Cardiac Valve Calcification as an Important Predictor for All-Cause Mortality and Cardiovascular Mortality in Long-Term Peritoneal Dialysis Patients: A Prospective Study

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Abstract. Calcification complications are frequent among long-term dialysis patients. However, the prognostic implication of cardiac valve calcification in this population is not known. This study aimed to determine if cardiac valve calcification predicts mortality in long-term dialysis patients. Baseline echocardiography was performed in 192 patients (mean ± SD age, 55 ± 12 yr) on continuous ambulatory peritoneal dialysis (mean ± SD duration of dialysis, 39 ± 31 mo) to screen for calcification of the aortic valve, mitral valve, or both. Valvular calcification was present in 62 patients. During the mean follow-up of 17.9 mo (range, 0.6 to 33.9 mo), 46 deaths (50% of cardiovascular causes) were observed. Overall 1-yr survival was 70% and 93% for patients with and without valvular calcification ($P < 0.0001$, log-rank test). Cardiovascular mortality was 22% and 3% for patients with and without valvular calcification ($P < 0.0001$). Multivariable Cox regression analysis showed that cardiac valve calcification was predictive of an increased all-cause mortality (hazard ratio [HR], 2.50; 95% CI, 1.32 to 4.76; $P = 0.005$) and cardiovascular death (HR 5.39; 95% CI, 2.16 to 13.48; $P = 0.0003$) independent of age, male gender, dialysis duration, C-reactive protein, diabetes, and atherosclerotic vascular disease. Eighty-nine percent of patients with both valvular calcification and atherosclerotic vascular disease, 23% of patients with valvular calcification only, 21% of patients with atherosclerotic vascular disease only, and 13% of patients with neither complication died at 1-yr ($P < 0.0005$). The cardiovascular death rate was 85% for patients with both complications, 13% for patients with valvular calcification only, 14% for patients with atherosclerotic vascular disease only, and 5% for those with neither complication ($P < 0.0005$). The number of calcified valves was associated with all-cause mortality ($P < 0.0005$) and cardiovascular death ($P < 0.0005$). One-year all-cause mortality was 57% for patients with both aortic and mitral valves calcified, 40% for those with either valve calcified, and 15% for those with neither valve calcified. In conclusion, cardiac valve calcification is a powerful predictor for mortality and cardiovascular deaths in long-term dialysis patients. Valvular calcification by itself has similar prognostic importance as the presence of atherosclerotic vascular disease. Its coexistence with other atherosclerotic complications indicates more severe disease and has the worst outcome.
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Vascular or tissue calcification is increasingly recognized to be a frequent complication in patients with end-stage renal disease (ESRD). Braun *et al.* (1) reported that two thirds of the adult hemodialysis patients had electron beam computed tomographic (EBCT) evidence of coronary artery calcification (CAC) and that over half had cardiac valve calcification. The calcification score in dialysis patients was not only substantially higher than age-matched and gender-matched patients with angiographically confirmed coronary artery disease but also progressed rapidly within short period. Using echocardiography as the screening method, we demonstrated cardiac valve calcification to be a frequent complication with a prevalence of at least 30% in the ESRD patients (2). Recent study has indicated an association between aortic sclerosis and cardiovascular mortality and risk of myocardial infarction in the elderly (3). However, the prognostic importance of valvular calcification in the dialysis population remains undetermined.

Autopsy studies showed an association between CAC and atherosclerosis and confirmed an association between CAC and valvular calcification (4–5), suggesting that valvular calcification may be a marker of atherosclerosis. Our recent demonstration of the association between inflammation and valvular calcification (2) gave further evidence that calcification and atherosclerosis are likely associated syndromes, sharing similar pathogenic mechanism, namely inflammation. In the general population, EBCT evidence of vascular calcification is a useful index of atherosclerotic burden. It not only predicts adverse coronary events (6–8), but it is also associated

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with a lower event-free survival (9). The significant correlation observed between valvular calcification and aortic atheroma (10) suggests that valvular calcification may be a manifestation of generalized atherosclerosis and associated with poor outcomes.

We hypothesized that the presence of valvular calcification at baseline echocardiography may be associated with an increased risk of all-cause mortality and death from cardiovascular causes in the dialysis population. Moreover, the extent of valvular calcification, namely the number of valves calcified as well as the presence of valvular calcification in relation to the presence or absence of other atherosclerotic vascular disease may have prognostic significance.

Materials and Methods

Study Subjects

This prospective cohort study was initiated in the dialysis unit in the Prince of Wales Hospital, Hong Kong, in September 1999. Altogether 192 continuous ambulatory peritoneal dialysis (CAPD) patients who had undergone dialysis treatment for at least 3 mo were randomly recruited into the study over a period of 16 mo. These patients represented 70% of the total number of patients undergoing peritoneal dialysis at our unit. Exclusion criteria for the study included patients with underlying malignancy, chronic liver disease, systemic lupus erythematosus, chronic rheumatic heart disease, or congenital heart disease. All patients were of Chinese origin. All patients who were suitable for study entry provided informed consent. The study protocol was approved by the Human Research Ethics Committee of the Chinese University of Hong Kong.

Echocardiography

Two-dimensional echocardiography was performed with a GE-VingMed System 5 echocardiographic machine (GE-VingMed Sound AB, Horten, Norway) with a 3.3-mHz multiphase array probe in subjects lying in the left decubitus position. Two-dimensional assessment of the aortic valve and mitral valve together with continuous-wave Doppler ultrasound was performed on the basis of the parasternal long-axis and short-axis views. All echocardiographies were performed according to the recommendations of the American Society of Echocardiography (11–12) and were analyzed by a single experienced cardiologist who was blinded to all clinical details. Cardiac valve calcification 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. Sensitivity and specificity for echocardiographic detection of calcium in the mitral valve or mitral annulus and aortic valves were reported to be 76% and 89 to 94%, respectively (13). The intraobserver agreement for the echocardiographic detection of valvular calcification was 90% ($\kappa = 0.76$) in this study. Aortic stenosis was defined as thickened leaflets with reduced systolic opening on two-dimensional imaging and an increased velocity across the aortic valve ($\geq$2.5 m/s). Moderate aortic stenosis was considered to be present if the jet velocity was between 3 and 4 m/s, and the stenosis was considered to be severe if the jet velocity was $>$4 m/s (14). Mitral stenosis was defined as thickened leaflets with reduced diastolic opening on two-dimensional imaging. Severity of mitral stenosis was assessed by the pressure half-time valve area estimated using continuous wave Doppler imaging. Moderate mitral stenosis was present if the mitral valve area (MVA) was between 1 and 1.5 cm^2, and the stenosis was considered to be of severe degree if the MVA was <1 cm^2 (14). The ejection fraction was obtained using a modified biplane Simpson's method from apical two- and four-chamber views.

Data Collection

Atherosclerotic vascular disease was defined as the presence of ischemic heart disease and history of angina, previous myocardial infarction, coronary artery bypass surgery or stenting, cerebrovascular event, transient ischemic attack, or peripheral vascular disease with or without amputation. Systolic and diastolic BP measured every follow-up at 6-wk to 8-wk intervals were averaged for the 12 mo preceding echocardiography. Height, weight, and body mass index were measured at the time of echocardiography.

Biochemical Assays

At the time of echocardiography, fasting venous blood was collected for measurement of serum albumin, calcium, phosphate, parathyroid hormone (PTH), fasting lipid profile (total cholesterol, HDL and LDL cholesterol, and triglyceride), high sensitivity C-reactive protein (hs-CRP), and fibrinogen. Serum albumin, calcium, and phosphate concentrations were measured using dye-binding methods on the Dimension AR automatic analyzer (Du Pont Co, Wilmington, DE). PTH was determined by chemiluminescence immunoassay on the Immunlite analyzer (Diagnostic Products Corp, Los Angeles, CA). Total cholesterol and triglyceride were assayed enzymatically (Hitachi 911 analyser; Roche Diagnostics GmbH, Mannheim, Germany). HDL cholesterol was measured after precipitation of Apo B containing lipoproteins with phosphotungstate. LDL cholesterol was calculated from the Freidewald formula. Hs-CRP was measured using the Tina-quant CRP (Latex) ultra-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany), and fibrinogen by a prothrombin time-derived and turbidimetric clot detection method using the ACL Futura (Instrumentation Laboratory, MA).

Outcome

All patients were followed up prospectively after the baseline echocardiography in 1999. No patient was lost to follow-up. Patients who underwent kidney transplant or transferred to hemodialysis were censored at the time of transfer to alternative renal replacement therapy. If a patient died within 3 mo of transfer to hemodialysis, then he or she was not censored as the early mortality was considered to reflect the health status during the period of failing CAPD treatment. During the period of follow-up, all deaths were accurately recorded with the exact cause of death provided by the attending physician, who had no knowledge of the echocardiography results. In the case of death out of hospital, family members were interviewed by telephone to ascertain the circumstances surrounding death. The clinical outcomes evaluated were all-cause mortality and cardiovascular mortality. Cardiovascular mortality included death associated with a definite myocardial ischemic event, heart failure, cerebrovascular accident, arrhythmia, and peripheral vascular accident, all of which were defined according to standard clinical criteria and sudden death, which was defined as unexpected natural death within 1 h from the symptom onset and without any prior condition that would appear fatal (15–16).

Statistical Analyses

Continuous data were summarized as mean $\pm$ SD or median (interquartile range [IQR]). Comparisons between patients with and without valvular calcification were performed at study baseline using unpaired *t* test for mean data, Mann-Whitney test for median data, and χ^2 test for categorical data. Factors predictive of all-cause mortality and cardiovascular mortality were identified with Cox regression

analysis. Factors with $P < 0.25$ on univariate analysis were entered into the multivariable Cox regression model. A backward elimination procedure with $P > 0.05$ to remove was performed to identify independent predictors for all-cause mortality and cardiovascular mortality in dialysis patients.

Patients were also stratified according to the presence or absence of valvular calcification in relation to atherosclerotic vascular disease: group I, those with neither valvular calcification nor atherosclerotic vascular disease; group II, those with atherosclerotic vascular disease only; group III, those with valvular calcification only; and group IV, those with both valvular calcification and atherosclerotic vascular disease. Survival analysis was performed using Kaplan-Meier method and log-rank test. All statistical analyses were performed using SPSS version 10.0 (Illinois, Chicago) for Windows software. $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the baseline clinical and demographic characteristics of the entire study population as well as those with and without valvular calcification. The mean age of the 192 patients was 55 ± 12 yr, with 98 men and 94 women. The mean duration of dialysis was 39 ± 31 mo. Causes of ESRD included chronic glomerulonephritis in 62 patients, diabetic nephropathy in 50 patients, hypertensive nephrosclerosis in 21 patients, obstructive uropathy in 12 patients, polycystic kidney disease in 8 patients, tubulointerstitial nephritis in 6 patients, and unknown condition in 33 patients. Sixty-two patients (32%) had valvular calcification, among which 43 had mitral valve calcification, 33 had aortic valve calcification, and 14 had both mitral and aortic valves calcification. No significant difference was noted in the ejection fraction (67 ± 12 and 69 ± 12%; $P = 0.444$) between patients with and without valvular calcification, respectively. Among the 192 patients, 19 (44%) of the 43 patients with atherosclerotic vascular disease *versus* 43 (29%) of the 149 patients with no atherosclerotic vascular disease had valvular calcification ($P = 0.058$). None of the patients had mitral stenosis. Only one patient with valvular calcification had moderately severe aortic stenosis with a jet velocity of 3.7 m/s and none of the patient had severe aortic stenosis.

During the mean follow-up of 17.9 mo (range, 0.6 to 33.9 mo), 12 patients underwent kidney transplant (two in calcified

Table 1. Characteristics of patients with and without valvular calcification[a]

	Total ($n = 192$)	Valvular Calcification ($n = 62$)	No Valvular Calcification ($n = 130$)	P[c]
Demographic and clinical parameters				
age (yr)	55 ± 12	60 ± 10	53 ± 13	<0.001
male gender (*n* [%])	98 (51)	31 (50.0)	67 (51.5)	0.842
body mass index (kg/m^2)	23 ± 3	23.6 ± 3.2	22.9 ± 3.5	0.250
smoking habit (*n* [%])				
nonsmoker	116 (60.4)	30 (48.4)	86 (66.1)	0.062
ex-smoker	47 (24.5)	20 (32.2)	27 (20.8)	
current smoker	29 (15)	12 (19.4)	17 (13.1)	
duration of dialysis (mo)	39 ± 31	42 ± 32	37 ± 30	0.281
diabetes mellitus (*n* [%])	66 (34.4)	29 (46.8)	37 (28.5)	0.012
prevalence of atherosclerotic vascular disease (*n* [%])	43 (22.4)	19 (30.6)	24 (18.5)	0.058
systolic BP (mmHg)	147 ± 16	148 ± 16	147 ± 16	0.646
diastolic BP (mmHg)	82 ± 10	80 ± 9	83 ± 10	0.061
Biochemical parameters				
serum calcium (mmol/L)	2.57 ± 0.19	2.63 ± 0.18	2.54 ± 0.18	0.002
serum phosphate (mmol/L)	1.68 ± 0.45	1.79 ± 0.52	1.63 ± 0.41	0.016
calcium × phosphate product	4.32 ± 1.25	4.71 ± 1.43	4.13 ± 1.12	0.002
parathyroid hormone (pmol/L)	59 ± 52	74 ± 61	51 ± 46	0.006
fasting lipid				
total cholesterol (mmol/L)	5.55 ± 1.22	5.39 ± 1.24	5.62 ± 1.21	0.221
LDL cholesterol (mmol/L)	3.44 ± 0.97	3.31 ± 0.93	3.50 ± 0.99	0.206
HDL cholesterol (mmol/L)	1.19 ± 0.42	1.15 ± 0.38	1.21 ± 0.44	0.369
Triglyceride (mmol/L)	2.21 ± 1.77	2.27 ± 1.68	2.18 ± 1.82	0.738
serum albumin (g/L)	28.3 ± 4.0	26.8 ± 3.7	29.0 ± 4.0	<0.001
high sensitive C-reactive protein (mg/L[b])	2.7 (0.9, 7.8)	5.5 (1.5, 16.1)	1.8 (0.8, 5.1)	<0.001
Fibrinogen (g/L)	5.91 ± 1.53	6.31 ± 1.76	5.72 ± 1.37	0.012

[a] Plus-minus values are means ± SD.
[b] Expressed as median (interquartile range).
[c] Valvular calcification versus no valvular calcification.

and ten in noncalcified group). Ten patients (four in calcified and six in noncalcified group) were transferred to hemodialysis. There were altogether 46 deaths during the period of follow-up; half of them were of cardiovascular causes. Twenty-seven patients (43.6%) with valvular calcification *versus* 19 patients (14.7%) without valvular calcification died during this period. As shown in Table 2, 24.2% of patients with valvular calcification *versus* 6.2% of patients without valvular calcification died from cardiovascular causes. The overall 1-yr survival was 70% and 93% for patients with and without valvular calcification, respectively ($P < 0.0001$, log-rank test; Figure 1A). The 1-yr cardiovascular mortality was 22% and 3% for patients with and without valvular calcification, respectively ($P < 0.0001$; Figure 1B).

Using multivariable Cox regression analysis, valvular calcification was predictive of greater all-cause mortality (hazard ratio [HR], 2.50; 95% CI, 1.32 to 4.76; $P = 0.0052$) and cardiovascular deaths (HR, 5.39; 95% CI, 2.16 to 13.48; $P = 0.0003$] independent of age, male gender, dialysis vintage, diabetes, atherosclerotic vascular disease, and hs-CRP (Table 3).

The number of cardiac valves calcified was associated with all-cause mortality ($P < 0.0005$; Figure 2A) and cardiovascular death ($P < 0.0005$; Figure 2B). The 1-yr all-cause mortality was 57% for patients with both mitral and aortic valves calcified, 40% for patients having either valve calcified, and 15% for patients with neither valve calcified. Cardiovascular death was 45% at 1 yr for patients with both mitral and aortic valves calcified, 26% for patients with either valve calcified, and 7% for patients with neither valve calcified.

The survival of patients with and without valvular calcification was studied in relation to atherosclerotic vascular disease. Eighty-nine percent of patients with both valvular calcification and atherosclerotic vascular disease, 21% of patients with atherosclerotic vascular disease only, 23% of patients with valvular calcification only, and 13% of those with neither valvular calcification nor atherosclerotic vascular disease died at the end of 1 yr ($P < 0.0005$; Figure 3A). Death from cardiovascular causes was 83% for patients with both complications, 14% for patients with atherosclerotic vascular disease only, 13% for patients with valvular calcification only, and 5% for those with neither complication ($P < 0.0005$; Figure 3B). The overall survival and cardiovascular deaths did not differ significantly between patients with either valvular calcification or atherosclerotic vascular disease.

Discussion

This study is the first to demonstrate cardiac valve calcification as a strong and independent predictor for all-cause mortality and cardiovascular deaths in the ESRD patients. The increased mortality was apparent even though the follow-up period was relatively short. This is in keeping with recent prospective study showing that aortic sclerosis was independently associated with an approximately 50% increase in cardiovascular mortality and myocardial infarction in the elderly (3). The increased mortality was unlikely to be explained by valvular obstruction, as only one patient with valvular calcification had moderately severe aortic stenosis and none of them had mitral stenosis.

Our results indicate that valvular calcification may be useful in stratifying the severity of atherosclerotic vascular disease in peritoneal dialysis patients. Patients with both valvular calcification and atherosclerotic vascular disease had the worst outcome compared with all other groups, suggesting these patients had the most severe and advanced atherosclerotic disease. Among patients with no obvious atherosclerotic vascular disease, valvular calcification was predictive of higher

Table 2. Causes of death and fatal cardiovascular events in study patients[a]

Causes of Death	Total ($n = 192$)	Valvular Calcification ($n = 62$)	No Valvular Calcification ($n = 130$)
Cardiovascular causes			
myocardial infarction	4 (2.1)	3 (4.8)	1 (0.8)
cerebrovascular accident	6 (3.1)	4 (6.5)	2 (1.5)
sudden death	11 (5.8)	7 (11.3)	4 (3.1)
arrhythmia	1 (0.5)	0 (0)	1 (0.8)
peripheral vascular disease	1 (0.5)	1 (1.6)	0 (0)
subtotal	23 (12.0)	15 (24.2)	8 (6.2)
Other Causes			
unresolved peritonitis	4 (2.1)	2 (3.3)	2 (1.5)
other infections/sepsis	12 (6.3)	7 (11.3)	5 (3.9)
chronic obstructive pulmonary disease	1 (0.5)	1 (1.6)	0 (0)
liver failure	1 (0.5)	1 (1.6)	0 (0)
malignancy	1 (0.5)	0 (0)	1 (0.8)
treatment withdrawal	4 (2.1)	1 (1.6)	3 (2.3)
subtotal	23 (12.0)	12 (19.4)	11 (8.5)
Total	46 (24.0)	27 (43.6)	19 (14.7)

[a] Expressed as number (%).

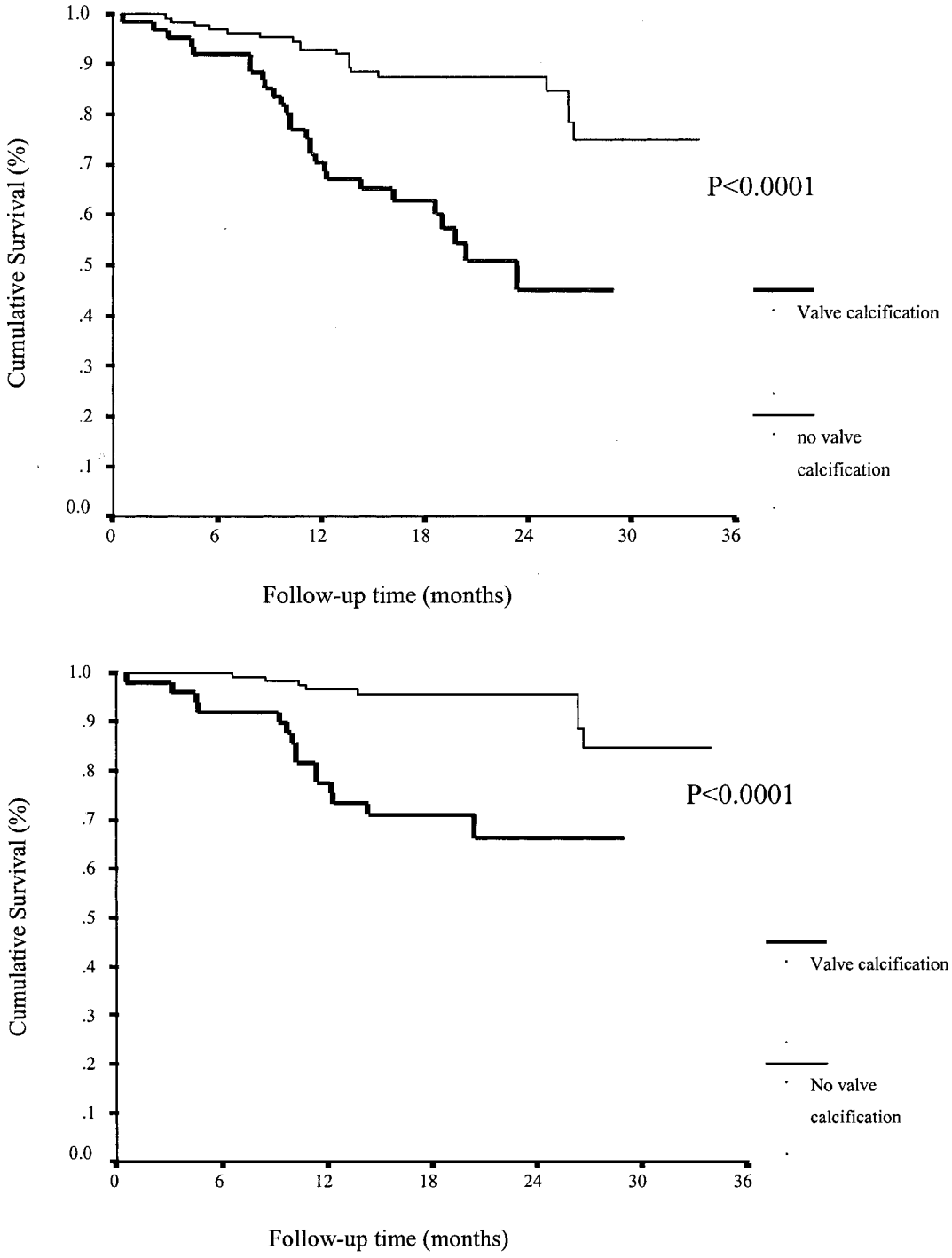


Figure 1. Kaplan-Meier analysis of (A) overall survival and (B) cardiovascular event-free survival of 192 patients with and without valvular calcification.

cardiovascular deaths than no valvular calcification. The all-cause mortality and cardiovascular death did not differ significantly between patients having either valvular calcification or atherosclerotic vascular disease, suggesting that valvular calcification may be a manifestation of atherosclerosis and may be considered as having similar pathologic and prognostic significance as the other atherosclerotic complications. On the other hand, the number of cardiac valves calcified is associated with mortality, suggesting the number of cardiac valves calcified may reflect the extent of calcification. It is however important to caution that even though certain factors may be common to the pathogenesis of valvular calcification and atherosclerotic calcification, the pathogenesis of valvular or vascular calcification in the ESRD patients treated by dialysis is likely differ-

Table 3. Multivariable Cox regression analysis showing important factors associated with all-cause mortality and cardiovascular mortality in dialysis patients

	All-Cause Mortality ($n = 46$)			Cardiovascular Mortality ($n = 23$)		
	Unit Increase	Hazard Ratio (95% CI)	*P*	Unit Increase	Hazard Ratio (95% CI)	*P*
Age	1 yr	1.05 (1.01 to 1.08)	0.012	1 yr	1.07 (1.02 to 1.12)	0.004
Male gender		3.18 (1.57 to 6.44)	0.001		3.60 (1.33 to 9.74)	0.012
Duration of dialysis	1 yr	1.27 (1.13 to 1.43)	<0.0005	1 yr	1.27 (1.13 to 1.60)	0.001
Diabetes mellitus		2.48 (1.22 to 5.05)	0.012		-	
Atherosclerotic vacular disease		2.90 (1.46 to 5.76)	0.002		11.70 (4.35 to 31.52)	<0.0005
Valvular calcification		2.50 (1.32 to 4.76)	0.005		5.39 (2.16 to 3.48)	<0.0005
High sensitive C-reactive protein	1 mg/L	1.02 (1.00 to 1.04)	0.022		-	

ent from the atherosclerotic calcification observed in the general population. This is evidenced by the difference in the pattern of calcification with mineral deposition mainly in the tunica media for the ESRD in contrast to calcification of the atherosclerotic plaque in the non-ESRD patients (17–18). Hence, whether the significant association demonstrated between mitral annulus calcification and the severity of carotid (19) and aortic atheroma (10), peripheral (20) as well as coronary artery disease (21) in the general population is also applicable to patients on dialysis requires further determination.

Previous study demonstrated significant correlation between valvular calcification and the CAC score as detected by EBCT in both ESRD (1) and non-ESRD patients (22–23). The calcified regions of the cardiac valves not only share common features with arterial atherosclerotic plaque with infiltration of inflammatory cells, lipoproteins, and calcium deposits but also express "bone" matrix proteins (24), suggesting the process of valvular calcification simulates bone formation. Interstitial cells with osteoblastic characteristics identified in cardiac valves were suggested to be partly responsible for the increased expression of bone matrix proteins (25). The recent demonstration of bone matrix protein deposition also in vascular calcification in the ESRD patients (26) suggests valvular and vascular calcification are likely associated syndromes, both involving an active cell-mediated process and not just passive accumulation of minerals.

In this study, peritoneal dialysis patients with valvular calcification had significantly higher serum calcium, phosphate, calcium × phosphate product, and parathyroid hormone than those with no valvular calcification. Moreover, those with valvular calcification were significantly older and had greater prevalence of diabetes mellitus. Our findings extend that of Braun *et al.* (1), showing a profound age-related effect on vascular calcification, and are consistent with the recent cross-sectional survey by Raggi *et al.* (27), which demonstrated associations between age, diabetes, dialysis vintage, higher serum calcium and phosphorus, and coronary calcification in maintenance hemodialysis patients. The increased mortality with increasing duration on dialysis may also be explained by increased calcification with time on dialysis (2). Goodman *et al.* (28) demonstrated a doubling of CAC score within a 2-yr period among young adults treated by dialysis. The rate of progression of calcification greatly exceeds that observed in older persons with normal renal function. This gives evidence that in addition to the established atherosclerotic risk factors, the ongoing increased calcium load and the poor calcium-phosphate control are responsible for accelerating the progression of calcification in dialysis patients. The attenuation of coronary and aortic calcification with sevelamer (29) was further evidence to support the above hypothesis. In this study, even though patients with valvular calcification had higher serum calcium, phosphate, and calcium × phosphate product, we found no significant independent relationship between calcium × phosphate product and mortality. This is contrary to results from the United States Renal Data System (USRDS), which show that hyperphosphatemia and increased calcium × phosphate product were independent risk factors for mortality in hemodialysis patient (30). We attributed this difference to the fact that calcific complications were not particularly taken into account in the USRDS. In our study, even though calcium × phosphate product was not independently predictive of mortality, it was strongly associated with the presence of valvular calcification, which had a more direct impact on survival.

A high mortality rate was observed in our dialysis patients within a relatively short follow-up period, with cardiovascular disease being the leading cause of death, and is comparable to other reports (31–32). Although CAPD may represent only a minority of the ESRD patients in many Western nations, the prevalence and the nature of cardiovascular problems are similar to hemodialysis. It is intriguing to find a very high incidence of sudden death among our population, especially those with valvular calcification. The exact mechanism is unclear but may be related to coexisting coronary atherosclerosis and calcification.

Limitations of this study include the prevalence-incidence bias, the use of echocardiography instead of EBCT to detect calcification, and the lack of an objective and accurate way to assess the severity of calcification with echocardiography. As prevalent instead of incident cases were studied, there may be an under-representation of cases, possibly resulting in either an overestimate or underestimate of the true risk associated with

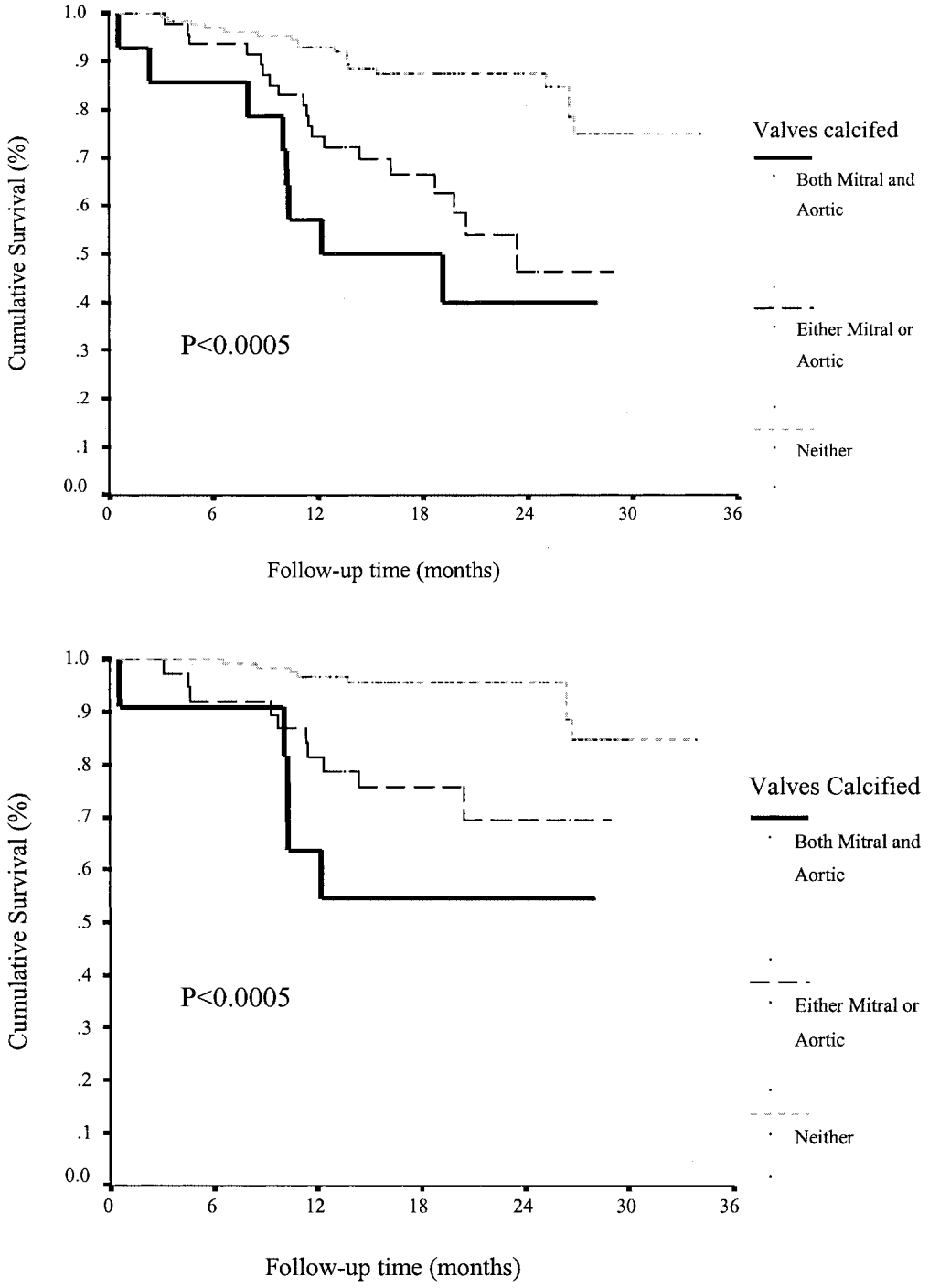
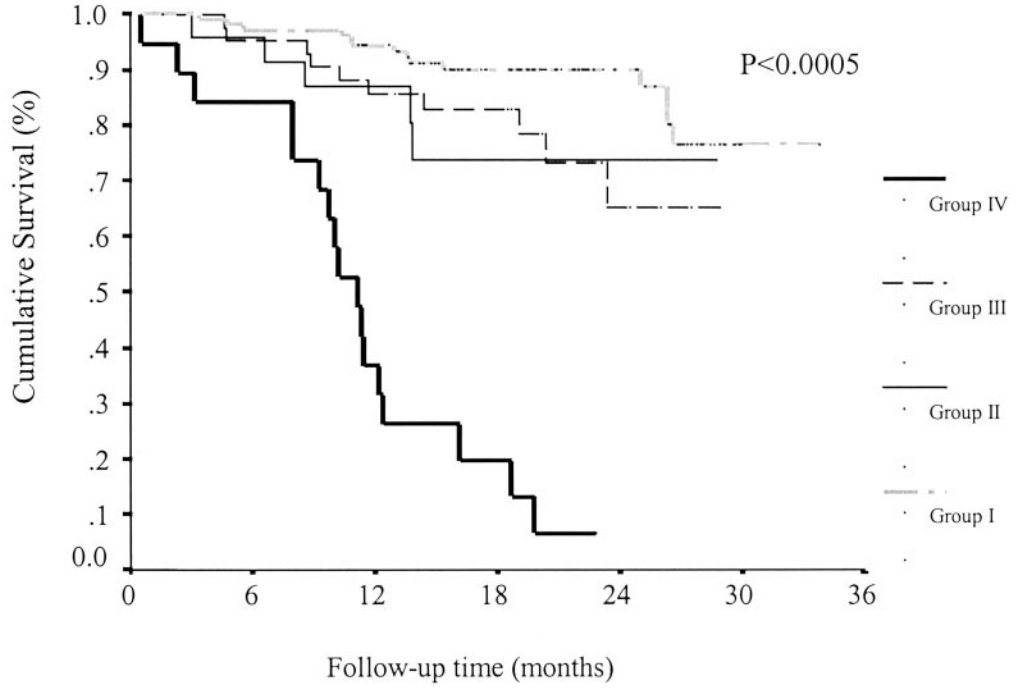


Figure 2. Kaplan-Meier analysis of (A) overall survival and (B) cardiovascular event-free survival for 14 patients with both aortic and mitral valves calcified *versus* 48 patients with either mitral or aortic valve calcified *versus* 130 patients with neither valve calcified.

valvular calcification. Despite the known limitation of echocardiography in diagnosing valvular calcification compared with EBCT, we demonstrated high intraobserver reproducibility with echocardiography. Moreover, echocardiography is more widely available, easier to perform, and has no radiation. We defined the presence but not the severity of valvular calcification, because assessing the severity of valvular calcification by echocardiography is very subjective and can be inaccurate.

In summary, cardiac valve calcification is a powerful predictor for mortality and fatal cardiovascular events in ESRD patients. More attention should be focused on screening for this clinically silent yet potentially lethal complication in the ESRD population and identifying treatment strategies that will pre-



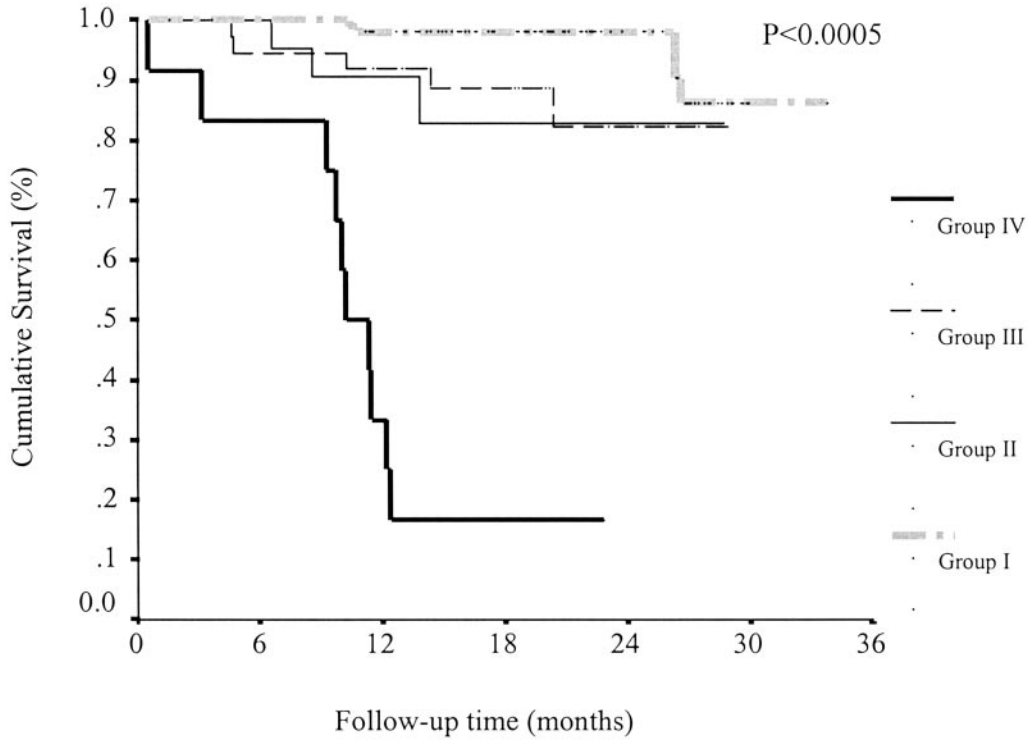


Figure 3. Kaplan-Meier analysis of (A) overall survival and (B) cardiovascular event-free survival of 106 patients with no valvular calcification and atherosclerotic vascular disease (group I), 24 patients with atherosclerotic vascular disease but no valvular calcification (group II), 43 patients with valvular calcification but no atherosclerotic vascular disease (group III), and 19 patients with both valvular calcification and atherosclerotic vascular disease (group IV). (A) Overall survival: I *versus* II ($P = 0.091$, log-rank test); I *versus* III ($P = 0.057$); I *versus* IV ($P < 0.0001$); II *versus* III ($P = 0.923$); II *versus* IV ($P < 0.0001$), and III *versus* IV ($P < 0.0001$). (B) Cardiovascular event-free survival: I *versus* II ($P = 0.019$); I *versus* III ($P = 0.043$); I *versus* IV ($P < 0.0001$); II *versus* III ($P = 0.831$); II *versus* IV ($P = 0.0001$), and III *versus* IV ($P < 0.0001$).

vent or retard the progression of valvular and vascular calcification.

Acknowledgments

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