The Impact of Plasma Homocysteine on Cardiac Valve Calcification in Patients Undergoing Maintenance Haemodialysis

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ABSTRACT

Objective: To investigate the impact of plasma homocysteine (Hcy) levels on the cardiac valve calcification (CVC) in patients undergoing maintenance haemodialysis (MHD).

Study Design: A retrospective observational analysis.

Place and Duration of the Study: Department of Nephrology, Hangzhou First People's Hospital, Hangzhou, China, from May 2022 to August 2023.

Methodology: Patients undergoing MHD were classified into two groups based on the echocardiographic results: CVC group and Non-CVC group. The former had CVC, and the latter was without calcified valves. The differences in baseline data between the two groups were compared, and logistic regression analysis was employed to investigate the impact of plasma Hcy on the CVC.

Results: Of the total 98 patients undergoing MHD, 64 (65.3%) had CVC, and 79 (80.6%) had hyperhomocysteinaemia. The proportion of hyperhomocysteinaemia was greater in the CVC group than in the Non-CVC group (90.6% *vs*. 61.8%, p = 0.001). Multivariate logistic regression indicated that, after adjusting for age, duration of dialysis, serum calcium levels, diabetes, and other variables, elevated plasma Hcy levels were independently linked to an increased risk of CVC, irrespective of whether Hcy was considered as a continuous variable (OR = 1.121, 95% CI 1.051-1.195; p <0.001) or a binary variable (OR = 5.191, 95% CI 1.379-19.54; p = 0.015).

Conclusion: Elevated plasma Hcy levels are independently linked to a greater risk of CVC in patients undergoing MHD.

Key Words: *Homocysteine, Cardiac valve calcification, Haemodialysis*.

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INTRODUCTION

Cardiovascular disease is the primary cause of death in patients undergoing maintenance haemodialysis (MHD), with a cardiovascular mortality risk 10 to 20 times greater than that of the general population.[1] Among these patients, heart failure and arrhythmia rank as the primary causes of death.[2] Cardiac valve calcification (CVC) is an actively regulated pathological process characterised by ectopic hydroxyapatite deposition, primarily mediated by the multifactorially driven osteogenic differentiation of valvular interstitial cells, which leads to valvular dysfunction and haemodynamic compromise.[3,4] Research indicates that the prevalence of CVC in haemodialysis patients varies from 23% to 68%, mainly affecting the mitral and aortic valves.[1,5]

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The reported aortic valve calcification and mitral valve calcification vary between 25% and 59%.[6,7] Severe calcification can lead to valve dysfunction, myocardial ischaemia, arrhythmias, and heart failure, along with other complications.[8] While the exact pathogenesis of CVC is not fully elucidated, and there are no effective preventive medicine, studying the risk factors associated with CVC in patients undergoing MHD is important for prevention and treatment of the disease.

Homocysteine (Hcy) is an amino acid that contains sulphur, and its concentration in the plasma of healthy adults usually does not exceed 15 µmol/L. In patients with chronic kidney disease (CKD), the decline in kidney function leads to a metabolic disorder of Hcy, causing an increase in its concentration within the body. Most patients suffering from chronic renal failure experience hyperhomocysteinaemia, with an occurrence rate 33 times higher than in the general population.[9] Research indicates that high concentrations of Hcy can damage the blood vessel walls, leading to thickening and plaque formation in the vascular intima, disrupting coagulation, increasing the risk of thrombosis, and constituting a separate risk factor for atherosclerosis, stroke, other cardiovascular, and cerebrovascular diseases.[10,11] Although the relationship between Hcy and cardiovascular and kidney diseases has been widely studied,

current literature on the correlation between Hcy and CVC in patients undergoing MHD is relatively limited. Consequently, this study aimed to explore the association between Hcy and CVC in patients undergoing MHD, to enhance a deeper understanding of risk factors for CVC, and simultaneously to offer new insights for strategies in clinical prevention and treatment.

METHODOLOGY

This study was conducted as a retrospective observational analysis. Based on the selection criteria, those patients were included who underwent haemodialysis at Hangzhou First People's Hospital, Hangzhou, China, between May 2022 and August 2023. Inclusion criteria included patients with a clinical diagnosis of end-stage renal disease secondary to chronic renal failure, who had undergone MHD regularly for at least three months, with a frequency of 2-3 sessions per week, and were aged 18 years or older. Exclusion criteria included congenital or acquired valvular heart disease, prior valvular interventions, acute kidney injury, dialysis duration under three months, age below 18 years, and incomplete medical records. Patients were divided into two groups: CVC group and Non-CVC group.

Demographic data, underlying diseases, laboratory results, echocardiographic data, and one-year follow-up for mortality were collected. Hyperhomocysteinaemia was defined as plasma Hcy levels exceeding 15 μmol/L.

Cardiac ultrasound (probe frequency of 8-10MHz) was used to assess the heart valves. Diagnosis of CVC is characterised by the presence of one or more mass-like or spot-like strong echogenic foci with a diameter of ≥1mm on the cardiac valves or valvular annulus.

Data were analysed using SPSS version 26.0. Continuous data with a Gaussian distribution were represented as the mean ± standard deviation ($x \pm s$) and compared using the t-test. Continuous data without a Gaussian distribution were expressed as median and interquartile range [M (P25, P75)] and compared using the Wilcoxon rank-sum test. Categorical data were described as percentages and compared using the Chi-square or Fisher's exact test. Univariate logistic regression analysis was used to identify potential risk factors for CVC, and variables with a significance level of $p < 0.05$ were included in multivariate regression to determine independent correlates of CVC. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 98 eligible patients were inducted, including 40 (40.8%) female patients, with a median age of 67 years (59.75, 76) and a median dialysis duration of 16 months (11.75, 39.50). Of which, 64 (65.3%) patients had CVC. Aortic valve calcification was observed in 53 patients, mitral valve calcification in 42 patients, single-valve calcification 32 patients, and two-valve calcification in 29 patients.

Table I: Comparing clinical and laboratory variables between the groups.

Variables	All patients (n = 98)	Non-CVC group (n = 34)	CVC group (n = 64)	p-values[0]
Demographic data				
Age (year)	67 (59.75, 76)	61 (57, 68.75)	69.5 (63, 79.75)	0.001
Gender, female (%)	40 (40.8)	17 (50.0)	23 (35.9)	0.178
Duration of dialysis (months)	16 (11.75, 39.50)	12.50 (5, 31)	24 (13, 47)	0.001
Previous history (%)				
Hypertension	82 (83.7)	25 (73.5)	57 (89.1)	0.048
Diabetes mellitus	62 (63.3)	13 (38.2)	49 (76.6)	<0.001
Coronary heart disease	29 (29.6)	7 (20.6)	22 (34.4)	0.155
Cerebrovascular disease	24 (24.5)	5 (14.7)	19 (29.7)	0.101
Primary kidney disease (%)				
Diabetic nephropathy	35 (35.7)	8 (23.5)	27 (42.2)	0.067
Glomerulonephritis	14 (14.3)	8 (23.5)	6 (9.4)	0.057
Polycystic kidney	7 (7.1)	5 (14.7)	2 (3.1)	0.088
Unknown aetiology	42 (42.9)	13 (38.2)	29 (45.3)	0.500
Laboratory data				
Haemoglobin (g/L)	105 (87, 117.3)	90 (82.5, 115)	108 (88, 119)	0.133
Platelet counts ($x10^9$/L)	165.9 ± 55.79	177.1 ± 56.22	159.9 ± 55.07	0.148
Albumin (g/L)	35.5 (31.57, 37.2)	35.5 (30.88, 37.73)	35.4 (31.6, 36.88)	0.560
Prealbumin (mg/L)	218 (168.8, 305.6)	239 (169, 315)	215 (168, 292.3)	0.252
Uric acid (mmol/L)	333.5 ± 122.5	322.7 ± 146.7	339.3 ± 108.5	0.526
Triglycerides (mmol/L)	1.32 (0.808, 2.210)	1.625 (1.11, 2.58)	1.18 (0.705, 2.173)	0.071
Total cholesterol (mmol/L)	3.364 ± 1.049	3.568 ± 1.049	3.256 ± 1.041	0.162
Lipoprotein-a (mg/dl)	170 (98, 261.3)	174 (143.3, 307)	131 (98, 229.3)	0.255
Hcy (mmol/L)	28.7 (17.7, 36.12)	19.3 (13.1, 27.68)	34.5 (25.75, 39.45)	<0.001
Hyperhomocysteinaemia (%)	79 (80.6)	21 (61.8)	58 (90.6)	0.001
Parathyroid hormone (pg/mL)	130.7 (56.28, 277.9)	99.86 (36.99, 193.5)	175.4 (69.99, 292.6)	0.041
Calcium (mmol/L)	2.21 (2.12, 2.31)	2.195 (2.085, 2.3)	2.23 (2.15, 2.39)	0.103
Phosphorus (mmol/L)	1.715 (1.34, 2.403)	1.72 (1.265, 2.418)	1.715 (1.358, 2.37)	0.481
Ferritin (mg/L)	111.1 (45.75, 219.4)	111.3 (54,67, 366.8)	111.1 (44.56, 208.8)	0.378
Doppler echocardiography data				
Ejection fraction	0.591 ± 0.100	0.619 ± 0.105	0.576 ± 0.095	0.043
Prognosis				
One-year mortality (%)	18 (18.3)	2 (5.89)	16 (25)	0.04

[0] *Chi-square or Fisher's exact test (for categorical variables), t-test (for continuous variables), and Wilcoxon rank-sum test.*

Table II: Logistic analysis for CVC in patients undergoing MHD.

Variables	Univariate logistic analysis		Multivariate logistic analysis	
	OR (95% CI)	p-values	OR (95% CI)	p-values*
Hyperhomocysteinaemia (Yes/No)	5.984 (2.015~17.77)	0.001	5.191 (1.379~19.54)	0.015
Dialysis duration (months)	1.029 (1.006~1.052)	0.012	1.024 (1.001~1.049)	0.043
Age (year)	1.055 (1.017~1.094)	0.004	1.055 (1.012~1.099)	0.012
Calcium (mmol/L)	14.13 (1.261~158.3)	0.032		
Hypertension (Yes/No)	2.931 (0.982~8.753)	0.054		
Diabetes mellitus (Yes/No)	5.277 (2.142~13.00)	<0.001	4.070 (1.382~11.99)	0.011
Ejection fraction	0.009 (0.001~0.932)	0.047		
Haemoglobin (g/L)	1.014 (0.995~1.033)	0.159		
Phosphorus (mmol/L)	1.354 (0.675~2.715)	0.393		

**Variables with p <0.05 were included in the Multivariate logistic analysis. CI: Confidence interval.*

Table III: Logistic analysis for CVC in patients undergoing MHD.

Variables	Univariate logistic analysis		Multivariate logistic analysis	
	OR (95% CI)	p-values	OR (95% CI)	p-values*
Hcy (mmol/L)	1.134 (1.075~1.197)	<0.001	1.121 (1.051~1.195)	<0.001
Dialysis duration (months)	1.029 (1.006~1.052)	0.012	1.024 (1.001~1.048)	0.041
Age (year)	1.055 (1.017~1.094)	0.004	1.065 (1.014~1.119)	0.011
Calcium (mmol/L)	14.13 (1.261~158.3)	0.032		
Diabetes mellitus (Yes/No)	5.277 (2.142~13.00)	<0.001	3.953 (1.181~13.23)	0.026
Ejection fraction	0.009 (0.001~0.932)	0.047		

**Variables with p <0.05 were included into the multivariate logistic analysis. CI: Confidence interval.*

Baseline data of the both groups were presented in Table I. There was no significant statistical difference between the two groups regarding gender, cerebrovascular disease, coronary heart disease, haemoglobin, platelet counts, albumin, pre-albumin, and other variables.

In comparison to the non-CVC group, the incidence of hyperhomocysteinaemia was higher in the CVC group [58 (90.6%) *vs*. 21 (61.8%); p = 0.001]. The percentage of patients with hypertension [57 (89.1%) *vs*. 25 (73.5%); p = 0.048] and diabetes [49 (76.6%) *vs*. 13 (38.2%); p <0.001] was found to be higher in the CVC group than in the Non-CVC group. Compared with the Non-CVC group, patients with CVC had higher plasma Hcy levels [34.50 (25.75, 39.45) *vs*. 19.3 (13.1, 27.68); p <0.001], were older [69.5 (63, 79.75) *vs*. 61 (57, 68.75); p = 0.001], had longer dialysis duration [24 (13, 47) *vs*. 12.50 (5, 31) months; p = 0.001], lower ejection fraction [(0.58 ± 0.10 *vs*. 0.62 ± 0.11; p = 0.043)], and higher parathyroid hormone [175.4 (69.99, 292.6) *vs*. 99.86 (36.99, 193.5); p = 0.041]. After one year of follow-up, the mortality rate observed in the CVC group was significantly higher than that in the Non-CVC cohort [16 (25%) vs. 2 (5.89%); p = 0.04].

Univariate logistic regression analysis indicated that factors such as advanced age, long dialysis, duration of hyperhomocysteinaemia, hypercalcaemia, hypertension, diabetes, and lower EF were associated with an increasing risk of CVC in patients receiving MHD. When Hcy was used as a bitaxonomic variable, additional statistically significant variables identified in the univariate analysis were included in the multivariate logistic model. It was found that the independent risk factors affecting CVC included: hyperhomocysteinaemia (OR = 5.191, 95% CI 1.379-19.54; p = 0.015), longer dialysis duration (OR = 1.024, 95% CI 1.001-1.0049; p = 0.043), advanced age (OR = 1.055, 95% CI 1.012-1.099; p = 0.012), and diabetes (OR = 4.070, 95% CI 1.382-11.99; p = 0.011; Table II).

When Hcy was treated as a continuous numerical variable by repeating the above statistical analysis, it was also found that Hcy (OR = 1.121, 95% CI 1.051-1.195; p <0.001) remained an independent risk factor for CVC (Table III).

DISCUSSION

Previous studies have reported that the incidence of CVC in patients with mild renal dysfunction is significantly higher than that in the general population. It has been reported that the occurrence of CVC in individuals undergoing MHD is as high as 23-68%, mainly with aortic and mitral valve calcification, with tricuspid and pulmonary valve calcification.[5] In individuals undergoing MHD, CVC is recognised as a significant indicator of both total mortality and cardiovascular mortality, increasing the risk of cardiovascular death by 181% and overall mortality by 73%.[12] Consequently, it is essential to screen for and intervene on the risk factors associated with CVC in patients with MHD to reduce its incidence as much as possible.

CVC represents an active, multifactorial pathophysiological process, the core mechanism of which involves the pathological phenotypic transformation of valvular interstitial cells under the influence of diverse risk factors, including mechanical stress, metabolic disturbances, and chronic inflammation.[3] Lipid infiltration and inflammatory cell recruitment create a cytokine-rich microenvironment, such as TGF-β and BMPs, driving quiescent valvular interstitial cells toward myofibroblastic or osteogenic differentiation. The osteogenic phenotype upregulates core transcription factors, such as RUNX2 and alkaline phosphatase, thereby

actively promoting hydroxyapatite crystallisation. Concurrently, endothelial-mesenchymal transition (EndMT) accelerates fibrocalcific leaflet remodelling.[3,4,13,14] This process is accompanied by the disruption of the endogenous calcification inhibition system. Under chronic pathological conditions, a decline in endogenous calcification inhibitors (*e.g.*, fetuin-A,[15] inorganic pyrophosphate)[16] creates a homeostatic imbalance that drives progressive fibrocalcific remodelling and functional deterioration of the valve leaflets. Although the precise cellular and molecular mechanisms underlying cardiac valvular fibrocalcific remodelling in patients undergoing MHD remain incompletely elucidated, current evidence indicates that cardiovascular calcification in this population arises from multifactorial interactions. Established risk factors include advanced age, prolonged dialysis vintage, hypercalcaemia, secondary hyperparathyroidism, low-grade inflammation, decreased levels of calcification inhibitors (such as pyrophosphate and fetuin-A), and hyperhomocysteinaemia.[1,12,15-17] Similarly, this study also found that age, duration of dialysis, calcium levels, diabetes mellitus, hypertension, and cardiac ejection fraction may affect the occurrence and development of CVC.

Hcy is found to be a risk factor for several cardiovascular diseases, such as coronary artery disease, hypertension, atherosclerosis, and valve calcification.[9,11] Recent research has indicated that Hcy is closely related to kidney disease and may serve as a biomarker for kidney disease progression, especially in patients receiving haemodialysis, those with acute kidney injury (AKI), and individuals with IgA nephropathy.[18-20] Research has suggested that baseline hyperhomocysteinaemia is an independent risk factor for unfavourable renal outcomes in patients with IgA nephropathy, and the cumulative renal survival rate is considerably lower in individuals with elevated Hcy compared to those with normal levels.[20] In this study, the retrospective analysis of CVC risk factors in MHD patients found that plasma Hcy levels were identified as an independent risk factor for CVC, regardless of whether it was a bicategorical variable or continuous variable, and the one-year mortality risk was significantly increased.

Elevated Hcy appears to affect CVC in patients undergoing MHD, although the underlying mechanism of the correlation between them remains unclear. The following pathophysiological mechanisms may contribute to this process. Firstly, haemodialysis patients commonly develop hyperhomocysteinaemia due to impaired Hcy metabolism, which arises from deficiencies in essential cofactors (vitamin B6, B12, and folate) caused by inadequate dietary intake or malabsorption, combined with inflammation-mediated suppression of key enzymatic activity.[21] Hyperhomocysteinaemia activates inflammatory cells, stimulating the release of cytokines—such as interleukin-6 and tumour necrosis factor-α, thereby initiating an inflammatory response. This inflammatory milieu promotes the osteogenic differentiation of valvular interstitial cells and accelerates cardiovascular calcification.[22] Hcy may directly induce osteogenic differentiation of valvular interstitial cells by upregulating osteogenic genes and proteins, promoting intracellular calcium overload and enhancing calcium salt deposition, thereby driving CVC.[11,17] In MHD patients, disturbances in calcium and phosphate metabolism are common disorders, and the interaction between these two factors may accelerate calcification of heart valves. Earlier studies have confirmed that high levels of Hcy can induce endoplasmic reticulum stress, leading to endothelial cell injury and endothelial dysfunction, which results in a decreased secretion of vasodilators, such as nitric oxide, and enhanced vasoconstriction. Additionally, it increases platelet adhesion and aggregation, thereby promoting thrombosis and creating favourable conditions for CVC.[23,24] Haemodialysis patients are already a high-risk group for cardiovascular diseases, and elevated Hcy concentration may further raise the risk of cardiovascular events, although the underlying mechanisms require further investigation.

This study has several limitations. First, it is a retrospective observational study performed at a single centre, which may introduce an observational bias and unaccounted confounding factors. Second, the relatively small sample size prevented subgroup analysis by valve type.

CONCLUSION

Hyperhomocysteinaemia is independently linked to an increased risk of CVC in patients undergoing MHD. Regular monitoring of Hcy levels in this patient population facilitates the assessment of disease severity and cardiovascular risk, thereby enabling timely clinical interventions.

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ETHICAL APPROVAL:
Ethical approval was obtained from the hospital's Ethics Committee of Hangzhou First People's Hospital, Hangzhou, China (No. 2022-380).

PATIENTS' CONSENT:
Informed consent was obtained from the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
ML: Conception and design of the study and writing of the original draft.
RY: Data acquisition and analysis.
LY, NZ: Conception of the study.
YH: Data analysis.
XY: Critical revision.
All authors approved the final version of the manuscript to be published.

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