcification · Cardiovascular events · Heart valvular calcification · Hemodialysis · Mitral valve calcification

Abstract

Introduction: Heart valvular calcification (HVC) is an important predictor of cardiovascular events (CEs) and all-cause mortality in dialysis patients. Patients in the early stage of dialysis or those with central venous catheters (CVC) are also at high risk of cardiovascular and all-cause mortality. It could be a confounding factor for the prognosis of HVC on CE. **Methods:** From March 2017 to April 2022, the prognosis of HVC on CE and all-cause mortality was studied retrospectively in 158 hemodialysis (HD) patients who used arteriovenous fistulas or arteriovenous grafts as vascular access and entered HD for more than 12 months. **Results:** Out of 158 patients, 70 (44.3%) were diagnosed with HVC via echocardiography. A total of 180 CEs occurred during follow-up. Among them, acute heart failure accounted for 62.66%, and its prevalence was significantly higher in the HVC group than that in the non-HVC group ($p < 0.0001$). The cumulative incidence of CE-free survival in the HVC group

was significantly lower than that in the non-HVC group ($p = 0.030$). Only 11 patients died, and there was no significant difference in all-cause mortality between the two groups ($p = 0.560$). Multivariate COX regression analyses showed that HD vintage, mitral valve calcification, and aortic valve regurgitation (AR)/aortic valve stenosis (AS) but not aortic valve calcification were risk factors for CE ($p < 0.05$). **Conclusion:** After excluding the factors of the early stage of HD and CVC, HVC remained a predictor of adverse CE in HD patients.

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Published by S. Karger AG, Basel

Introduction

With the prolongation of dialysis vintage, the risk of heart valvular calcification (HVC) in patients on dialysis is significantly higher than that in the general population [1, 2]. HVC is a form of systemic vascular calcification, and its extent and progression often indicate a poor prognosis in dialysis patients [3–5]. There have been many studies on the relationship between vascular

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calcification, such as that affecting the abdominal aorta, coronary artery, carotid artery, and peripheral artery [6, 7], and adverse cardiovascular event (CE) or all-cause mortality in dialysis patients. Vascular calcification has become a non-traditional risk factor for cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) [8].

However, most previous studies enrolled patients without distinguishing whether they had been on dialysis for over 12 months. Cardiovascular mortality and all-cause mortality were highest among patients in the early stage of dialysis [9, 10]. After 1 year of regular dialysis, the adverse factors, such as volume overload, uremic toxins, and uncontrolled hypertension or hyperglycemia, could be treated. CVD, including heart valvular disease, may also be improved. Adverse CE, cardiovascular mortality, and all-cause mortality may be decreased significantly. Different routes of vascular access also affect patients' clinical outcomes; the all-cause mortality in patients with central venous catheter (CVC) is significantly higher than that in patients with arteriovenous fistulas (AVFs) or arteriovenous grafts (AVGs) [11, 12]. Additionally, there is a choice bias in vascular access [13]. Patients who choose CVC have more underlying diseases and worse vascular conditions. These factors may interfere with the assessment of HVC on CE and all-cause mortality in hemodialysis (HD) patients. To eliminate the above adverse factors, patients with regular HD for over 1 year and with AVFs or AVGs as vascular access were selected in our study to evaluate the prognosis of HVC on CE and all-cause mortality.

Materials and Methods

Study Population

This was a retrospective cohort study performed at the Department of Nephrology, Wuhan Central Hospital, based on a previous vascular access study conducted over a 5-year period (March 1, 2017 to April 30, 2022). The deadline for follow-up was June 31, 2022. Our inclusion criteria were as follows: (1) age 18–80 years, (2) HD vintage ≥ 12 months, (3) functional AVF/AVG as vascular access, and (4) the provision of written informed consent to participate in the study. Our exclusion criteria were as follows: (1) severe acute complications such as acute myocardial infarction and chronic obstructive pulmonary disease (COPD); (2) gastrointestinal hemorrhage, cerebral hemorrhage, etc.; (3) previous renal transplantation; (4) previous conversion from peritoneal dialysis (PD) to HD; (5) CVC as vascular access; (6) autoimmune disease (e.g., systemic lupus erythematosus, rheumatic heart disease); and (7) pregnancy.

Laboratory Examination

Laboratory data, including serum concentrations of albumin, calcium, phosphorus, intact parathyroid hormone (iPTH), triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL), and high-sensitivity C-reactive protein (hs-CRP), were collected. All patients were examined at baseline and at least every 3–6 months (as required by the local HD Quality Control Committee). The serum calcium level was adjusted for the serum albumin concentration using the formula corrected calcium = (total measured calcium + $0.8 \times [4.0 - \text{albumin in g/dL}]$). A time-averaged value was given as values averaged over the follow-up period and was used in the COX analysis.

Echocardiography

HVC echocardiography was performed using the IE Elite echocardiograph and the S5-1 probe (1–5 MHz frequency range, Philips Medical Systems, Bothell, WA, USA) to evaluate the condition of the heart valves, and the character of calcification, left ventricular ejection fraction, atrioventricular diameter, interventricular septal thickness, and pulmonary arterial pressure (PASP) were measured. HVC is defined as the presence of one or more bright echoes of the main aortic valve (AV) or mitral valve (MV) exceeding the 1 mm threshold [14].

Cardiovascular Events

CEs were defined as stroke, transient ischemic attack, angina, acute myocardial infarction, sudden cardiac arrest or sudden death, acute heart failure, and severe arrhythmia (requiring hospitalization or lasting for more than 24 h). The endpoints of follow-up were death and CEs. During follow-up, CEs and causes of death were recorded, and renal transplant patients or those who were converted to PD or CVC were recorded as canceled. The families of patients who died outside the hospital were interviewed by telephone to find out the possible causes of their deaths. When patients had multiple CEs, the time of the first event was used for the survival analysis.

Statistical Analysis

All data were processed using the SPSS 23.0 statistical software. Frequencies and percentages were reported for categorical data, while mean values with standard deviations were reported for normally distributed continuous data, and median values with ranges or interquartile ranges were reported for skewed continuous data. Continuous data were compared using the *t* test or Mann-Whitney U test, and categorical data were compared using the χ^2 test. The relationship between the degree of valvular disease and the number of CE episodes was tested via Spearman's correlation analysis. The relationship between CVC, CE, and all-cause mortality was determined by the Kaplan-Meier survival analysis (log-rank) and Cox regression analysis. The threshold for statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

A total of 158 patients (98 males and 60 females) were followed up for a median period of 49 months

Table 1. Baseline demographic and clinical characteristics of HD patients with or without HVC

Characteristics	HVC (n = 70)	Non-HVC (n = 88)	p value/ χ^2
Age, years	64.21±10.20	54.82±13.12	0.0002
Gender (M/F)	47/23	51/37	0.126
HD vintage ^a	60.00 (29–74)	42.00 (20–69)	0.069
SBP, mm Hg	150.81±23.07	143.84±21.72	0.099
DBP, mm Hg	80.82±13.23	79.91±14.51	0.732
BMI	22.21±2.32	21.90±2.10	0.994
Smoking history n (%)	35 (50.00)	39 (43.18)	0.425
Comorbidities n (%)			
Ischemic cardiopathy	33 (47.14)	37 (42.05)	0.587
Stroke	8 (11.43)	8 (9.09)	0.629
COPD	6 (8.57)	5 (5.68)	0.281
Peripheral arterial disease	4 (5.71)	1 (1.14)	0.171
Baseline disease n (%)			
Diabetes	34 (48.57)	23 (26.14)	0.003
Hypertension	60 (85.71)	71 (80.68)	0.763
CGN	14 (20)	26 (29.55)	0.170
Kidney stones ^b n (%)	4 (5.71)	5 (5.68)	0.993
ADPKD ^b	1 (1.43)	5 (5.68)	0.228
Others ^b	5 (7.14)	6 (6.82)	1.0
LVEF, %	64.01±6.13	64.55±3.54	0.854
PASP, mm Hg	32.16±9.30	29.45±10.54	0.075
>30	37	39	0.286
≤30	33	49	
Ultrafiltration	3.05±0.82	2.72±0.69	0.009
Antihypertensive medications, n (%)			
Calcium channel blockers	51 (72.86)	70 (79.55)	0.713
RASi	50 (71.42)	73 (82.95)	0.174
Beta blockers	31 (44.29)	39 (44.32)	0.996
Sacubitril and valsartan	18 (25.71)	35 (39.77)	0.063
Medicines for CKD-MBD, n (%)			
VDRA	53 (75.71)	70 (79.55)	0.565
Calcimimetics	18 (25.71))	32 (36.36)	0.153
Phosphate binders	64 (91.43)	80 (91.91)	0.909
Laboratory examinations			
Albumin, g/L	39.67±4.21	40.83±3.59	0.066
Calcium, mmol/L	2.32±0.18	2.29±0.18	0.268
Phosphorus, mmol/L	1.84±0.56	1.79±0.47	0.575
PTH, pg/mL	303.62±123.21	274.45±80.56	0.082
Hb, g/L	108.56±14.75	107.24±16.79	0.611
TC, mmol/L	3.85±0.94	3.69±1.08	0.321
Triglycerides, mmol/L ^a	1.52±1.16	1.58±1.45	0.419
LDL, mmol/L	2.24±0.70	2.07±0.80	0.057
HDL, mmol/L	1.04±0.35	1.04±0.37	0.913
hs-CRP, mg/L ^a	3.00±2.91	2.53±2.81	0.050
≥3	27	27	0.299
<3	43	61	
Valve disease (moderate to severe)			0.976
MV ^b	3	4	1.0
AV	6	5	0.463
TV	6	8	0.909

HD, hemodialysis; HVC, heart valve calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial pressure; RASi, renin-angiotensin-aldosterone system inhibitor; PTH, parathyroid hormone; Hb, hemoglobin; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; MV, mitral valve; AV, aortic valve; TV, tricuspid valve; VDRA, vitamin D receptor agonists; CKD-MBD, chronic kidney disease-mineral bone disorder; COPD, chronic obstructive pulmonary disease; ADPKD, autosomal dominant polycystic kidney disease; CGN, chronic glomerulonephritis; TC, total cholesterol. ^aMann-Whitney U test. ^bFisher's exact probability.

Table 2. Comparison of all-cause mortality and CE between the HVC and the non-HVC patients

	HVC (n = 70)	Non-HVC (n = 88)	p value
All-cause mortality	6	5	0.560
Angina pectoris or AMI	13	8	0.063
AHF	66	46	0.0001
Stroke	8	12	0.711
Others (peripheral arterial disease, arrhythmia for hospitalization, or cardiac stroke)	10	7	0.193

CE, cardiovascular events; HVC, heart valve calcification; AMI, acute myocardial infarction; AHF, acute heart failure.

Table 3. Relationship between heart valve disease and incident times of CE

	0 (n = 73)	1–2 (n = 57)	3~ (n = 28)	χ^2	p value
MVC	9	11	8	4.157	0.125
AVC	22	25	16	6.044	0.049
MR/MS	17	19	9	1.928	0.381
AR/AS	13	21	15	14.403	0.001
TR	33	33	19	5.535	0.063

CE, cardiovascular events; MVC, mitral valve calcification; AVC, aortic valve calcification; MR, mitral valve regurgitation; MS, mitral valve stenosis; AR, aortic valve regurgitation; AS, aortic valve stenosis; TR, tricuspid valve regurgitation.

(interquartile range 24, 70). The HVC group included 62 aortic valve calcification (AVC), 8 mitral valve calcification (MVC), and 21 overlapping calcifications (both AVC and MVC). Age, diabetes mellitus, and the ultrafiltration volume during a single dialysis session in the HVC group were significantly higher than those in the non-HVC group ($p < 0.05$). The hs-CRP ($p = 0.05$), PTH ($p = 0.082$), and LDL ($p = 0.057$) levels seemed higher while the Alb level seemed lower ($p = 0.066$) in the HVC group than in the non-HVC group; however, none of the differences were statistically significant. There was no statistical difference in other indexes, such as smoking history, comorbidities, dialysis vintage, PASP, blood pressure, body mass index, anti-hypertensive medicines, medicines for CKD-MBD, laboratory examinations, and heart valve disease (moderate to severe) (Table 1).

Comparison of CE and All-Cause Mortality between HVC and Non-HVC Patients

During follow-up, acute heart failure accounted for 62.66% of CE, and it was significantly higher in the HVC group than in the non-HVC group ($p < 0.0001$). There was no significant difference in other CEs ($p >$

0.05) between the two groups. Eleven patients died during follow-up, and there was no significant difference in all-cause mortality between the two groups ($p = 0.560$) (Table 2).

Relationship between HVC and CE

During follow-up, the rate of CE was significantly higher among patients with AVC and AR/AS ($p < 0.05$). Patients with tricuspid regurgitation (TR) seemed to have more CE than those without TR; however, the difference was not statistically significant ($p = 0.063$). There was mild correlation between CE and AR/AS ($r = 0.311$, $p < 0.0001$) and TR ($r = 0.221$, $p < 0.005$) (Table 3).

Survival Analysis of HVC, CE, and All-Cause Mortality

Kaplan-Meier survival analyses revealed that the cumulative incidence of CE-free survival in the HVC group was significantly lower than that in the non-HVC group ($p = 0.030$). The findings were similar in MVC ($p = 0.036$) and AVC ($p = 0.006$). There was no significant difference in all-cause mortality between the two groups ($p = 0.377$), shown in Figure 1.

Cox Regression for Risk Factors of CE in HD Patients

Traditional risk factors, such as age (HR = 1.018, 95% CI: 1.005–1.032, $p = 0.009$), sex (HR = 0.518, 95% CI: 0.301–0.891, $p = 0.017$), diabetes (HR = 1.729, 95% CI: 1.051–2.847, $p = 0.031$), and smoking history (HR = 2.880, 95% CI: 1.296–6.399, $p = 0.009$), showed significant associations with CE ($p < 0.05$). Non-traditional factors, including dialysis vintage (HR = 0.978, 95% CI: 0.970–0.987, $p < 0.0001$), MVC (HR = 2.09, 95% CI: 1.120–3.898, $p = 0.021$), AR/AS (HR = 1.727, 95% CI: 1.067–2.794, $p = 0.026$), and hs-CRP (HR = 2.479, 95% CI: 1.147–5.359, $p = 0.021$), were identified as risk factors for CE, but AVC, PTH, P, and LDL were not ($p > 0.05$) (Table 4).

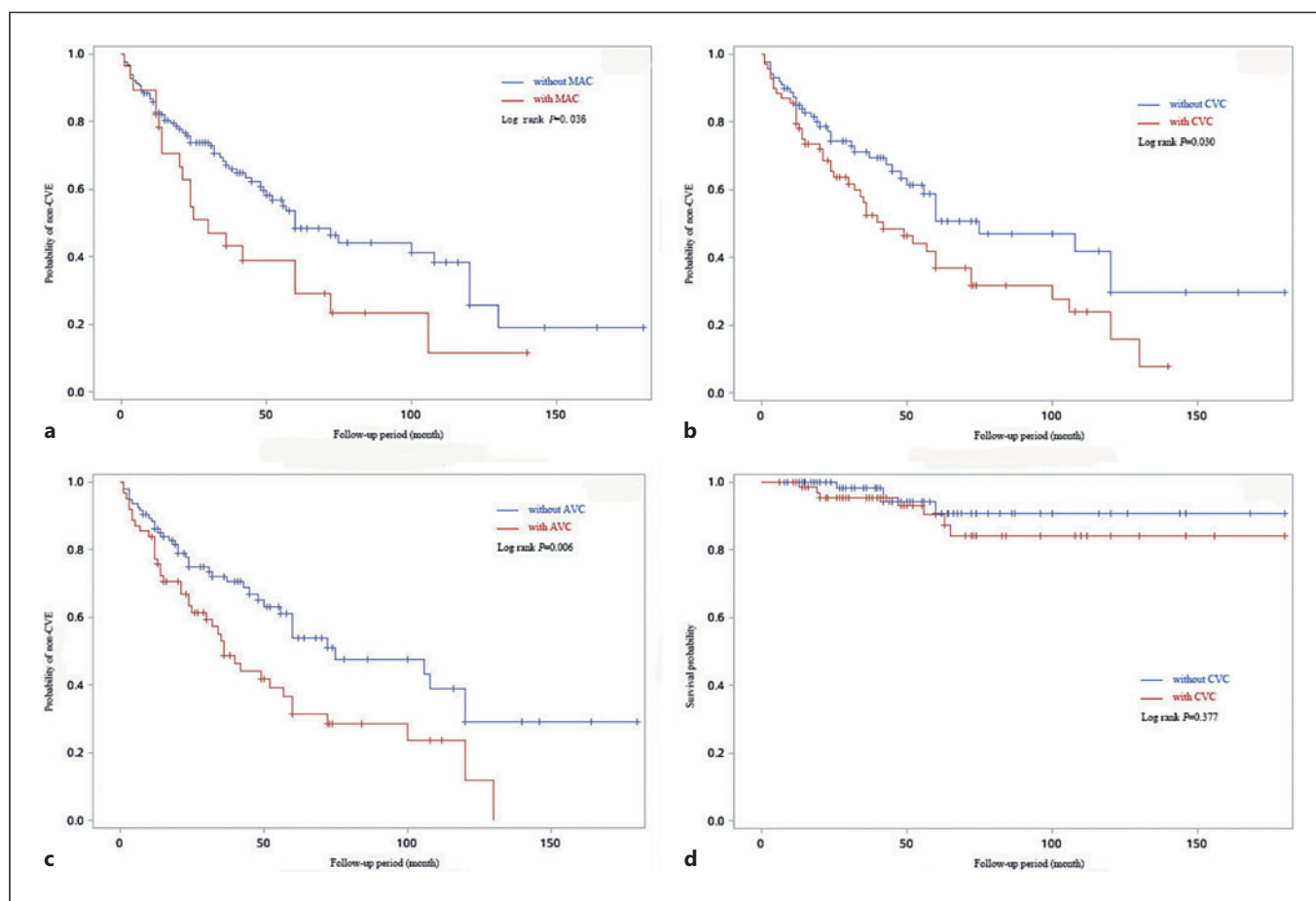


Fig. 1. Kaplan-Meier survival curves for CE and all-cause mortality in HD patients with or without HVC. **a** Kaplan-Meier survival curves for CE in HD patients with MVC and without MVC. **b** Kaplan-Meier survival curves for CE in HD patients with and without AVC. **c** Kaplan-Meier survival curves for CE in HD

patients with HVC and without HVC. **d** Kaplan-Meier survival curves for all-cause mortality in HD patients with HVC and without HVC. CE, cardiovascular events; HD, hemodialysis; HVC, heart valve calcification; MVC, mitral valve calcification; AVC, aortic valve calcification.

Discussion

Adverse CEs are the leading cause of death in patients with end-stage renal disease [15, 16]. In dialysis patients, vascular calcifications have become a non-traditional cardiovascular risk factor in addition to traditional cardiovascular risk factors such as hypertension and diabetes [17–19]. HVC and vascular calcifications are both manifestations of the development of cardiovascular disease [1, 3–5, 20]. Approximately 42.5% of HD patients did not have HVC when they began dialysis; however, with dialysis continuing, the proportion of HVC was 25–75% [21–23]. In this study, the median HD vintage was more than 40 months, and the proportion of HVC was 44.3%. The proportions of diabetes, age, and dialysis vintage in the HVC group were significantly higher than those in the non-HVC group.

Patients with CVC and HD vintages of less than 1 year were not included in our study. Baseline characteristics such as blood pressure, left ventricular ejection fraction, PASP, hemoglobin, blood calcium, phosphorus, Alb, and PTH were well controlled. It means prejudice factors such as severe anemia, malnutrition, catheter-related complications, and moderate and severe pulmonary hypertension (PH) were controlled. Therefore, during the follow-up period, only 11 patients died, and the all-cause mortality did not differ significantly between the two groups. It is suggested that after excluding adverse factors in the early stage of dialysis and CVC, the effect of HVC on all-cause mortality was not significant during the median of 49 months of follow-up. If the observation time was longer or the sample size was increased, there could have been differences.

Table 4. Multivariate Cox regression analysis for risk factors of CE

	Univariate			Multivariate		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age, year	1.012	1.003–1.020	0.007	1.018	1.005–1.032	0.009
Gender (M/F)	0.587	0.367–0.937	0.026	0.518	0.301–0.891	0.017
DM	2.437	1.543–3.851	0.009	1.729	1.051–2.847	0.031
HD vintage, months	0.979	0.970–0.987	<0.0001	0.978	0.968–0.987	<0.0001
Smoking history	2.750	1.741–4.342	<0.0001	2.880	1.296–6.399	0.009
Ischemic disease	2.595	1.638–4.11	<0.0001	1.228	0.484–3.116	0.666
Albumin, g/L	0.933	0.883–0.987	0.015	0.969	0.894–1.05	0.440
hs-CRP, mg/L	3.780	1.97–7.254	<0.0001	2.479	1.147–5.359	0.021
LDL, mmol/L	1.191	0.882–1.609	0.254	0.953	0.663–1.37	0.796
PTH, pg/L	0.999	0.998–1	0.084	1	0.998–1.001	0.750
Phosphorus, mmol/L	0.716	0.417–1.229	0.226	1.062	0.526–2.145	0.866
PASP, mm Hg	1.112	0.579–3.214	0.217	1.063	0.425–2.247	0.303
MR/MS	1.477	0.915–2.385	0.110	1.028	0.574–1.841	0.926
MVC	1.703	1.024–2.834	0.040	2.309	1.217–4.381	0.011
AR/AS	1.767	1.125–2.774	0.013	1.64	0.981–2.74	0.039
AVC	1.841	1.182–2.868	0.007	1.419	0.807–2.493	0.224
TR	1.178	0.749–1.854	0.477	1.043	0.593–1.848	0.871

CE, cardiovascular events; HR, hazard ratio; F, female; M, male; DM, diabetes mellitus; HD, hemodialysis; MVC, mitral valve calcification; AVC, aortic valve calcification; MR, mitral valve regurgitation; MS, mitral valve stenosis; AR, aortic valve regurgitation; AS, aortic valve stenosis; TR, tricuspid valve regurgitation; PTH, parathyroid hormone; LDL, low-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein.

HVC can accelerate the process of heart valve stenosis or regurgitation. The AV and MV are more often involved. Previous studies suggested that AVC developed in 46 months (3–120 months) and MVC developed in 50 months (13–127) in de novo HD patients [6]. In this study, the dialysis vintage was 60 months in the HVC group. Although the proportion of HVC was as high as 44.3%, those of moderate or severe heart valvular diseases were not high, being only 4.43% in MV and 6.96% in AV. Although HVC is a risk factor for adverse CEs and cardiovascular mortality [3], different studies have different predictions. Some studies suggested that AVC and MVC are associated with adverse CEs, while some reported that both AVC and MVC are associated with higher rates of adverse CEs [6, 24, 25]. The cumulative incidence of CE-free survival in the HVC group was significantly lower than that in the non-HVC group. AVC and AR/AS were related to the number of CE episodes in the subgroup. The relationship between moderate and severe TV regurgitation and CE was not significant because it is reversible when the preload and afterload of the heart are improved.

In the univariate COX analysis, MVC and AVC were identified as independent risk factors for CE in HD

patients; however, AVC was no longer an independent risk factor in the multivariate analysis. There may be several explanations for this observation; first, all patients enrolled in this study were with AVFs or AVGs, and dialysis vintage was more than 1 year. Predilections for a particular form of vascular access and the early stage of HD were avoided. Second, previous studies have classified the localization of HVC, and it is suggested that aortic leaflet calcification but not the aortic annulus is related to aortic sclerosis and coronary atherosclerosis [25]. The blood flow velocity at AV is faster than that at MV, and endothelial cell injuries and inflammatory reactions may be the main risk factors for AVC. In this study, the proportion of AVC was higher than that of MVC. However, there was no distinction between leaflets and annular calcification, and the proportion of moderate-to-severe AR/AS was only 6.96%. These may affect the prognosis of AVC on CE in HD patients. Third, if the sample size is further enlarged or the follow-up period is increased, for example, to 10 years, the results could be different.

The incidence of PH in patients with MHD is approximately 25–49%. PH leads to an increased risk of all-cause mortality [26, 27]. In this paper, PASP >30 mm Hg

was found in 48.10% of HD patients; however, there was no statistically significant difference between the two groups, and most of the PASP values were mildly elevated, as there were 18 (11.39%) patients with PASP >45 mm Hg and only 2 (1.27%) with PASP >60 mm Hg. In the COX analysis, PASP was not an independent risk factor for CEs. In addition, uremic toxins, oxidative stress, and microinflammatory states in HD have altered traditional CV risk factors such that the LDL level is no longer an independent cardiovascular risk factor; however, hs-CRP (HR = 2.479, 95% CI: 1.147–5.359; p = 0.021) has become a cardiovascular risk factor.

In conclusion, after excluding factors from the early stages of HD and CVC, HVC remained a predictor of adverse CEs, and MVC remained an independent risk factor for CEs. There was no significant difference in all-cause mortality between the HVC group and the non-HVC group. The relationship between the location and degree of HVCs and CEs and all-cause mortality needs to be further studied.

Statement of Ethics

This study was approved by the Ethics Committee of Wuhan Central Hospital (Hospital-Heng-Lun letter-2021 [9]). All study-related procedures were performed in accordance with the

principles of the Declaration of Helsinki. Written informed consent to participate in the study was obtained.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was funded by the Chen Xiao-ping Foundation for the Development of Science and Technology of Hubei Province (CXPJH121003-2115) and the Health Commission of Hubei (WJ2107M185).

Author Contributions

Xiao-mei Huang and Yi Zhang designed the study and wrote the paper. Min Du analyzed and interpreted the data. Yin Wang and Xiao-feng Sun performed the literature search and were responsible for data interpretation. Lian-qing Gu, Hui-ling Fu, Fen Yu, Li Xu, and Jing-jing Li conducted the study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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