Multicenter Prospective Cohort on Aortic Valve Stenosis in Japanese Patients With End Stage Kidney Disease in Tokai Region (ASKIT)

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Abstract

Background:

The prevalence of aortic valve stenosis (AS) in patients on maintenance dialysis is high and the prognosis is poor. Because only few large cohort studies have analyzed patients with AS on dialysis, the factors that cause AS in such patients remain unclear.

Methods:

This multicenter, prospective cohort study included 2,786 patients on dialysis who underwent transthoracic echocardiography between July 1, 2017 and June 30, 2018. Patients with a maximum aortic jet velocity ($V_{\max}$) ≥ 2.0 m/s, pressure gradient (PG) between the left ventricle and ascending aorta (mean PG) ≥ 20 mmHg, or aortic valve area (AVA) ≤ 1.0 cm² were categorized into the AS group. Of these, patients with $V_{\max} \geq 3.0$ m/s, mean PG ≥ 20 mmHg, or AVA ≤ 1.0 cm² were categorized into the severe AS group. The AS and severe AS groups were then compared with the non-AS group to identify the risk factors for AS using multivariate logistic analysis. We also compared the risk factors for AS with and without aortic valve calcification, which is the stage prior to age-related AS.

Results:

Of the 2,786 patients analyzed, 555 (20.0%) and 139 (6.9%) were categorized into the AS and severe AS groups, respectively. Multivariate logistic analysis revealed that aging, long-term dialysis, and elevated serum phosphorus levels were associated with AS in the AS and severe AS groups ($p < 0.05$). Additional investigation using stratified multivariate analysis revealed that groups with serum phosphorus levels of 5.0–5.9 mg/dL and > 6.0 mg/dL had a higher risk of AS than those with serum phosphorus levels of < 4.0 mg/dL (odds ratio: 2.24; $p = 0.01$ and odds ratio: 2.66, $p = 0.005$, respectively). Aortic valve calcification was associated with aging, long-term dialysis, diabetes mellitus, administration of vitamin D receptor activators, elevated serum calcium levels, and anemia ($p < 0.05$ for all).

Conclusions:

Dialysis patients had a high prevalence of AS, and AS was associated with aging, long dialysis duration, and elevated serum phosphorus levels.

Trial registration: UMIN000026756, Registered on March 29, 2017.

Background

Chronic kidney disease (CKD) is known as a serious risk factor for cardiovascular disease (CVD). (1–5) Among dialysis patients, the prevalence of CVD, particularly aortic valve stenosis (AS), was reported to range from 13–25%, (6, 7) which is higher than the 2.3–4.3% prevalence in the general elderly population. (8, 9) Previous clinical studies have reported that AS in patients undergoing dialysis is characterized by a

rapid decrease in the aortic valve area (AVA) and a rapid progression of aortic valve calcification.(10, 11) In addition, patients with AS and CKD have been reported to have a lower survival rate than those without CKD.(12, 13)

In the general population, age-related changes of the aortic valve, which gradually develops sclerosis and calcification,(14) have replaced rheumatic fever as the main cause of AS.(15) Morphological changes in the aortic valve are triggered by several factors, which include mechanical stress, endothelial damage, inflammation, and valve hemorrhage.(16) Consequently, the aortic valve leaflet becomes thickened, fibrotic, and calcified, leading to stenosis. However, the mechanisms involved remain unclear. While some studies have pointed out aging, male gender, hypertension, dyslipidemia, and smoking as factors that cause valve degeneration, (9, 17, 18) other studies have rejected hypertension, dyslipidemia, diabetes mellitus, or renal insufficiency as factors that promote AS.(19–21) Currently, there is no consensus as to the risk factors that promote the development of AS.

Patients undergoing dialysis have a higher prevalence of hypertension, diabetes mellitus, and Mineral and Bone Disorder (MBD) than the general population. These conditions are associated with arteriosclerosis and CVD;(22–28) however, it is unclear if they are associated with AS because there are no large cohort studies that have examined the factors that influence the development of AS in patients undergoing dialysis. Therefore, we conducted a multicenter prospective cohort study to investigate the factors related to AS, the prevalence of AS, and the prognosis of patients undergoing dialysis with AS. In this report, we analyzed the results obtained at the baseline.

Materials And Methods

Study Population

This study is a prospective multicenter observational study of patients undergoing maintenance dialysis. The subjects are patients aged 20 years or older who had been undergoing outpatient maintenance dialysis for over a year at 58 hospitals in the Tokai region of Japan. The baseline was set at the time of transthoracic echocardiography (TTE) between July 1, 2017 and June 30, 2018. Patients who had previously undergone aortic valve surgery and who did not agree to be part of this study were excluded. We enrolled 2,786 patients and collected their background, history, comorbidities, medications, laboratory data, chest X-ray results, electrocardiogram tracings, and TTE images. Of the 2,786 patients, 130 patients were excluded because the duration of dialysis was less than a year, the initiation of dialysis was unknown, the aortic valve surgery had been performed, or the TTE was performed outside the observation period.

Definition of aortic stenosis

The AS parameters were measured using TTE and performed at each hospital. We obtained the maximum aortic jet velocity (V_{max}), pressure gradient (PG) between the left ventricle and ascending aorta (mean PG), and AVA to evaluate AS. We defined AS based on the 2014 American Heart

Association/American College of Cardiology (AHA/ACC) Guidelines for the Management of Patients with Valvular Heart Disease. AS was defined as 1) $V_{\max} \geq 2.0$ m/s, or 2) Mean PG ≥ 20 mmHg, or 3) $AVA \leq 1.0$ cm². The patients who met any of the criteria were classified into the AS group; otherwise, they were classified into the non-AS group. Of 555 patients in the AS group, 514 (92.6%) met the condition of $V_{\max} \geq 2.0$ m/s, 107 (19.3%) met mean PG ≥ 20 mmHg, and 102 (18.6%) met $AVA \leq 1.0$ cm². Based on this result, we newly classified the severe AS group, which changed the standard of $V_{\max}$ from ≥ 2.0 m/s to ≥ 3.0 m/s without changing the standard of mean PG and AVA. Of 193 patients in the severe AS group, 98 (50.8%) met $V_{\max} \geq 3.0$ m/s, 107 (55.4%) met mean PG ≥ 20 mmHg, and 102 (52.8%) met $AVA \leq 1.0$ cm². Figure 1 shows the process of the enrollment and classification of the patients into the different groups.

Statistics

Baseline data were presented as mean (standard deviation), median (interquartile range), or percentage for categorical measures in patients. We used Fisher's exact test for nominal variables and the Mann–Whitney U test for continuous variables to compare the baseline data of the AS group with that of the non-AS group, and that of the severe AS group with that of the non-AS group. For the multivariate Cox regression, we performed a univariate analysis to extract factors associated with AS and added factors associated with MBD to them. We defined a model that included the gender, age, duration of dialysis, nephrosclerosis as the primary cause of CKD, diabetes mellitus as a comorbidity, use of calcimimetics, use of vitamin D receptor activators, use of phosphate binders, serum albumin level, serum corrected calcium level, serum phosphorus level, serum intact parathyroid hormone level, serum C-reactive protein level, and serum hemoglobin level. For the stratified multivariate Cox regression, we divided the patients into 4 categories based on their age: <60, 60–69, 70–79, and ≥ 80 years. We also divided the patients into 4 categories based on their dialysis duration and serum phosphorus level: <5, 5–9, 10–14, and ≥ 15 years, and <4.0, 4.0–4.9, 5.0–5.9, and ≥ 6.0 mg/dL, respectively. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).⁽²⁹⁾ Two-sided values of $p < 0.05$ were considered statistically significant in all analyses.

Results

1. Baseline characteristics

A total of 2,786 patients were enrolled; 555 patients (20.0%) were defined as the AS group and 2,231 (80.0%) were defined as the non-AS group. Among the patients in the AS group, 193 patients (6.9%) were classified into the severe AS group. Table 1 shows the baseline characteristics of the patients. The median ages of the AS, severe AS, and non-AS groups were 75, 77, and 68 years, respectively. The median hemodialysis duration of the AS, severe AS, and non-AS groups were 8.0, 7.4, and 6.2 years, respectively. The prevalence rates of diabetes mellitus in the AS, severe AS, and non-AS groups were 36.0%, 39.9%, and 46.0%, respectively. There was no significant difference in the average serum phosphorus and serum-

corrected calcium levels among the three groups. For the TTE results, the aortic valve calcification rates in the AS and severe AS groups were 80.7% and 83.8%, respectively, which were higher than the 53.3% in the non-AS group.

Table 1
Baseline characteristics of the non-AS, AS, and severe AS groups

	Non-AS Group	AS Group	p value (vs Non-AS)	Severe AS Group	p value (vs Non-AS)
Basic Characteristics					
Male, %	67.0	63.6	0.13	59.6	0.04
Age, years	68 (59-75)	75 (68-82)	<0.001	77 (70-83)	<0.001
Dialysis duration, years	6.2 (3.1-12.4)	8.0 (3.8-15.1)	<0.001	7.4 (4.0-14.8)	0.005
Primary Disease					
Nephrosclerosis, %	11.9	17.3	0.001	16.6	0.07
Diabetic nephropathy, %	39.8	29.5	<0.001	31.6	0.03
Chronic glomerulonephritis, %	19.5	23.8	0.03	23.8	0.16
Comorbidity					
Diabetes mellitus, %	46.0	36.0	<0.001	39.9	0.11
Admission due to HF < 1 year, %	2.0	5.2	<0.001	8.3	<0.001
Percutaneous coronary intervention, %	10.8	15.5	0.003	16.1	0.03
Coronary artery bypass grafting, %	4.7	6.7	0.07	9.3	0.01
Aortic disease, %	4.8	10.8	<0.001	14.0	<0.001
Usage rate of medicine related to MBD					
Vitamin D receptor activators, %	81.3	79.6	0.40	78.2	0.29
Calcimimetics, %	34.9	35.5	0.80	38.3	0.35
Phosphate binders, %	84.7	78.6	<0.001	77.2	0.01
Blood Test					

Data are presented as the mean $\pm$ standard deviation or percentages. Age, dialysis duration, intact PTH, and C-reactive protein are expressed as the median (interquartile range). Abbreviations: Admission due to HF < 1 year, admission due to heart failure within 1 year before echocardiography; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter.

	Non-AS Group	AS Group	p value	Severe AS Group	p value
Corrected Calcium, mg/dl	9.1±0.6	9.1±0.6	0.16	9.1±0.7	0.55
Phosphorus, mg/dl	5.3±1.3	5.2±1.2	0.76	5.2±1.2	0.59
Intact PTH, pg/ml	132 (80-193)	122 (76-185)	0.05	118 (76-162)	0.04
Albumin, g/dl	3.6±0.4	3.5±0.4	<0.001	3.4±0.37	<0.001
C-reactive protein, mg/dl	0.12 (0.05-0.37)	0.12 (0.06-0.43)	0.15	0.11 (0.06-0.55)	0.15
Hemoglobin, g/dl	11.1±1.1	10.9±1.2	<0.001	10.8±1.1	0.002
Chest X-ray					
Cardiothoracic ratio, %	50.2±5.1	52.2±5.0	<0.001	53.0±5.0	<0.001
Aortic calcification, %	57.0	70.4	<0.001	73.3	<0.001
Electrocardiogram					
Atrial fibrillation, %	5.7	9.6	0.002	12.0	0.002
Heart rate, /min	74±13	74±13	0.91	75±13	0.63
Transthoracic Echocardiography					
Left atrial diameter, mm	36.6±6.5	38.5±6.4	<0.001	39.1±5.9	<0.001
LVDd, mm	46.9±6.8	46.9±6.1	0.63	46.2±6.4	0.26
LVDs, mm	30.6±6.4	30.5±6.0	0.96	30.1±6.6	0.17
Left ventricular ejection fraction, %	63.4±9.7	63.5±10.0	0.52	63.5±11.3	0.37
Aortic valve calcification, %	53.3	80.7	<0.001	83.8	<0.001
Mean pressure gradient, mmHg	5.1±2.7	15.5±9.6	<0.001	23.3±11.8	<0.001
Aortic valve area, cm ²	2.51±0.77	1.56±0.62	<0.001	1.08±0.46	<0.001
Velocity max, m/s	1.43±0.28	2.52±0.62	<0.001	2.96±0.87	<0.001
Data are presented as the mean ± standard deviation or percentages. Age, dialysis duration, intact PTH, and C-reactive protein are expressed as the median (interquartile range). Abbreviations: Admission due to HF < 1 year, admission due to heart failure within 1 year before echocardiography; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter.					

2. Multivariate analysis for AS

We included the aforementioned 14 items, which we predicted to be related to AS, as the multivariable adjusted model's factors. We performed a multivariate analysis comparing the AS and severe AS groups with the non-AS group (Table 2). In a comparison between the AS and non-AS groups, it was revealed that aging, long-term dialysis, and elevated serum phosphorus levels were associated with AS (multivariate-adjusted odds ratio [MOR], 1.93; 95% confidence interval [CI], 1.71–2.19; $p < 0.001$, MOR, 1.41; 95% CI, 1.21–1.64; $p < 0.001$, MOR, 1.16; 95% CI, 1.06–1.28; $p = 0.001$, respectively). Regarding these three factors, similar tendencies were observed for the severe AS group against the non-AS group (MOR, 2.51; 95% CI, 2.02–3.12; $p < 0.001$, MOR, 1.35; 95% CI, 1.06–1.71; $p = 0.01$, MOR, 1.24; 95% CI, 1.07–1.44; $p = 0.005$, respectively). On the other hand, nephrosclerosis as the cause of CKD was not associated with AS. Having diabetic mellitus had a significantly lower risk of AS in the AS group than the non-AS group (MOR, 0.74; 95% CI, 0.58–0.95; $p = 0.02$); however, no significant difference was found between the severe AS and non-AS group (MOR, 0.95; 95% CI 0.64–1.40, $p = 0.79$).

Table 2
Odds ratio for aortic valve stenosis by multivariate Cox regression

	AS group		Severe AS group	
	OR (95% CI)	p value	OR (95% CI)	p value
Male	1.02 (0.81-1.29)	0.86	0.94 (0.65-1.37)	0.75
Age (per 10 years)	1.93 (1.71-2.19)	<0.001	2.51 (2.02-3.12)	<0.001
Dialysis duration (per 10 years)	1.41 (1.21-1.64)	<0.001	1.35 (1.06-1.71)	0.01
Nephrosclerosis as the primary disease of CKD	0.94 (0.67-1.32)	0.72	0.88 (0.52-1.50)	0.65
Diabetes complications	0.74 (0.58-0.95)	0.02	0.95 (0.64-1.40)	0.79
Use of calcimimetics	1.16 (0.91-1.48)	0.24	1.59 (1.07-2.34)	0.02
Use of VDRA	0.94 (0.70-1.25)	0.66	0.91 (0.58-1.44)	0.69
Use of phosphate binders	0.87 (0.65-1.17)	0.35	0.86 (0.55-1.35)	0.52
Corrected Calcium (per 1 mg/dl)	1.27 (1.04-1.54)	0.02	1.17 (0.86-1.59)	0.31
Phosphorus (per 1 mg/dl)	1.16 (1.06-1.28)	0.001	1.24 (1.07-1.44)	0.005
Intact PTH (per 10 pg/ml)	1.00 (0.99-1.01)	0.41	1.00 (0.98-1.02)	0.91
Albumin (per 1 g/dl)	1.51 (1.05-2.17)	0.03	1.04 (0.58-1.84)	0.91
C-reactive protein (per 1 mg/dl)	0.98 (0.89-1.08)	0.67	1.02 (0.91-1.14)	0.77
Hemoglobin (per 1 g/dl)	0.85 (0.76-0.95)	0.003	0.86 (0.72-1.03)	0.10
Analyses were performed using the multivariable adjusted model. Abbreviations: OR, odd ratio; CI, confidence interval, CKD, chronic kidney disease; VDRA, Vitamin D receptor activator.				

In addition, we divided the patients into two groups (with and without aortic valve calcification) and performed multivariate analysis (Table 3). The results showed that aortic valve calcification was

associated with aging, long-term dialysis, diabetes mellitus, Vitamin D receptor activators (VDRA) administration, elevated serum calcium level, and anemia, but not with elevated serum phosphorus level.

Table 3
Odds ratio for aortic valve calcification by multivariable Cox regression

	Aortic valve calcification	
	OR (95% CI)	p value
Male	0.93 (0.75-1.16)	0.53
Age (per 10 years)	1.70 (1.54-1.88)	<0.001
Dialysis duration (per 10 years)	1.42 (1.22-1.64)	<0.001
Nephrosclerosis as the primary disease of CKD	0.88 (0.69-1.06)	0.43
Diabetes comorbidity	1.53 (1.23-1.90)	<0.001
Use of calcimimetics	0.86 (0.69-1.06)	0.16
Use of VDRA	0.70 (0.54-0.91)	0.007
Use of phosphate binders	0.92 (0.69-1.23)	0.57
Corrected Calcium (per 1 mg/dl)	1.30 (1.09-1.54)	0.004
Phosphorus (per 1 mg/dl)	1.03 (0.95-1.12)	0.46
Intact PTH (per 10 pg/ml)	1.00 (0.99-1.01)	0.56
Albumin (per 1 g/dl)	1.19 (0.87-1.63)	0.28
C-reactive protein (per 1 mg/dl)	0.98 (0.90-1.07)	0.65
Hemoglobin (per 1 g/dl)	0.89 (0.81-0.98)	0.02

3. Comparison of AS parameters with and without aortic valve calcification

The mean PG, AVA, and Vmax as measured using TTE were compared between the patients with and without aortic valve calcification (Table 4). The results significantly showed that those with aortic valve calcification had characteristics of AS in all parameters.

Table 4
Comparison of AS parameters with and without aortic valve calcification

	With aortic valve calcification	Without aortic valve calcification	p value
Velocity max, m/s	1.78±0.64	1.51±0.50	<0.001
Mean pressure gradient, mmHg	8.3±7.9	6.3±4.8	<0.001
Aortic valve area, cm ²	2.19±0.79	2.50±0.90	<0.001
Analyses were performed using Mann-Whitney U test.			

4. Stratified multivariate analysis for AS

We determined the MOR for AS between the categories of age, duration of dialysis, and serum phosphorus level (Figures 2A, 2B, and 2C). The MOR in both the AS and the severe AS groups significantly increased with age. Regarding the duration of dialysis, the MOR in the AS group tended to increase as the duration of dialysis increased. It was found that in the severe AS group, the MOR of >15 years of dialysis was 1.86 fold greater (95% CI, 1.06–3.24; $p = 0.03$) compared to that of <5 years. Regarding the serum phosphorus level, the MOR tended to increase as the serum phosphorus level increased. The MORs of the categories of serum phosphorus levels of 5.0–5.9 and >6.0 mg/dL were 1.52 and 1.83 fold and 2.24 and 2.66 fold greater in the AS group and severe AS group, respectively, compared to that of a serum phosphorus level <4.0 mg/dL.

Discussion

In the results of this study, the prevalence of AS in dialysis patients was as high as 20.0%, similar to previous reports. It was also observed that aortic valve calcification and AS are closely related. Aging had a strong effect on the development of AS in patients undergoing dialysis as well as the general population. Notably, hyperphosphatemia and long-term dialysis were found to be associated with AS.

Hyperphosphatemia is present in many patients undergoing dialysis. According to the United States Renal Data System in 2018, 38.1% of patients undergoing dialysis in the USA had a serum phosphorus level ≥ 5.5 mg/dL. According to the data from the Japanese Society for Dialysis Therapy in 2019, 53.9% of patients undergoing dialysis in Japan had a serum phosphorus level ≥ 5.0 mg/dL. Hyperphosphatemia causes CVD by promoting the calcification of vascular smooth muscle cells, resulting in a high mortality in CKD patients.(30–38) Phosphorus is thought to play a major role in the process of calcification not only in blood vessels but also in aortic valves.(39) Hussein et al. reported that SLC20A1/Pit1, a phosphorus transporter associated with calcification found in calcified blood vessels, was also expressed in calcified aortic valves.(40) In two different observational studies of approximately 100 patients undergoing dialysis, Tarras et al. and Petrović et al. reported that phosphorus was associated with aortic valve calcification by univariate analysis and multivariate analysis, respectively.(41, 42) However, no

studies have been performed that investigated the association between hyperphosphatemia and AS. In our study, an elevated serum phosphorus level was not associated with aortic valve calcification but was associated with AS. On the other hand, an elevated serum calcium level was not associated with AS but was associated with aortic valve calcification. Although we could not prove the hypothesis that hyperphosphatemia causes AS after calcification of the aortic valve, MBD, including hypercalcemia and hyperphosphatemia, was suspected to be strongly associated with aortic valve calcification and AS. Further, it is interesting to note that the group of patients with a serum phosphorus level ≥ 5.0 mg/dL, which is lower than the upper limit of 6.0 mg/dL as per the Japanese guidelines, was associated with AS. This ongoing cohort study will assess the prognosis of patients with AS and concomitant hyperphosphatemia and hypercalcemia. We hope that it will help in setting target values not only for serum phosphorus levels and serum calcium levels but also in selecting phosphorus binders.

Our study showed that long-term dialysis was associated with both AS and aortic valve calcification by multivariate analysis, including aging and MBD-related factors. Because long-term dialysis involves various factors that affect the cardiovascular system, such as fluid retention, chronic inflammation, and uremic toxins, it is difficult to identify which factors induce the development of AS.(43–48) Although we cannot measure them directly, we will investigate the types of dialysis methods, such as hemodialysis, on-line hemodiafiltration, and intermittent hemodiafiltration, and the dialysis time per week to evaluate their effects on the progression of AS.

Limitations

This present study has some limitations. First, since we excluded patients having a history of aortic valve surgery, this study may have overlooked a serious risk factor for AS. Second, since we only evaluated one baseline point, the baseline results alone did not adequately assess the prognosis of AS and AS-related factors in patients undergoing dialysis. Third, because this study was a multicenter study, the accuracy of TTE was not consistent. All the above problems may be solved by comparing the annual results with the baseline results.

Conclusion

Patients on maintenance dialysis have a high prevalence of AS and a high rate of aortic valve calcification, which were associated with hyperphosphatemia and duration of dialysis. We will continue our prospective studies to evaluate the factors involved in the development and prognosis of AS in patients undergoing dialysis.

Abbreviations

chronic kidney disease (CKD)

cardiovascular disease (CVD)

aortic valve stenosis (AS)

aortic valve area (AVA)

Mineral and Bone Disorder (MBD)

transthoracic echocardiography (TTE)

pressure gradient (PG)

maximum aortic jet velocity (Vmax)

multivariate-adjusted odds ratio (MOR)

confidence interval (CI)

Vitamin D receptor activators (VDRA)

Declarations

Ethics approval and consent to participate: This study was performed according to the Ethics of Clinical Research (the Helsinki Declaration). This study was approved by Fujita Health University Center for Clinical Trial and Research Support (approval number: HM16–373). All participants involved in this study were gave informed consent after explanation of the purpose of the study and agreed to participate. This study was registered in the clinical trial registry (UMIN 000026756) on April 1, 2017.

Consent for publication

Not applicable.

Availability of data and materials

The dataset analyzed in the present study is presented in the additional file and available (title of data: dataset 1). The dataset included the patient profiles, comorbidities, medications, laboratory data, ECG, chest X-ray, and TTE.

Competing interests

D. Inaguma received lecture fees from Ono Pharmaceutical Co., Ltd. and Kyowa Kirin Co., Ltd. Y. Yuzawa received research support grants from Otsuka Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., and Chugai Pharmaceutical Co., Ltd. The other authors declare that they have no competing interests.

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Aichi Kidney Foundation

Authors' contributions

DI and YS participated in the design of the study and interpretation of data. YS surveyed and collected information about prognosis. YS performed statistical analyses. YS drafted the manuscript and DI revised it critically for important intellectual content. All authors read and approved the final manuscript.

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Figures

Figure 1.

Figure 1

A flow diagram of the present study Abbreviations: Vmax, Velocity max; PG, pressure gradient; AVA, aortic valve area

Figure 2

Multivariate-adjusted odds ratio (MOR) for AS between the categories of age, duration of dialysis, and serum phosphorus level The graph on the left was a comparison between the AS group and the non-AS group, and the graph on the right was a comparison between the severe AS group and the non-AS group.

The multivariate analysis model included the gender, age, duration of dialysis, nephrosclerosis as the primary cause of CKD, diabetes mellitus as a comorbidity, use of calcimimetics, use of vitamin D receptor activators, use of phosphate binders, serum albumin level, serum corrected calcium level, serum phosphorus level, serum intact parathyroid hormone level, serum C-reactive protein level, and serum hemoglobin level as adjustments. A: MOR for AS between the categories of age B: MOR for AS between the categories of duration of dialysis C: MOR for AS between the categories of serum phosphorus level