Atherosclerosis 331 (2021) 12–19

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

All-cause and cardiovascular mortality in patients undergoing hemodialysis with aortic sclerosis and mild-to-moderate aortic stenosis: A cohort study

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ARTICLE INFO

Keywords:
Aortic stenosis
Aortic sclerosis
Calcific aortic valve disease
Aortic valve calcification
All-cause death
Cardiovascular death
Hemodialysis

ABSTRACT

Background and aims: Mild-to-moderate aortic stenosis (AS) and aortic sclerosis, a precursor of AS, are associated with mortality in the general population; however, their association in patients undergoing hemodialysis with higher morbidity of AS is unknown. Thus, we investigated the mortality of aortic sclerosis and mild-to-moderate AS in patients undergoing hemodialysis.

Methods: This was a retrospective multicenter cohort study of consecutive patients undergoing hemodialysis at nine dialysis facilities who underwent screening echocardiography between January 2008 and December 2019. We investigated the mortality of patients with aortic sclerosis or mild-to-moderate AS using multivariable Cox proportional hazards regression.

Results: Among 1,878 patients undergoing hemodialysis, those with normal aortic valves, aortic sclerosis, mild AS, moderate AS, severe AS, and prosthetic aortic valves were 844 (45%), 793 (42%), 161 (8.6%), 38 (2.0%), 11 (0.6%), and 31 (1.7%), respectively. After excluding patients with severe AS and prosthetic aortic valves, we performed comparative analysis on 1,836 patients (mean age, 67 years; 66% male). In a median follow-up of 3.6 years, crude death rates (per 100 person-years) were 5.2, 10.6, and 13.0 in patients with normal aortic valves, aortic sclerosis, and mild-to-moderate AS, respectively. Compared with normal aortic valves, both aortic sclerosis and mild-to-moderate AS were associated with all-cause and cardiovascular death: adjusted hazard ratios (95% confidence intervals) were 1.36 (1.13–1.65) and 1.36 (1.02–1.80) for all-cause death; and 1.52 (1.06–2.17) and 1.74 (1.04–2.92) for cardiovascular death, respectively.

Conclusions: Aortic sclerosis and mild-to-moderate AS were independent risk factors for all-cause and cardiovascular death in patients undergoing hemodialysis.

1. Introduction

Aortic stenosis (AS) is the most prevalent valvular heart disease, and calcific aortic stenosis has recently become the most common cause of AS, especially in industrialized countries [1,2]. However, effective treatment to slow or halt the progression of AS has not been established. Aortic valve calcification is widespread in patients with end-stage renal disease due to various factors, including mineral and bone disorders, and chronic inflammation [3]. AS in patients undergoing hemodialysis (HD) develops 10–20 years earlier and progresses faster than in the general population [4–6], and patients undergoing HD with severe AS have higher mortality than non-dialysis patients [7–9]. Moreover, due to high surgical risk, aortic valve replacement (AVR) is often avoided in patients undergoing HD [10], often causing intradialytic hypotension [4]. Thus, AS causes severe clinical problems, especially in patients undergoing HD.

Aortic valve calcification without hemodynamic obstruction is called aortic sclerosis, which puts patients at risk of developing AS [11]. The continuum from aortic sclerosis to calcific AS is termed calcific aortic valve disease (CAVD). In the general population, aortic sclerosis is an independent risk factor for mortality [12,13]. However, few reports exist regarding mortality from early CAVD, such as aortic sclerosis and

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https://doi.org/10.1016/j.atherosclerosis.2021.06.910
Received 19 March 2021; Received in revised form 28 May 2021; Accepted 24 June 2021
Available online 25 June 2021

mild-to-moderate AS, in patients undergoing HD with higher morbidity and progression rates of AS. Previous reports did not distinguish between aortic sclerosis and AS or aortic and mitral valve calcification [14–18]. Thus, CAVD, including AS of any severity, is reported to be a mortality risk, but it is unclear whether it is also a mortality risk when limited to aortic sclerosis or mild-to-moderate AS. The distribution of CAVD severity in patients undergoing HD is also unclear. Additionally, reports on factors associated with CAVD in patients undergoing HD correspond to relatively small sample size, and it is unclear whether the factors vary across CAVD severity.

We hypothesized that in patients undergoing HD, CAVD would be more prevalent and present a mortality risk from an early stage, and that factors associated with CAVD would vary with severity. To prove these hypotheses, we evaluated the prevalence, mortality risk, and associated factors of aortic sclerosis and AS, expecting to pave the way for early detection and prevention.

2. Patients and methods

2.1. Study design and population

We conducted a retrospective cohort study of patients undergoing HD at nine Kaikoukai Healthcare Group facilities. In principle, annual screening echocardiography was recommended to all patients in these facilities. Patient inclusion was initiated at each facility introducing the electronic medical chart, with the earliest facility in January 2008 and the latest in January 2018 (Supplementary Table 1). Eligibility criteria for the CAVD prevalence investigation (descriptive cohort) included outpatients undergoing maintenance HD and echocardiography after the first 90 days of HD. For patients with multiple echocardiogram data, we used the oldest one, and the baseline was defined as the date of that echocardiogram. Exclusion criteria included age <18 years, requiring reinitiation of HD treatments, combined peritoneal dialysis and HD therapy, non-determinable CAVD severity due to missing aortic valve data, rheumatic aortic valve disease, other than tricuspid aortic valve, and an observation period <30 days. Patients with a short observation period were excluded because the echocardiography may have been event-related. Patients included in the descriptive cohort, excluding those with prosthetic aortic valves, were divided into five groups based on the presence or absence of aortic valve calcification, and peak aortic jet velocity (Vmax): normal aortic valves: absence of aortic valve calcification regardless of Vmax; aortic sclerosis: presence of aortic valve calcification and Vmax <2 m/s; mild AS: Vmax 2–2.9 m/s; moderate AS: Vmax 3–3.9 m/s; and severe AS: Vmax ≥4 m/s [11]. Of these, excluding severe AS, were included in the analysis of the comparative study (analytic cohort), which was classified into three groups: normal aortic valves, aortic sclerosis, and mild-to-moderate AS (Supplementary Fig. 1).

This study was designed in compliance with the Declaration of Helsinki. The ethics committee of each institution approved the study protocol (approval number, 2014–0422) and waved patient consent.

2.2. Conditions of hemodialysis

In principle, all patients received in-center HD three times a week, for three to 5 h per session, with vascular access via an arteriovenous fistula or graft, except for one case with a permanent catheter.

2.3. Echocardiography

Medical technologists at Nagoya Kyoritsu Hospital performed transthoracic echocardiography using Vivid 7, Vivid E9, or Vivid E90 (GE Healthcare Japan Corporation, Tokyo, Japan). Aortic valve calcification was determined as thickening with increased brightness of the aortic valve leaflet [19]. Vmax was measured by the continuous wave Doppler method [20]. The ejection fraction (EF) was measured using the modified Simpson method or the Teichholz method [21].

2.4. Outcomes

The primary endpoint was all-cause death. The secondary endpoint was cardiovascular death, defined as death attributable to acute myocardial infarction, cardiac arrest due to arrhythmia or unknown cause, heart failure, stroke, cardiovascular procedure, cardiovascular hemorrhage, peripheral arterial disease, or other cardiovascular causes [22].

2.5. Data collection

Baseline and outcome information was extracted from the medical records. Outcome information after transfer to another institution was collected by contacting the patient's medical institution of transfer or family members. Information on the comorbid conditions and smoking status was obtained by medical interview. History of ischemic heart disease was defined as prior myocardial infarction, angina, coronary artery bypass graft, or percutaneous coronary intervention. History of cerebrovascular disease was defined as prior intracranial hemorrhage, cerebral infarction, transient ischemic attack, carotid endarterectomy, or carotid artery stenting. Smoking included current smokers and former smokers who quit within five years. Baseline laboratory measurements were taken from the most recent pre-dialysis blood test after two non-dialysis days, within 12 weeks before and after the baseline date. Body mass index (BMI) was calculated using the following formula: BMI = (post-dialysis weight)/height^2. Medications were considered to be used if prescribed within four weeks before or after the baseline date.

2.6. Statistical analyses

In the descriptive cohort, we calculated the prevalence of each of the six CAVD severities at baseline, overall, and by age category (<50, 50–59, 60–69, 70–79, and ≥80 years) and dialysis vintage category (<2, 2–9.9, and ≥10 years).

Baseline characteristics of the analytic cohort were summarized in three groups: normal aortic valves, aortic sclerosis, and mild-to-moderate AS, presenting normally distributed variables, non-normally distributed variables, and categorical variables as mean (standard deviation [SD]), median [interquartile range (IQR)], and percentage, respectively. Normality of each continuous variable was determined by whether the histogram was bell-shaped or not.

Patients in the analytic cohort were followed until death or other censoring events, including transfer to other facilities and HD discontinuance because of transition to peritoneal dialysis, kidney transplantation, or kidney function recovery, up to December 31, 2019. Crude rates for all-cause and cardiovascular death, and AVR were calculated by the study group. The Kaplan-Meier method with log-rank test was used to assess the difference in all-cause and cardiovascular deaths between the three groups. Unadjusted, age- and sex-adjusted, and multivariable-adjusted Cox proportional hazards models were used to calculate hazard ratios (HRs) with their 95% confidence intervals (CIs) of aortic sclerosis and mild-to-moderate AS using normal aortic valves as the reference, after confirming the proportional hazards assumption by plotting Schoenfeld residuals and log-log survival curves. Covariates in the multivariable models included age, sex, dialysis vintage, BMI, diabetic nephropathy, reduced EF (≤50%), hemoglobin, albumin, creatinine, C-reactive protein (CRP), total cholesterol, calcium, phosphorus, parathyroid hormone, single-pool Kt/V, and medication data (including renin-angiotensin system inhibitors, β-blockers, number of antihypertensive drug classes (0, 1–2, and 3–4), phosphate binders, vitamin D receptor activators, statins, and antiplatelet drugs) at baseline. CRP was calculated as the time average of all values (12 weeks before and after the baseline date) to avoid the effect of temporary elevation [23]. Time-averaged CRP and parathyroid hormone were log-transformed

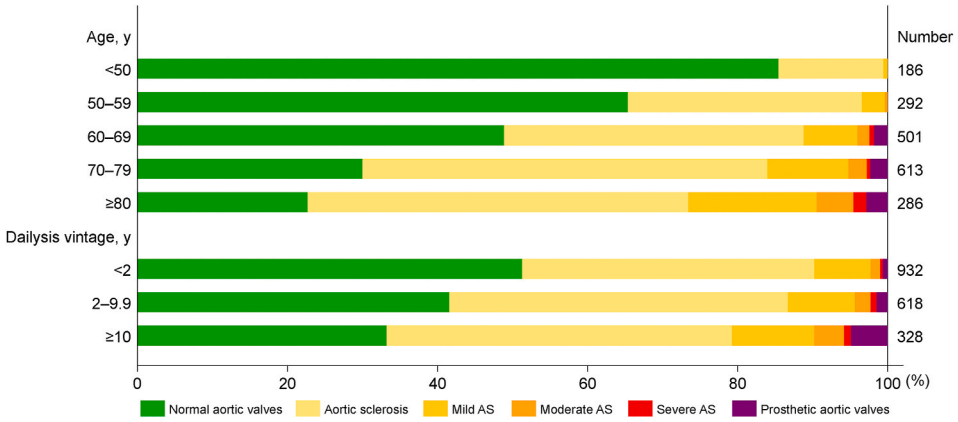

Fig. 1. Distribution of severity of calcific aortic valve disease by age and dialysis vintage category.
AS, aortic stenosis.

Table 1
Baseline characteristics of the analytic cohort by study group.

	Total (N = 1,836)	Normal aortic valves (n = 844)	Aortic sclerosis (n = 793)	Mild-to-moderate AS (n = 199)
Demographics				
Age, y	67 (12)	62 (13)	71 (10)	74 (9)
Male sex	66%	67%	66%	63%
Dialysis vintage, y	2.0 [0.7–7.0]	1.4 [0.6–5.4]	2.8 [0.8–7.8]	3.6 [0.8–9.9]
Body mass index, kg/m^2	22.0 (4.1)	22.6 (4.4)	21.5 (3.8)	21.7 (3.4)
Smoking	22%	26%	20%	13%
Comorbid conditions				
Diabetic nephropathy	48%	45%	51%	44%
Reduced ejection fraction (≤50%)	7.3%	6.4%	8.6%	5.6%
History of ischemic heart disease	24%	17%	30%	28%
History of cerebrovascular disease	23%	17%	28%	27%
Laboratory measurements				
Hemoglobin, g/dL	10.9 (1.2)	10.9 (1.2)	10.8 (1.1)	10.9 (1.3)
Albumin, g/dL	3.6 (0.4)	3.6 (0.4)	3.5 (0.4)	3.4 (0.4)
Time-averaged C-reactive protein, mg/dL	0.17 [0.08–0.53]	0.14 [0.07–0.44]	0.20 [0.09–0.60]	0.22 [0.10–0.59]
Creatinine, mg/dL	9.6 (2.9)	10.1 (3.1)	9.3 (2.7)	9.0 (2.5)
Corrected calcium, mg/dL	9.0 (0.6)	8.9 (0.7)	9.0 (0.6)	9.1 (0.7)
Phosphorus, mg/dL	5.2 (1.3)	5.3 (1.3)	5.1 (1.3)	5.2 (1.3)
Parathyroid hormone, pg/mL	134 [75–202]	138 [78–208]	124 [74–202]	116 [64–194]
Alkaline phosphatase, IU/L	264 (109)	255 (106)	273 (109)	269 (121)
Total cholesterol, mg/dL	154 (33)	156 (33)	152 (32)	154 (37)
Low-density lipoprotein cholesterol, mg/dL	82 (27)	83 (27)	81 (26)	83 (29)
High-density lipoprotein cholesterol, mg/dL	45 (14)	46 (14)	43 (14)	45 (14)
Triglycerides, mg/dL	113 (82)	122 (98)	109 (70)	96 (50)
Transferrin saturation, %	24 (11)	25 (12)	24 (11)	24 (11)
Ferritin, ng/mL	80 [40–152]	78 [38–151]	83 [40–152]	88 [45–158]
Single-pool Kt/V	1.5 (0.3)	1.5 (0.3)	1.5 (0.3)	1.6 (0.3)
Medications				
Antihypertensive drugs	78%	80%	76%	76%
Renin-angiotensin system inhibitors	50%	52%	49%	49%
β -blockers	39%	38%	41%	32%
Calcium channel blockers	57%	59%	55%	59%
Other antihypertensive drugs	10%	10%	11%	10%
Number of antihypertensive drug classes				
0	22%	20%	24%	24%
1–2	55%	58%	52%	55%
3–4	22%	22%	24%	22%
Phosphate binders	73%	78%	69%	66%
Vitamin D receptor activators	70%	73%	67%	70%
Calcimimetics	14%	14%	13%	17%
Statins	26%	27%	25%	26%
Antiplatelet drugs	44%	36%	50%	48%

Continuous variables are presented as mean (standard deviation) if normally distributed, and median [interquartile range] if non-normally distributed. Categorical variables are presented as percent.

Table 2
Event numbers and incidence rates by study group and hazard ratios of each group for all-cause and cardiovascular death.

Number and incident rate of event						
	Normal aortic valves (n = 844)		Aortic sclerosis (n = 793)		Mild-to-moderate AS (n = 199)	
Event	Number	Rate/100 PY	Number	Rate/100 PY	Number	Rate/100 PY
All-cause death	203	5.2	326	10.6	82	13.0
Cardiovascular death	54	1.4	97	3.2	26	4.1
Aortic valve replacement	1	0.026	14	0.46	17	2.7
Cox proportional hazards regression analysis						
	Normal aortic valves HR (95% CI)		**Aortic sclerosis HR (95% CI)**		**Mild-to-moderate AS HR (95% CI)**	
All-cause death						
Unadjusted model	1.00 (Reference)		2.09 (1.75–2.49)		2.72 (2.10–3.52)	
Age- and sex-adjusted model	1.00 (Reference)		1.46 (1.22–1.75)		1.57 (1.20–2.05)	
Multivariable-adjusted model[a,b]	1.00 (Reference)		1.50 (1.14–1.98)		1.67 (1.11–2.53)	
Multivariable-adjusted model using MI[a]	1.00 (Reference)		1.36 (1.13–1.65)		1.36 (1.02–1.80)	
Cardiovascular death						
Unadjusted-model	1.00 (Reference)		2.31 (1.65–3.22)		3.19 (1.99–5.11)	
Age- and sex-adjusted model	1.00 (Reference)		1.72 (1.22–2.43)		2.03 (1.25–3.31)	
Multivariable-adjusted model[a,b]	1.00 (Reference)		2.03 (1.16–3.57)		2.95 (1.34–6.49)	
Multivariable-adjusted model using MI[a]	1.00 (Reference)		1.52 (1.06–2.17)		1.74 (1.04–2.92)	

AS, aortic stenosis; PY, person-years; HR, hazard ratio; CI, confidence interval; MI, multiple imputation.
Events are presented as number and incident rate per 100 PY. Values in Cox proportional hazards regression analysis are given as HR (95% CI).
[a] The multivariable-adjusted models were adjusted for age, sex, dialysis vintage, body mass index, diabetic nephropathy, reduced ejection fraction, history of ischemic heart disease, history of cerebrovascular disease, hemoglobin, albumin, creatinine, time-averaged C-reactive protein, corrected calcium, phosphorus, parathyroid hormone, total cholesterol, single-pool Kt/V, renin-angiotensin system inhibitors use, β-blockers use, number of antihypertensive drug classes (0, 1-2, and 3-4), phosphate binders use, vitamin D receptor activators use, statins use, and antiplatelet drugs use.
[b] Complete-case analysis (n = 1,063).

before inclusion in the multivariable models. The calcium level was corrected using the following formula if the albumin level was <4.0 g/dL: corrected calcium = total calcium + (4 - albumin) [24]. Because some covariates were missing, analyses using multiple imputation by chained equations were conducted in the multivariable models. We generated 20 imputed datasets and combined the estimates of analysis per dataset using Rubin's rule. Complete-case analyses were also conducted as sensitive analyses.

After the overall analysis, we also performed subgroup analyses of multivariable Cox models using multiple imputation with all-cause death as the outcome, by age (<70 *vs.* ≥70 years), sex, dialysis vintage (<2 *vs.* ≥2 years), etiology of end-stage renal disease (non-diabetic nephropathy *vs.* diabetic nephropathy), EF (>50 *vs.* ≤50%), and history of cardiovascular disease.

We performed ordinal logistic regression analysis with CAVD severity as the dependent variable to identify factors associated with more advanced CAVD. The proportional odds assumption was confirmed by the Brant test. In addition, focusing on the initiation phase until valve calcification occurred, we performed logistic regression analysis with aortic sclerosis *vs.* normal aortic valves as the dependent variable. Conversely, focusing on the disease progression phase after valve calcification had occurred, we also performed multiple regression analysis with Vmax as the dependent variable in a subgroup with aortic valve calcification (aortic sclerosis and mild-to-moderate AS). In this analysis, patients with reduced EF (≤50%) were excluded to avoid underestimation of Vmax. The assumption of homogeneity was confirmed by residuals versus fits plot. Multiple imputation was used in each analysis.

A two-tailed *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata/SE 15.1 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Baseline characteristics

Of the 2,692 patients undergoing HD during the inclusion period, 1,878 eligible patients were included in the descriptive cohort and 1,836 in the analytic cohort (Supplementary Fig. 1). In the descriptive cohort, the number of patients with normal aortic valves, aortic sclerosis, mild AS, moderate AS, severe AS, and prosthetic aortic valves was 844 (45%), 793 (42%), 161 (8.6%), 38 (2.0%), 11 (0.6%), and 31 (1.7%), respectively. The proportion of more advanced CAVD increased with older age and longer dialysis vintage (Fig. 1; Supplementary Table 2).

Table 1 shows the baseline characteristics of the analytic cohort by study group. In the group with normal aortic valves, aortic sclerosis, and mild-to-moderate AS, the mean (SD) age was 62 (13), 71 (10), and 74 (9) years, 67%, 66%, and 63% were male, and the median dialysis vintage was 1.4, 2.8, and 3.6 years, respectively. The prevalence of diabetic nephropathy was higher in the aortic sclerosis group than in the other two groups. Missing data were found in approximately 3%–4% of most variables (Supplementary Table 3).

3.2. Survival

The median [IQR] observation period was 3.6 [1.7–6.2] years. The numbers and incidence rates of all-cause and cardiovascular death, and AVR in each group are shown in Table 2. Crude death rates (per 100 person-years) were 5.2, 10.6, and 13.0 in patients with normal aortic valves, aortic sclerosis, and mild-to-moderate AS, respectively. Detailed causes of death are shown in Supplementary Table 4. The proportion of sudden cardiac death and death due to heart failure and peripheral arterial disease increased with CAVD progression. During follow-up, 248 (14%) censored cases included 229 transfers to other institutions, mainly due to relocation and, 19 HD discontinuance. The Kaplan-Meier curves showed a decreased survival rate in step with CAVD progression ($p < 0.001$; Fig. 2A). In the analysis of multiple imputed data, compared with normal aortic valves, both aortic sclerosis and mild-to-moderate AS were associated with increased mortality: multivariable-adjusted HRs were 1.36 (95% CI, 1.13–1.65) and 1.36 (95% CI, 1.02–1.80), respectively (Table 2). Similarly, the event-free survival rate for cardiovascular death decreased in step with CAVD progression ($p < 0.001$; Fig. 2B), and aortic sclerosis and mild-to-moderate AS were associated with increased cardiovascular mortality: multivariable-adjusted HRs were 1.52 (95%

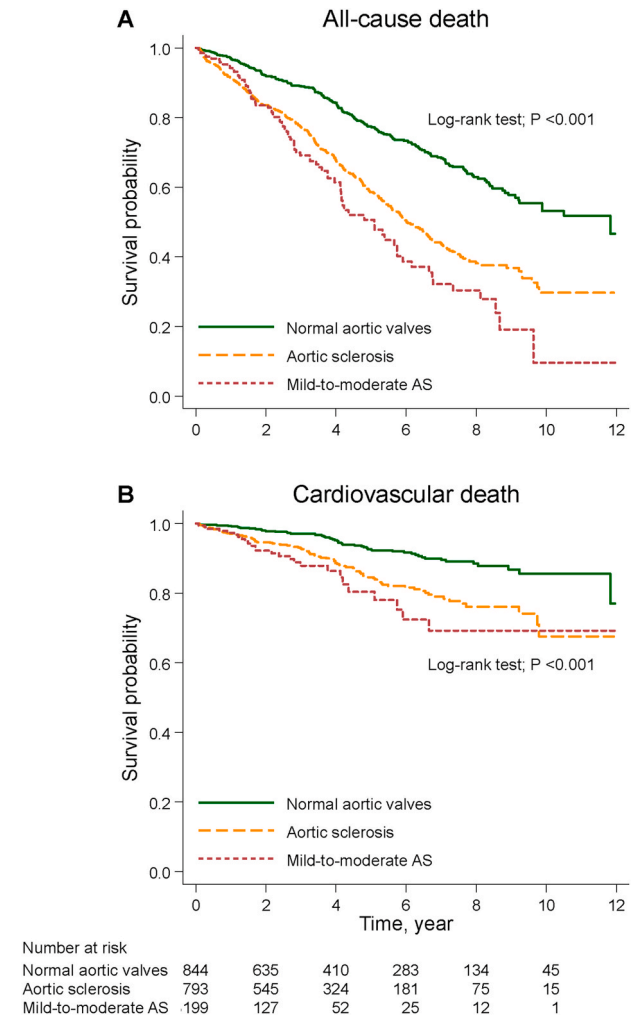

Fig. 2. Event-free survival for (A) all-cause death and (B) cardiovascular death by study group.
AS, aortic stenosis.

CI, 1.06–2.17) and 1.74 (95% CI, 1.04–2.92), respectively (Table 2).

3.3. Subgroup analyses

The tendency of aortic sclerosis and mild-to-moderate AS toward an elevated mortality risk was mostly consistent across subgroups, but there was a significant interaction between CAVD severity and diabetic nephropathy, with a relatively low HR of mild-to-moderate AS in patients with diabetic nephropathy ($p = 0.002$; Supplementary Fig. 2).

3.4. Associated factors of calcific aortic valve disease

Table 3 shows the results of ordinal logistic regression with CAVD severity as the dependent variable, logistic regression with aortic sclerosis *vs.* normal aortic valves as the dependent variable, and multiple regression with Vmax as the dependent variable in the subgroup with aortic valve calcification (aortic sclerosis and mild-to-moderate AS) and preserved EF (>50%). Factors associated with the dependent variables in each analysis were as follows: all analyses: age and dialysis vintage; ordinal logistic regression and logistic regression: diabetic nephropathy and history of ischemic heart disease; ordinal logistic regression and multiple regression: calcium, phosphorus, and number of antihypertensive drug classes (≥3); only multiple regression: β-blockers.

4. Discussion

4.1. Findings

There are three notable findings in this multicenter cohort study of patients undergoing HD focusing on aortic sclerosis and AS. First, we reported the distribution of CAVD severity in patients undergoing HD in detail. Second, aortic sclerosis and mild-to-moderate AS were independent risk factors for all-cause and cardiovascular death. Third, the results of the three regression analyses clearly identified factors separately associated with the development and progression of CAVD. To our knowledge, this is the first study to report these findings in patients undergoing HD.

4.2. Data interpretation and clinical implications

Of note, aortic valve calcification was found in more than half of the registered patients, and the proportion of more advanced CAVD notably increased with older age and longer dialysis vintage. In this study, the prevalence of aortic sclerosis and AS in each age group of patients undergoing HD were comparable to those reported previously in general populations that were between 15 and 20 years older [2,13,25,26].

Although the mortality risk of aortic sclerosis in this study was similar to that of the previous report involving general population [12], this result in patients undergoing HD with a high prevalence of CAVD has enormous clinical implications, suggesting the importance of preventing CAVD development, as well as its early detection and treatment. The HR for all-cause death was also similar to that of aortic valve calcification in a previous report on patients undergoing HD [15], which may not have reached significance due to its relatively small sample size. The cohort of this large scale, multicenter, comprehensive study is highly representative of a cohort of patients undergoing HD in Japan because it included more than 1,800 patients, comprising approximately 70% of all patients undergoing HD during the inclusion period, and the average age and sex ratio of the cohort was similar to the national average [27]. Although the patients in our study underwent HD at different facilities, they visited a single-center for echocardiography; therefore, minimizing inter-institutional errors in echocardiographic assessment. The almost consistent tendency of the elevated mortality risk of aortic sclerosis and mild-to-moderate AS across subgroups enhances the robustness of the main result, but there was a significant interaction between CAVD severity and diabetic nephropathy. The reason for this could be survival bias, given the lower prevalence of diabetic nephropathy in patients with mild-to-moderate AS. Other possible reasons include unmeasured confounders and random error.

Importantly, aortic sclerosis and mild-to-moderate AS were associated not only with cardiovascular death, but also with all-cause death, and the adjusted HR of aortic sclerosis was as high as that of mild-to-moderate AS regarding all-cause death. This result suggests that aortic valve calcification is not just a surrogate maker for cardiovascular disease, and this is clinically useful because the risk of mortality can be easily assessed by checking the presence of aortic valve calcification by echocardiography. Some of the deaths may be attributed to CAVD progression, considering the increased proportion of sudden cardiac death and death due to heart failure in step with CAVD progression, and that 14 patients with aortic sclerosis at baseline progressed to severe AS requiring AVR in a relatively short period in this study, unlike the general population, which has a lower rate of progression to AS [28]. However, most deaths were not a direct effect of CAVD. Although the exact mechanism is still uncertain, a possible mechanism is that aortic valve calcification is a surrogate marker of not only the general vascular disease but also inflammation, which can lead to death due to various causes [13,29]. Alternatively, adverse events, such as heart failure, may trigger inflammation [30] or increase deaths due to various causes through worsening general conditions.

Although most factors associated with CAVD were consistent with

Table 3
Multivariable ordinal logistic regression and logistic regression for calcific aortic valve disease and multiple regression for peak aortic jet velocity in a subgroup with aortic valve calcification and preserved ejection fraction.

	Ordinal logistic regression model (N = 1,836)	Logistic regression model (N = 1,637)	Multiple regression model (N = 909)		
	OR (95% CI)	OR (95% CI)	B	SE	β
Age, +1 y	1.09 (1.07–1.10)[a]	1.08 (1.07–1.09)[a]	0.012[a]	0.0023	0.30
Male sex	1.16 (0.89–1.50)	1.04 (0.77–1.40)	−0.010	0.050	−0.0099
Dialysis vintage, +1 y	1.06 (1.04–1.08)[a]	1.05 (1.03–1.08)[a]	0.015[a]	0.0033	0.19
Body mass index, +1 kg/m^2	1.03 (1.00–1.06)	1.01 (0.98–1.05)	0.0082	0.0060	0.070
Smoking	1.18 (0.87–1.62)	1.20 (0.85–1.68)	0.0074	0.060	0.0069
Diabetic nephropathy	1.58 (1.28–1.96)[a]	1.80 (1.40–2.32)[a]	−0.044	0.040	−0.045
Ejection fraction, +1%	1.01 (0.99–1.02)	1.00 (0.99–1.01)	0.0031	0.0028	0.043
History of ischemic heart disease	1.30 (1.00–1.69)[b]	1.38 (1.02–1.86)[b]	−0.0023	0.049	−0.002
History of cerebrovascular disease	1.14 (0.89–1.45)	1.24 (0.93–1.66)	−0.027	0.044	−0.024
Hemoglobin, +1 g/dL	1.03 (0.94–1.12)	1.00 (0.90–1.10)	−0.000028	0.017	0.000067
Albumin, +1 g/dL	0.76 (0.54–1.05)	0.85 (0.58–1.25)	−0.086	0.065	−0.066
Creatinine, +1 mg/dL	1.00 (0.95–1.06)	1.04 (0.98–1.10)	−0.011	0.011	−0.068
Log C-reactive protein, +1	1.03 (0.94–1.12)	1.02 (0.93–1.13)	0.012	0.016	0.033
Alkaline phosphatase, +10 IU/L	1.00 (0.99–1.01)	1.00 (0.99–1.01)	−0.0012	0.0018	−0.026
Total cholesterol, +10 mg/dL	1.00 (0.97–1.04)	0.99 (0.96–1.03)	0.0013	0.0063	0.0092
Corrected calcium, +1 mg/dL	1.33 (1.13–1.57)[a]	1.22 (1.00–1.48)	0.080[b]	0.032	0.11
Phosphorus, +1 mg/dL	1.12 (1.02–1.22)[b]	1.01 (0.92–1.12)	0.045[a]	0.016	0.12
Log parathyroid hormone, +1	1.01 (0.89–1.15)	1.07 (0.92–1.25)	−0.012	0.024	−0.20
Single-pool Kt/V, +1	1.20 (0.80–1.81)	1.21 (0.76–1.94)	−0.011	0.079	−0.0066
Renin-angiotensin system inhibitors	0.94 (0.71–1.24)	1.00 (0.72–1.38)	−0.013	0.054	−0.014
β-blockers	0.79 (0.60–1.04)	1.04 (0.76–1.43)	−0.17[a]	0.052	−0.17
No. of antihypertensive drug classes					
0	1.00 (Reference)	1.00 (Reference)		Reference	
1–2	1.08 (0.78–1.49)	0.86 (0.60–1.25)	0.099	0.060	0.14
3–4	1.69 (1.01–2.83)[b]	1.26 (0.69–2.27)	0.25[a]	0.097	0.35
Phosphate binders	0.94 (0.73–1.21)	0.92 (0.69–1.24)	0.027	0.047	0.024
Vitamin D receptor activators	0.90 (0.72–1.11)	0.86 (0.67–1.11)	0.013	0.042	0.012
Calcimimetics	1.04 (0.76–1.42)	0.88 (0.62–1.27)	0.018	0.060	0.013
Statins	1.12 (0.88–1.41)	1.02 (0.78–1.33)	0.052	0.047	0.047
Antiplatelet drugs	1.07 (0.85–1.34)	1.13 (0.87–1.46)	−0.049	0.042	−0.050

OR, odds ratio; CI, confidence interval; B, unstandardized regression coefficient; SE, standard error; β, standardized beta coefficient; AS, aortic stenosis.
In ordinal logistic regression, the dependent variable was the severity of calcific aortic valve disease: mild-to-moderate AS, aortic sclerosis, and normal aortic valves in descending order. In logistic regression, the dependent variable was aortic sclerosis *vs.* normal aortic valves. In multiple regression, the dependent variable was peak aortic jet velocity (m/s), and analysis was conducted in a subgroup of mild-to-moderate AS and aortic sclerosis with preserved ejection fraction (>50%). Multiple imputation was used in each analysis.
[a] $p < 0.01$.
[b] $p < 0.05$.

those in previous reports [31–33], our results revealed that some factors differed between the two phases of development and progression. As summarized in Supplementary Fig. 3, our results suggest that diabetic nephropathy and history of ischemic heart disease are predominantly associated with the initiation phase until valve calcification occurs, while serum calcium, phosphorus, and number of antihypertensive drug classes are predominantly associated with the calcification propagation phase. These findings could be explained by the pathophysiological theory dividing the progression of CAVD into two distinct phases: the initiation phase characterized by lipid deposition, inflammation, and calcification, with many similarities to atherosclerosis; and the propagation phase characterized by fibrosis and accelerated calcification, where deposition of hydroxyapatite, consisting of calcium and phosphorus, occurs [34]. Thus, it is necessary to recognize that the factors associated with CAVD can change biphasically. The reason that statins did not slow AS progression in three randomized controlled trials [35–37] may be that the subjects were in the propagation phase [38]. Statins have also been reported to be associated with increase of calcified plaque in coronary arteries as the plaque-stabilizing effect [39–41]; similarly, statins may not suppress aortic valve calcification once it has formed. Nevertheless, statins may still be effective only in the initiation phase of CAVD, as suggested in a previous observational study [42].

4.3. Limitations

This study has several limitations. First, regarding echocardiography, the aortic valve area (AVA) was not routinely measured, and the timing of examination (non-dialysis day or pre/post-dialysis) was not consistent. There were some AS cases without AVA measurement, and dobutamine stress echocardiography was not performed, even in cases with low Vmax and low AVA. AS severity based solely on Vmax was possibly underestimated in some cases, such as those with low-flow, low-gradient AS [43]; misclassification of severe AS as mild-to-moderate AS may lead to overestimation of the mortality risk of mild-to-moderate AS. Additionally, Vmax may vary with volume status, which is affected by the examination timing. These may lead to misclassification of AS severity. However, uniform classification of low AVA cases into severe AS may lead to overestimation [44,45]. Furthermore, severe AS was excluded from the analytic cohort, and the result of subgroup analysis by EF was consistent. It has also been reported that among the echocardiogram parameters, Vmax is less variable and more reproducible [46], and the difference in volume status in patients undergoing HD does not result in a significant difference in Vmax [47]. Therefore, it is considered valid to determine AS severity based solely on Vmax in this study. Second, there is the possibility of residual confounding. However, this is a common limitation in observational studies, and in this study, we included all available potential confounders in the analysis to minimize the effect of confounding. Third, some baseline data were missing. However, the impact of missing data on the results is considered to be minimal because the percentage of missing data was not large, and multiple imputation was conducted appropriately. Fourth, because the analyses to identify factors associated with CAVD were cross-sectional, the causation between the associated factors and CAVD progression is unknown.

4.4. Future perspectives

Our results suggest an increased need to establish treatments to prevent the development and progression of aortic sclerosis and AS, which have a poor prognosis among patients undergoing HD. As the results show, the treatment strategy may need to be divided into two phases: treatment similar to that for atherosclerosis in the initiation phase, and good management of mineral and bone disorders in the propagation phase may be the key. Investigations using longitudinal echocardiogram data are warranted prior to interventional studies to strengthen this hypothesis.

4.5. Conclusions

In conclusion, these results show that patients undergoing HD have a high prevalence of CAVD. Furthermore, aortic sclerosis, a precursor of AS, was found to be independently associated with mortality, with a risk comparable to mild-to-moderate AS.

Financial support

This study was supported by the Aichi Kidney Foundation (Grant number 11 in 2018). The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

CRediT authorship contribution statement

Shimon Kurasawa: Conceptualization, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Manabu Hishida:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Takahiro Imaizumi:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Masaki Okazaki:** Conceptualization, Writing – original draft, Funding acquisition. **Nobuhiro Nishibori:** Conceptualization. **Toru Kondo:** Conceptualization, Writing – original draft, Writing – review & editing. **Hirotake Kasuga:** Data curation, Project administration. **Shoichi Maruyama:** Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study would not have been possible without the contributions of the members of Kaikoukai Healthcare Group: Hiroshi Sakurai, for data collection; Masao Matsuzawa, for data extraction and management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.06.910.

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