

Original Paper

Aortic Arch Calcification Predicts Cardiovascular and All-Cause Mortality in Maintenance Hemodialysis Patients

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Key Words

Chest radiography • Aortic calcification • Hemodialysis • Mortality • Cardiovascular disease

Abstract

Background/Aim: Vascular calcification is associated with cardiovascular risk in maintenance hemodialysis (MHD) patients. Previous reports have shown that simple assessment of aortic arch calcification (AoAC) using plain radiography is associated with cardiovascular mortality in the general population. We conducted a prospective study to investigate factors associated with the presence at baseline and progression of AoAC in MHD patients and examined its prognostic value in a short-term outcome. **Methods:** We prospectively evaluated chest X-rays in 301 asymptomatic MHD patients. The extent of AoAC was divided into three Grades (0, 1, 2+3). Demographic data including age, gender, dialysis vintage, co-morbidity and biochemical data were assessed and the patients were then followed for 3 years. **Results:** AoAC was observed in 175 patients (58.1%) as Grade 1, in 112 patients (37.2%) as Grade 2 and 3 in 63 patients (20.9%) at baseline. An increase in the severity of calcification was associated with older male patients who had lower serum albumin levels. During the follow-up period of 3 years, multivariate Cox proportional hazards analysis revealed that high-grade calcification was associated with cardiovascular and all-cause mortality. Patients with AoAC were associated with a worse outcome in survival analysis and the grade of AAC also influenced their survival. Moreover, all-cause death rates were significantly higher in the progression groups than in the non-progression groups. **Conclusions:** The presence and progression of AoAC assessed by chest X-ray were independently associated with mortality in MHD patients. Regular follow-up by chest X-ray could be a simple and useful method to stratify mortality risk in MHD patients.

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Introduction

Cardiovascular disease is the major cause of death in patients with end-stage renal disease (ESRD) in Japan [1]. Since traditional risk factors, such as advanced age, hypertension, diabetes, smoking, and dyslipidemia, cannot fully account for the high prevalence of cardiovascular disease, uremia-related factors have been implicated in the pathogenesis of cardiovascular disease in ESRD patients [2]. Vascular calcification in the coronary arteries and the aorta has been recognized as an important risk factor for cardiovascular disease in maintenance hemodialysis (MHD) patients [3]. Recently, accumulating evidence has shown that disturbances in calcium-phosphate metabolism play a pivotal role in cardiovascular disease, partly via the development of vascular calcification [4, 5].

A previous study has demonstrated the association between the presence and extent of vascular calcification and outcome in the dialysis population [5]. The extent of vascular calcification can be quantified with electron beam computer tomography (EBCT) [6] and multi-slice computer tomography (MSCT) [7]. Even though EBCT and MSCT are well-validated noninvasive imaging methods that are considered the golden standard for quantifying vascular calcification, these methods cannot be routinely performed due to the relatively high cost of testing and exposure to a high radiation dose. Plain radiography is a convenient and inexpensive tool for the identification of vascular calcification. In the general population, aortic arch calcification (AoAC) identified in chest radiography has been shown to correlate with cardiovascular mortality [8].

We have recently reported the validity and usefulness of assessment of AoAC grade, as determined by a simple chest X-ray [9, 10]. AoAC grade was significantly associated with clustering of traditional risk factors. However, it is still unknown whether AoAC grade is a sensitive predictor of cardiovascular and all-cause mortality. The purpose of the present study was to determine the presence and progression of AoAC grade as an independent predictor of cardiovascular and all-cause mortality in MHD patients.

Materials and Methods

Study population

There were 356 MHD patients (dialysis duration > 6 months) at Jyoban Hospital Kidney Center, Fukushima, Japan, on January 2011. Of these, patients with acute illness, significant infection, or malignancy were excluded. Of the remaining patients, 301 patients (male/female = 198/103, mean age 63.8 ± 12.2 years) gave informed consent for evaluating a chest radiograph, as described next, and were investigated in the present study. The underlying causes of ESRD were diabetes ($n = 126$), chronic glomerulonephritis ($n = 95$), hypertension ($n = 70$), polycystic kidney ($n = 6$), and unknown etiology ($n = 4$). The enrolled patients underwent stable regular hemodialysis using bicarbonate dialysate.

At baseline, a chest radiograph of each patient was obtained. They comprised a non-selected sample of patients from the Kidney Center in Jyoban Hospital without a selection bias. All patients completed a detailed health history questionnaire just prior to follow-up of cardiovascular and all-cause mortality. However, we could not rule out the asymptomatic patients with coronary disease because of no history of coronary angiography. Patients then were followed up for 3 years, and relationships between baseline data and outcomes were assessed statistically. Data and causes of death were obtained by reviewing hospital record forms. In patients who moved to other dialysis units, we reviewed questionnaire forms filled out by the attending physicians at the Kidney Center. This study was in compliance with the Declaration of Helsinki and was approved by the ethics review committee of the Jyoban Hospital.

Assessment of aortic arch calcification

We performed a retrospective review of 301 patients undergoing dialysis therapy. Two radiologists (one specializing in chest radiography) independently reviewed all chest radiographs obtained from MHD patients studied. Radiographs were assessed for the presence of AoAC using a specific scale as previously described [9]. The scale which was divided into 16 circumferences was attached to the aortic arch on chest

radiography and then the number of sectors with calcification was divided by 16. Aortic arch calcification score (AoACS) was calculated after multiplication by 100 to express the results as a percentage. This value was used as the indicator of the AoAC. Our previous study confirmed that AoACS was highly correlated with AoAC volume evaluated by MSCT ($r=0.635$, $p<0.001$) [9].

AoAC extent was divided into four grades according to the following categorization. Briefly, we scored the extent of calcification in the aortic arch as follows: grade 0, AoACS=0%; grade 1, AoACS=1-24%; grade 2, AoACS=25-49%; grade 3, AoACS≥50%. Progression of AoAC was defined as an increase in AoACS on the follow-up chest X-ray at 1 year, 2 years, and 3 years after enrollment.

Laboratory and hemodynamic measurements

Blood was drawn just before starting a dialysis session in a fasting state. Serum albumin, calcium, phosphate, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, blood sugar, and C-reactive protein (CRP) and the concentration of hemoglobin were measured by using routine laboratory methods. Mean values of 3 measurements during the 3 months before chest radiography were used for analysis. Serum intact parathyroid hormone (PTH) was measured once at the time of radiography. Serum calcium levels were adjusted using the formula [calcium + (4-albumin)].

Clinical status of all subjects was evaluated by means of routine clinical examination before the regular HD session. Systolic and diastolic blood pressures were measured with a mercury sphygmomanometer with the patient in the supine position after 10 to 15 minutes of rest, and mean values for 1 month were used for the analysis. Hypertension was defined as predialysis systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90 mmHg, or if they were using any antihypertensive therapy.

Clinical outcomes

Subjects in this study were continuously monitored for the occurrence of cardiovascular events and death. In the present study, the cardiovascular events according to our definition were specified clearly as angina pectoris (criteria of angina pectoris were defined by presence of chest symptom and/or typical ST-T change in ECG), myocardial infarction, cerebrovascular disease (transient ischemic attack, stroke, cerebral hemorrhage), heart failure, and cardiovascular death. Individual diagnoses were classified according to the 9th International Classification of Disease (ICD-9) codes.

Statistical analysis

Continuous variables were expressed as means ± SD and categorical variables as percentages. Differences between the groups were analyzed using ANOVA for continuous variables and χ^2 test for categorical variables. Variables relevant to survival were identified by the univariate Cox proportional hazards method. Significant variables were then selected for further analysis using multivariate Cox proportional hazard models. The Kaplan-Meier method was used to estimate survival probabilities using the log-rank test. The impact of AoAC progression on patient outcome was also examined by the Kaplan-Meier analysis. All analyses were performed using JMP for Windows (version 11). A p value <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population

The mean age of the study population was 63.8 ± 12.2 years. The average dialysis vintage was 5.8 ± 6.4 years. Male patients accounted for 66%. About 40% of the patients had diabetes. A total of 301 patients were categorized 126 as Grade 0 (41.9%), 112 as Grade 1 (37.2%), and 63 as Grade 2 and 3 (20.9%). Table 1 shows the baseline clinical characteristics of all patients according to the severity of AoAC. There was no significant difference in dialysis vintage, and presence of diabetes and hypertension among all groups. The patients with severe calcification were older than those without calcification ($P < 0.0001$), and a significant increase in male gender ($P < 0.001$). We did not find significant differences in dialysis adequacy as assessed by Kt/V. Patients with AoAC had lower serum albumin levels ($P = 0.0368$). No significant differences in serum levels in phosphorus, calcium and intact

Table 1. Baseline demographic and biochemical data of the hemodialysis patients

	Grade 0	Grade 1	Grade 2+3	ALL	P-value
Patient, n (%)	126 (41.9%)	112 (37.2%)	63 (20.9%)	301 (100%)	
Dialysis vintage, years	5.0 ± 6.4	6.3 ± 6.9	6.3 ± 5.2	5.8 ± 6.4	0.2261
Age, years	58.3 ± 13.7	66.3 ± 9.2	70.2 ± 8.6	63.8 ± 12.2	<0.0001
Gender, M/F	98 / 28	63 / 49	37 / 26	198 / 103	0.0009
Diabetes, n (%)	53 (42.1%)	58 (51.8%)	34 (54.0%)	145 (48.2%)	0.1905
Hypertension, n (%)	106 (84.1%)	91 (81.3%)	54 (85.7%)	251 (83.4%)	0.7170
KT/V	1.4 ± 0.2	1.4 ± 0.3	1.4 ± 0.2	1.4 ± 0.2	0.2526
Hemoglobin, g/dl	10.8 ± 1.2	10.8 ± 1.1	10.5 ± 1.1	10.7 ± 1.1	0.3024
C-reactive protein, mg/dl	0.3 ± 0.6	0.4 ± 0.8	0.6 ± 1.0	0.4 ± 0.8	0.0917
Albumin, g/dl	3.7 ± 0.3	3.7 ± 0.3	3.6 ± 0.3	3.7 ± 0.3	0.0368
Corrected calcium, mg/dl	9.1 ± 0.7	9.1 ± 0.6	9.2 ± 0.5	9.1 ± 0.6	0.3077
Phosphorus, mg/dl	5.1 ± 1.6	4.9 ± 1.6	5.0 ± 1.7	5.0 ± 1.6	0.6378
Intact PTH, pg/dl	139.6 ± 159.6	121.3 ± 111.2	122.9 ± 102.3	129.3 ± 132.0	0.5188
Total cholesterol, mg/dl	145.2 ± 28.6	153.9 ± 33.2	153.3 ± 30.2	150.1 ± 30.9	0.0598
HDL cholesterol, mg/dl	44.0 ± 14.0	48.3 ± 15.5	45.3 ± 13.3	45.9 ± 14.5	0.0760
Triglyceride, mg/dl	119.0 ± 74.6	114.3 ± 79.3	107.3 ± 76.7	114.8 ± 76.7	0.6122
Non-HDL cholesterol, mg/dl	101.1 ± 29.1	105.7 ± 32.4	108.0 ± 30.6	104.3 ± 30.7	0.2901
RAS inhibitors	66 (52.4%)	52 (46.4%)	34 (54.0%)	152 (50.5%)	0.5422
CaCO ₃	88 (69.8%)	83 (74.1%)	46 (73.0%)	217 (72.1%)	0.7520
Non-Ca phosphate binders	65 (51.6%)	61 (54.5%)	36 (57.1%)	162 (53.8%)	0.7591
Active Vitamin D3	70 (55.6%)	56 (50.0%)	38 (60.3%)	164 (54.5%)	0.4003

Values are expressed as means ± SD, unless otherwise specified. PTH = parathyroid hormone; HDL = high-density lipoprotein; RAS = renin-angiotensin system; Non-Ca phosphate binder; non-calcium containing phosphate binder.

PTH were shown and the lipid profile did not differ. There was no significant difference in the prescription of renin-angiotensin system (RAS) inhibitor, CaCO₃, non-calcium containing phosphate binders and active vitamin D3.

Risk Factors Associated with Mortality

During a follow-up period of 3 years, there were 65 (21.6%) deaths in the study population. Cardiovascular death was detected in 43 deaths, which accounted for 66.2% of all deaths, followed by infectious disease (23.1%), malignancy (6.2%) and gastrointestinal bleeding (4.6%). As shown in Table 2, univariate analysis demonstrated that age, diabetes, hypertension, prescription of active vitamin D3 and AoAC (Grade 2 and 3) were significantly associated with cardiovascular mortality. In multivariate analysis, diabetes, hypertension, prescription of active vitamin D3 and Grade 2 and 3 AoAC were independently associated with cardiovascular mortality. Table 3 shows factors associated with all-cause mortality. Age, diabetes, serum levels of albumin and non-HDL cholesterol, prescription of active vitamin D3 and AoAC (Grade 2 and 3) were significant factors associated with all-cause mortality. Multivariate analysis demonstrated that age, diabetes, serum levels of albumin and non-HDL cholesterol and Grade 2 and 3 AoAC were independent factors related to overall survival.

Survival Analysis

Kaplan-Meier survival analysis of cardiovascular mortality is shown in Fig. 1. Patients without AoAC had less cardiovascular survival than those with AoAC (P = 0.0406). A higher mortality rate was observed in patients with high-grade AoAC (Grade 2+3). Fig. 2 displays the survival curve of different groups according to the severity of AoAC. Significant

Table 2. Univariate and multivariate Cox proportional hazards analysis for cardiovascular mortality

	Univariate			Multivariate		
	HR	95%CI	P-value	HR	95%CI	P-value
Dialysis vintage	1.007	0.939-1.064	0.8228			
Age	1.038	1.000-1.081	0.0488	1.035	0.993-1.082	0.1061
Male gender	1.502	0.624-4.163	0.3772			
Diabetes	4.151	1.656-12.572	0.0018	4.551	1.776-14.002	0.0011
Hypertension	0.354	0.154-0.880	0.0269	0.322	0.137-0.815	0.0185
KT/V	0.376	0.074-2.069	0.2611			
Hemoglobin	1.039	0.728-1.508	0.8386			
C-reactive protein	1.282	0.831-1.712	0.2199			
Albumin	0.336	0.113-1.117	0.0741			
Calcium	1.196	0.607-2.264	0.5966			
Phosphorus	0.919	0.708-1.184	0.5189			
Intact PTH	0.997	0.992-1.001	0.2307			
Total cholesterol	1.196	0.607-2.264	0.7011			
HDL cholesterol	1.018	0.991-1.043	0.1903			
Triglyceride	1.000	0.993-1.005	0.9228			
Non-HDL cholesterol	0.993	0.979-1.006	0.3046			
RAS inhibitor	0.620	0.258-1.414	0.2578			
CaCO ₃	1.111	0.461-3.079	0.8234			
Non-Ca Phosphate binder	0.919	0.403-2.118	0.8405			
Active Vitamin D3	0.287	0.103-0.690	0.0047	0.305	0.108-0.748	0.0087
AoAC						
Grade 1	2.838	1.053-8.920	0.0390	1.731	0.616-5.623	0.3065
Grade 2+3	4.636	2.794-9.149	0.0011	2.629	1.455-5.124	0.016

PTH = parathyroid hormone; HDL = high-density lipoprotein; RAS = renin angiotensin system; AoAC = aortic arch calcification.

differences were detected between patients with and without AoAC ($P = 0.0373$). There was no significant difference between Grade 1 and Grade 2+3.

Progression of AoAC as an Independent Risk Factor for Mortality

Kaplan-Meier analysis was used to determine the prognostic value of AoAC progression on mortality. MHD patients with AoAC progression had not significantly differences in cardiovascular mortality ($P = 0.1830$, Fig. 3). However, AoAC progression was significantly associated with higher all-cause mortality ($P = 0.0251$, Fig. 4).

Discussion

The results of the present study demonstrated a high prevalence of vascular calcification in MHD patients: more than 50% of the patients presented with AoAC and about one fourth of them had high-grade calcification. AoAC was associated with old age and male gender. Serum albumin levels were significant associates of AoAC. Furthermore, we found that AoAC progression was significantly associated with higher all-cause mortality but not cardiovascular mortality.

Vascular calcification has been considered a risk factor of cardiovascular mortality in ESRD patients. Arterial calcification increase stiffness and reduce elasticity of large arteries

Table 3. Univariate and multivariate Cox proportional hazards analysis for all-cause mortality

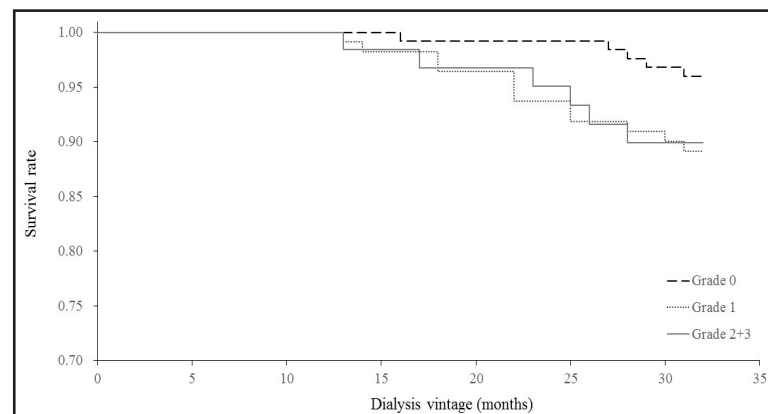
	Univariate			Multivariate		
	HR	95%CI	P-value	HR	95%CI	P-value
Dialysis vintage	1.013	0.963-1.056	0.6038			
Age	1.058	1.026-1.096	0.0002	1.060	1.022-1.102	0.0013
Male gender	1.485	0.746-3.215	0.2690			
Diabetes	2.835	1.445-5.963	0.0021	2.615	1.306-5.609	0.0061
Hypertension	0.608	0.299-1.362	0.2125			
KT/V	0.393	0.109-1.482	0.1678			
Hemoglobin	0.918	0.703-1.219	0.5490			
C-reactive protein	1.312	0.968-1.643	0.0751			
Albumin	0.202	0.091-0.481	0.0004	0.327	0.134-0.859	0.0242
Calcium	1.400	0.839-2.280	0.1939			
Phosphorus	0.972	0.795-1.181	0.7784			
Intact PTH	0.998	0.993-1.001	0.1481			
Total cholesterol	0.994	0.983-1.004	0.2393			
HDL cholesterol	1.019	0.999-1.039	0.0678			
Triglyceride	0.997	0.991-1.002	0.2207			
Non-HDL cholesterol	0.989	0.977-0.999	0.0363	0.984	0.972-0.997	0.0111
RAS inhibitor	0.868	0.455-1.643	0.6618			
CaCO ₃	0.962	0.490-2.023	0.9137			
Non-Ca Phosphate binder	0.684	0.356-1.295	0.2433			
Active Vitamin D3	0.420	0.209-0.807	0.0089	0.398	0.196-0.772	0.0062
AoAC						
Grade 1	2.006	0.934-4.545	0.0747	1.230	0.559-2.850	0.6112
Grade 2+3	3.409	2.015-5.781	0.0261	1.699	1.052-2.680	0.0222

PTH = parathyroid hormone; HDL = high-density lipoprotein; RAS = renin angiotensin system; AoAC = aortic arch calcification.

such as the aorta, which may result in substantial mortality and morbidity by impairing cardiovascular hemodynamics and vascular compliance [11]. Several imaging methods such as EBCT and MSCT are available to detect cardiovascular calcification in HD patients. These methods differ in the sensitivity, availability and cost [12, 13]. The KDIGO clinical practice

guideline recommends plain X-ray films of the lumbar spine for the detection and assessment of cardiovascular calcification in HD patients [14]. The AoAC identified in plain chest X-ray is associated with an increased risk of coronary artery disease and is linked to cardiovascular risk factors such as age, hypertension, dyslipidemia and diabetes mellitus in the

Fig. 1. Kaplan-Meier analysis for cardiovascular mortality of 301 maintenance hemodialysis patients.



general population [15, 16]. Moreover, compared with traditional risk factors, AoAC is an independent determinant of cardiovascular outcome [17]. The present study supports the additional value of plain chest X-ray films in MHD patients to predict their short-term outcome.

If the level of calcification in the aorta predicts future cardiovascular events, which area in the abdominal aorta or aortic arch is favorable and sensitive to evaluate the extent of calcification should be considered. First, there is much strong evidence that radiographic abdominal aortic calcification predicts cardiovascular events in huge populations during long-term follow-up. Okuno et al. also reported that the presence of abdominal aortic calcification is significantly associated with cardiovascular mortality in 515 HD patients (hazard ratio, 2.07; 95% confidence interval, 1.21-3.56; $P < 0.01$) [18], suggesting valuable evaluation of abdominal aortic calcification using abdominal X-ray. On the other hand, it is unclear whether the calcified level in the aortic arch is also a good predictor similar to the extent of calcification in the abdominal aorta. There are relatively few reports regarding the predictive value of AoAC against cardiovascular events, although many previous studies have shown a positive association of cardiovascular events with abdominal aortic calcification. One possible explanation is that it is not easier to evaluate calcium deposition semi-quantitatively in the aortic arch as compared to that in the abdominal aorta.

Fig. 2. Kaplan-Meier analysis for all-cause mortality of 301 maintenance hemodialysis patients.

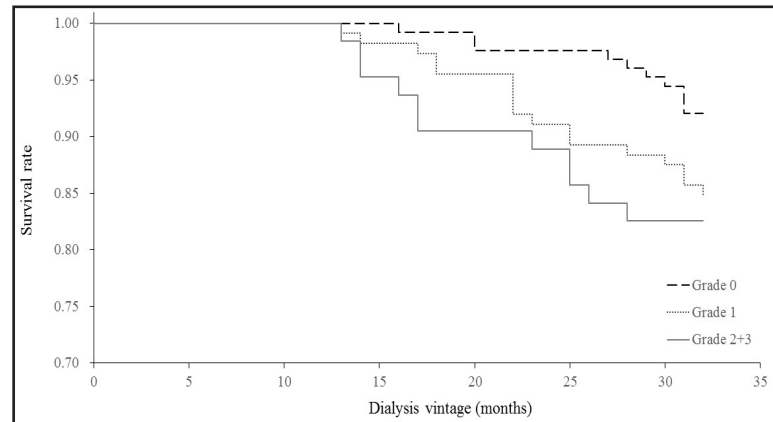


Fig. 3. Kaplan-Meier analysis of aortic arch calcification progression for cardiovascular mortality of 301 maintenance hemodialysis patients. Prog = progression.

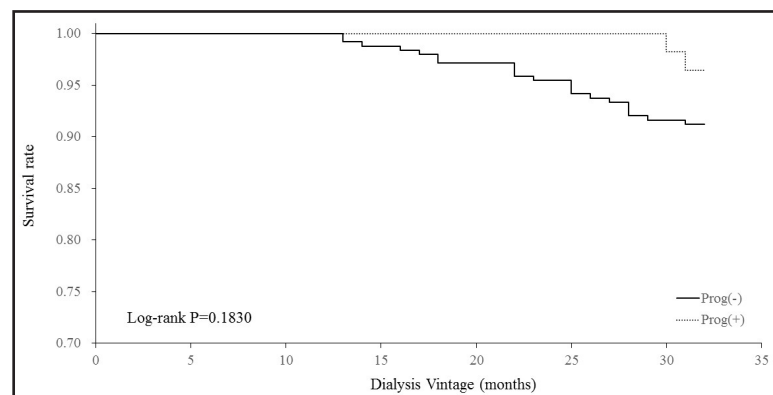
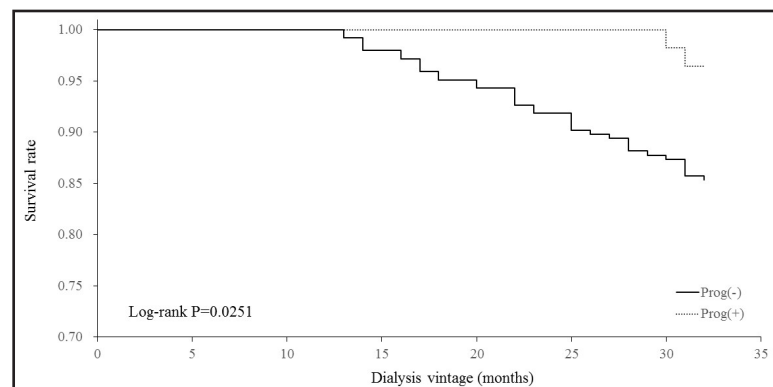


Fig. 4. Kaplan-Meier analysis of aortic arch calcification progression for all-cause mortality of 301 hemodialysis patients. Prog = progression.



A report handling a population-based cohort has showed that the presence of AoAC was independently associated with an increased risk of cardiovascular mortality (hazard ratio, 2.556; 95% confidence interval, 1.006-6.490; $P < 0.05$) [19], suggesting that the present results are consistent with this evidence. However, that study evaluated whether AoAC was present or absent using chest X-ray without considering the extent of calcification. There are several advantages and differences of our study as compared to the previous report. Our assessment by AoAC grading certified a strong predictive value of higher AoAC grade (grades 2 + 3) against incident cardiovascular events more precisely. However, AoAC grade 1 had no statistical significance of predictive value compared to grade 0. This result suggests that trivial calcium deposition in the aortic arch only may not be a noticeable cardiovascular risk. Hashimoto et al. recently confirmed that the AoAC grade was significantly correlated with the calcified level in the abdominal aorta using two independent non-invasive examinations [20]. In fact, huge differences in the hemodynamic state are found between patients with trivial AoAC and those with severe AoAC. Therefore, it is recommended to consider the AoAC grade in routine clinical work of dialysis therapy.

The results of the present study have shown the association between AoAC at baseline and short-term outcome, indicating the importance of screening for cardiovascular calcification in MHD patients. In multivariate analysis, patients with high-grade AoAC had a significant association with cardiovascular death and all-cause mortality. Among factors relevant to survival, diabetes was independently associated with both cardiovascular and all-cause mortality. These data are almost identical with those recently reported by Lee et al. [21]. However, Lee et al. did not include the prescription of RAS inhibitors, CaCO_3 , non-calcium phosphate binders and active vitamin D as confounders. Especially, the prescription of active vitamin D is associated with cardiovascular and all-cause mortality (Table 2 and 3). It has been reported that pre-dialysis fasting glucose levels correlate with short-term outcome in HD patients [22]. Kim et al. have recently reported that diabetes accelerates the progression of AoAC in HD patients [23]. They showed that hyperglycemia mostly associated with type 2 diabetes, was the only significant predictor of vascular calcification in ESRD patients. Recent evidence suggests that medial calcification in diabetes is an active, cell-mediated process, similar to that observed in ESRD patients [24].

One of the important findings in the present study is the association between prescription of active vitamin D3 and short-term outcome. The use of active vitamin D3 is an independent predictor for cardiovascular and all-cause mortality. We previously demonstrated that alfacalcidol therapy was associated with a significantly lower risk of cardiovascular and all-cause mortality in chronic HD patients [25]. Low doses and more physiological doses of active vitamin D have been found to have a cardioprotective effect [26, 27]. We previously reported finding that low-dose oral vitamin D therapy protect HD patients from developing vascular calcification [28]. In a study of 242 HD patients, Shoji et al. [29] reported that HD patients treated with alfacalcidol were at reduced risk of cardiovascular death according to an adjusted Cox model. Naves-Diaz et al. [30] reported that a mean daily oral vitamin D dose below 0.25 μg was able to reduce the mortality rate by 53% in HD patients whose serum PTH levels were below 150 pg/ml, independently of their serum calcium or phosphorus levels. These findings suggest that low dose active vitamin D3 may improve cardiovascular and all-cause mortality of HD patients in association with the modulation of vascular calcification.

There are several limitations in the present study. First, evaluation of AoAC is the semi-quantitative method, thus this method using four grades to evaluate AoAC is relatively crude. Therefore, the true calcium deposition in the aortic wall may be underestimated. However, our previous study confirmed that AoACS was highly correlated with aortic arch calcification volume evaluated by MSCT [9]. Second, the largely observational design reduced the quality of the study, and the population size in this study was also small. Therefore, a largely prospective study using examinations for AoAC evaluated by both plain chest X-ray and CT is necessary.

Conclusion

The presence and progression of AoAC assessed by chest X-ray were independently associated with mortality in MHD patients. Regular follow-up by chest X-ray could be a simple and useful method to stratify mortality risk in MHD

Disclosure Statement

We have no conflict of interest to disclose.

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