ORIGINAL ARTICLE

Abdominal Aortic Calcifications in Patients with CKD and Cardiovascular Outcome

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Background: Abdominal aortic calcification (AAC) is a marker of advanced atherosclerosis and has been associated with an increased risk of cardiovascular events and mortality in chronic kidney disease (CKD) patients.

Objective: To investigate the association between AAC and cardiovascular outcomes in CKD stage 3 to 5 dialysis patients, as well as the progression of AAC and its impact on end-stage kidney disease (ESKD) progression in CKD stage 3 to 5 non-dialysis patients.

Materials and Methods: The present study was a retrospective cohort and cross-sectional study included 90 CKD stage 3 to 5D patients from IMPACT CKD study at Ratchaburi Hospital. Baseline lateral abdominal radiograph was obtained in 2014 to assess the presence and severity of AAC using the Kauppila scoring system. Patients were retrospectively reviewed for ten years, and surviving patients underwent a second radiograph assessment for AAC progression. The primary outcome was the composite of cardiovascular events and all-cause mortality. Secondary outcomes included the progression of AAC and the development of ESKD requiring renal replacement therapy (RRT).

Results: Ninety CKD stage 3 to 5D patients were enrolled. Patients with diabetes, dyslipidemia, and history of congestive heart failure were more likely to have AAC at baseline. The presence of AAC at baseline had higher primary outcome at 64.1%, than those without AAC at baseline at 29.4%, hazard ratio 4.281 (95% CI 1.761 to 10.429, p=0.001). Among survivals, those with progressive AAC score were more likely to progress to ESKD and required RRT compared to those without AAC progression.

Conclusion: AAC is a significant risk factor for cardiovascular events and all-cause mortality in CKD stage 3 to 5D patients. Progression of AAC is associated with an increased risk of ESKD progression and need for RRT. Routine assessment of AAC using lateral abdominal radiograph may aid in risk stratification and guide appropriate management strategies to reduce cardiovascular and renal complication in the present study patient population.

Keywords: Abdominal aortic calcification; Chronic kidney disease; End-stage kidney disease; Renal replacement therapy

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Chronic kidney disease (CKD) is a significant risk factor for cardiovascular disease (CVD), and the risk increases as CKD stages progress. Vascular calcification, particularly abdominal aortic calcification (AAC), is a common manifestation of mineral and bone disorders in CKD patients and has been associated with an increased risk of cardiovascular events and mortality[1,2]. AAC, the deposition of calcium and other mineral within the abdominal aorta wall, is a common complication in CKD patients and is associated with increased arterial stiffness, endothelial dysfunction, and a marker of advanced atherosclerosis, reflecting the burden of vascular calcification[3]. Kidney Disease: Improving Global Outcomes (KDIGO) for CKD-mineral bone disorder (MBD) recognizes the importance of assessing vascular calcification in CKD patient stage 3 to 5D and suggests using a plain lateral abdominal radiograph, which is a simple, inexpensive, and widely available imaging modality[4]. Several scoring systems have been developed to quantify the extent of AAC on lateral abdominal radiographs, such as the Kauppila score and the Adragao score[5,6].

Previous studies have shown that the presence and severity of AAC are associated with an increased risk of cardiovascular events and mortality in both the general population and CKD patients[7,8]. In CKD patients, AAC has been linked to the development of coronary artery calcification, left ventricular

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hypertrophy, and reduced arterial compliance, which may contribute to the increased cardiovascular risk[9,10].

However, the relationship between AAC and cardiovascular outcomes in pre-dialysis and dialysis CKD patients stage 3 to 5D, has not been extensively studied especially in Thai CKD patients. Given the high cardiovascular burden in this population, it is important to explore the potential role of AAC as a risk stratification tool and its association with cardiovascular events in CKD patients stage 3 to 5D as well as its impact on the initiation of renal replacement therapy (RRT) in this population.

Materials and Methods

Study design and population

The present study was a single-center retrospective cohort and cross-sectional study conducted in the CKD patient of Ratchaburi Hospital, Ratchaburi Province, Thailand by using the participants previously enrolled into IMPACT CKD study. The IMPACT CKD study was a large multicenter nationwide cross-sectional study in Thailand that aimed to identify the prevalence and risk factors of AAC in 1,500 CKD stage 3 to 5D patients since 2014[11].

The patients aged more than 18 years old with CKD stage 3 to 5D, defined as an estimated glomerular infiltration rate (eGFR) of less than 60 mL/minute/1.73 m^2, as calculated by CKD epidemiology formula for more than three months were enrolled to the study[12]. The exclusion criteria were active malignancy, undergone kidney transplantation, and the patients lost to follow up. The present study has been approved by the Ethic Research Ethic Board at Ratchaburi Hospital (ID COA-RBHEC 021/2024).

Data collection

Demographic, clinical, laboratory and medication data were collected at baseline by direct interview and reviewed of medical records from Ratchaburi Hospital database. At the time of enrollment in the IMPACT CKD study (2014), all participants underwent a baseline lateral abdominal radiograph to assess the presence and severity of AAC. The radiographs were evaluated by two radiologists at Ratchaburi Hospital, blinded to the patient data. The Kauppila scoring system was used to quantify the extent of AAC on the lateral abdominal radiographs[5]. The location and severity of calcific deposits at each lumbar vertebra segment (L1-L4) will be evaluated. The severity of the anterior and posterior aortic calcification had grades individually on a 0 to 3 scale for each lumbar segment with 0 for no calcification, 1 for calcification covering less than 1/3 of the aortic segment, 2 for calcification covering 1/3 to 2/3 of the segment, and 3 for calcification covering more than 2/3 of the segment. The individual segment scores were summed to obtain the Kauppila score, ranging from 0 to 24. If the two radiologist scores differed by 5 points or more, a re-evaluation was performed to reconcile the scores. If the difference was 4 points or less, the average of the two scores was used as the final AAC score for that participant.

Participants were retrospective reviewed for ten years after being enrolled in the IMPACT CKD study. Data on cardiovascular events such as myocardial infarction, stroke, and cardiovascular-related hospitalizations, cardiovascular and all-cause mortality were collected. After ten years, survivors underwent a second lateral abdominal radiograph to assess the progression of AAC using the same scoring system that was used at baseline.

Outcome measurements

The primary outcome of the present study was the composite of cardiovascular events and all-cause mortality. Secondary outcomes included the progression of AAC and the development of end-stage kidney disease (ESKD) requiring RRT. Data were obtained from medical records, from chart review and/or telephone interview with patients or patients' relatives.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the present study population. Appropriate statistical tests such as chi-square, t-test, or non-parametric tests were used to compare baseline characteristics and outcomes between groups as patients with or without AAC at baseline. Survival analysis method (Kaplan-Meier curves) was used to assess the association between AAC and the primary composite outcome. Univariate and multivariate cox proportional hazard model had performed to investigate the potential risk factors for AAC, such as age, diabetes mellitus, and dyslipidemia, high blood pressure, high serum phosphate, and serum intact parathyroid hormone (PTH). In subgroup analysis of patients who survived and did not initiate RRT at baseline, association between AAC progression and RRT initiation will be analyzed by chi-square or Fisher's exact test.

Table 1. Baseline characteristics of chronic kidney disease patients according to the presence or absence of abdominal aortic calcification

	Total (n=90)	AAC=0* (n=51)	AAC ≥1* (n=39)	p-value
Age (years); mean±SD	54.39±10.44	51.67±11.9	58.36±6.76	0.07
BMI** (kg/m^2); mean±SD	23.70±30.49	23.35±3.49	24.76±3.24	0.49
eGFR (mL/minute/1.73 m^2); mean±SD	15.94±12.33	15.85±13.17	14.19±8.72	0.33
Serum laboratory value; mean±SD				
Phosphate (mg/dL)	4.46±1.37	4.46±1.28	4.10±0.93	0.09
Albumin (g/dL)	4.19±0.44	4.20±0.42	4.13±0.39	0.99
Cholesterol (mg/dL)	188.13±40.76	192.80±33.78	182.93±50.62	0.16
LDL (mg/d L)	113.77±38.44	118.22±31.50	112.57±45.89	0.06
Triglyceride (mg/dL)	140.19±65.61	138.14±60.31	138.50±70.40	0.95
HDL (mg/dL)	48.47±14.65	49.84±15.14	43.00±13.16	0.14
Hemoglobin (g/dL)	10.73±1.89	10.93±2.08	11.14±1.01	0.39
HbA1C (%)	6.65±1.68	6.97±1.93	6.84±1.38	0.13
BUN (mg/dL)	45.14±18.95	45.15±19.51	48.43±17.93	0.45
Creatinine (mg/dL)	6.12±4.65	6.81±5.30	5.42±3.23	0.24
PTH (pg/mL)	250.01±298.52	189.05±184.39	185.21±153.37	0.22
Calcium >10 mg/dL; n (%)	31 (34.44)	15 (29.41)	16 (41.03)	0.38
Systolic BP (mmHg)	146.50±25.20	144.88±26.12	148.43±23.81	0.25
Diastolic BP (mmHg)	79.71±13.59	79.73±14.31	80.07±15.63	0.52
Sex: male; n (%)	45 (50.00)	28 (54.90)	17 (43.59)	0.29
Receiving RRT; n (%)	32 (35.56)	20 (39.22)	12 (30.77)	0.41
Comorbidities; n (%)				
Diabetes mellitus	40 (44.44)	15 (29.41)	25 (64.10)	0.001
Hypertension	83 (92.22)	45 (88.24)	38 (97.44)	0.11
Dyslipidemia	45 (50.00)	20 (39.22)	25 (64.10)	0.02
Coronary artery disease	7 (7.78)	2 (3.92)	5 (12.82)	0.12
Stroke	6 (6.67)	4 (7.84)	2 (5.13)	0.61
Peripheral arterial disease	2 (2.22)	0 (0)	2 (5.13)	0.10
Congestive heart failure	3 (3.33)	0 (0)	3 (7.69)	0.04
Smoking; n (%)	2 (2.22)	1 (1.96)	1 (2.56)	0.85
Medication; n (%)				
Vitamin D	3 (3.33)	0 (0)	3 (7.69)	0.09
ACEI/ARBs	25 (27.78)	18 (35.29)	7 (17.95)	0.07
CCB	70 (77.78)	37 (72.55)	33 (84.62)	0.17
Elemental calcium	26 (28.89)	15 (29.41)	11 (28.21)	0.88

AAC=abdominal aortic calcification; BMI=body mass index; eGFR=estimated glomerular filtration rate; BUN=blood urea nitrogen; PTH=parathyroid hormone; RRT=renal replacement therapy; PAD=peripheral arterial disease; ACEI=angiotensin-converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; CCB=calcium channel blockers; SD=standard deviation

* Abdominal aortic calcification calculated by Kauppila scoring system, ** The body-mass index is the weight in kilograms divided by the square of the height in meters

Results

One hundred one patients of IMPACT CKD cohort were screened. After excluding 11 patients who undergone kidney transplantation, active malignancy at baseline and lost to follow up within 10 years, 90 patients were enrolled in the present study. The mean age was 54±10 years. AAC was present in 39 patients (43.3%). Table 1 lists the baseline characteristic of patients according to the presence or absence of AAC. The history of diabetes, hyperlipidemia and congestive heart failure were significant greater in patients with than without AAC. There were no significant differences in value of hemoglobin, serum albumin, calcium, phosphate, or intact PTH between patients with and without AAC.

During the 10 years period after enrolling in the present study, there were 40 all-cause mortalities, of which 10 were from CVD. Patients with and without

Table 2. Main outcomes of chronic kidney disease patients according to the presence or absence of abdominal aortic calcification

	Total (n=90); n (%)	AAC*=0 (n=51); n (%)	AAC* ≥1 (n=39); n (%)	p-value
Cardiovascular events	23 (25.55)	5 (9.8)	18 (46.15)	0.029
Mortality				
All-cause	40 (44.44)	15 (29.41)	25 (64.1)	0.001
Cardiovascular	10 (11.11)	1 (1.96)	9 (23.08)	0.001

AAC=abdominal aortic calcification

* Abdominal aortic calcification calculated by Kauppila scoring system

AAC, 64% and 29% died, respectively, with 23% and 1.96% from cardiovascular cause, respectively. Cardiovascular mortalities included death from ischemic heart disease in five cases, congestive heart failure in four cases, and cerebrovascular disease in one case. Non-cardiovascular mortalities consisted of infection in 17 cases, cancer in three cases, and others in ten cases. All-cause mortality was significantly greater in patients with AAC compared to those without (p=0.001). Similarly, cardiovascular mortality was more significant in the former than in the latter group (p=0.001) (Table 2). However, the 10-year survival plots between the patients with and without AAC at baseline characteristics were not different (p=0.211) (Figure 1).

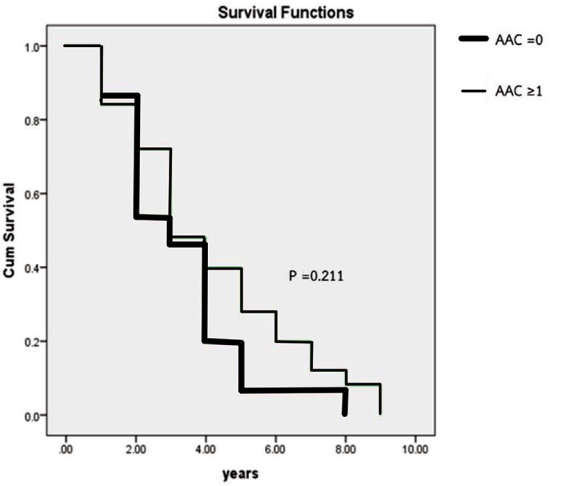

Figure 1. Cumulative patient survival between the patient with and without abdominal aortic calcification (AAC) at baseline.

Twelve potential mortality risks were primarily analyzed for association with all-cause mortality, but only diabetes mellitus (HR 0.319, 95% CI 0.132 to 0.747, p=0.009) and presence of AAC score at baseline (HR 4.281, 95% CI 1.761 to 10.429, p=0.001) were found statistically significant. In multivariate cox proportional hazard model, only presence of AAC score at baseline (HR 3.385, 95% CI 1.333 to 8.594, p=0.010) was associated with all-cause mortality (Table 3). For cardiovascular mortality, presence of AAC score at baseline (HR 6.718, 95% CI 0.745 to 60.590, p=0.05) was the only risk factor that had significant association by using multivariate analysis (Table 4).

In a subgroup of 50 patients who survived, only 39 patients received a second lateral abdominal film to evaluate change in AAC score. Among this subgroup, 24 patients have not had RRT at baseline. Nine out of 13 patients who had progressive AAC, an increasing AAC score from baseline, had initiated RRT. In contrast, two out of 11 patients who had similar AAC score from base line, had initiate RRT (p=0.019).

Discussion

The present study demonstrated that the presence of AAC at baseline in CKD population is associated with increased long-term clinical outcomes including mortality and cardiovascular event. This finding has confirmed that the presence AAC is a strong predictor of increased cardiovascular morbidity and mortality in this high-risk population, which is consistent with the previous evidence[13].

In multivariate analysis, the AAC is verified for a strong risk factor of all-cause and cardiovascular mortality. However, known risk factors such as diabetes, history of CAD, high serum phosphate, and high blood pressure are not demonstrated as significant association with the mortality. This might be due to the low sample size and missing data.

In addition to mortality outcomes, the present study also shows the association between AAC score and renal outcome. Increased RRT initiation increased in the patients with increasing AAC score more than non-progressive AAC score. However, the analysis was done in a subgroup of patients who survived, had undergone second radiography, and did not initiate RRT at baseline.

The identification of congestive heart failure, diabetes mellitus, and hyperlipidemia as significant risks associated with AAC is in line with the current

Table 3. Univariate and multivariate cox proportional hazard analysis of risk factors associated with all-cause mortality in CKD patients

Risk	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age ≥60	1.556	0.648 to 3.731	0.322			
Male	0.483	0.207 to 1.125	0.098			
Diabetes mellitus	0.319	0.132 to 0.747	0.009	0.444	0.175 to 1.127	0.88
Dyslipidemia	0.483	0.207 to 1.128	0.091			
Coronary artery disease	7.00	0.783 to 62.57	0.082			
Stroke	0.605	0.105 to 3.480	0.574			
ACEI/ARBs	0.778	0.305 to 1.985	0.595			
AAC ≥1	4.281	1.761 to 10.429	0.001	3.385	1.333 to 8.594	0.010
Serum phosphate ≥4.5	1.165	0.489 to 2.772	0.730			
Systolic BP ≥140	2.077	0.876 to.924	0.097			
Diastolic BP ≥90	1.536	0.505 to 4.673	0.450			
Hb ≥10	0.475	0.195 to 1.158	0.102			

ACEI=angiotensin-converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; AAC=abdominal aortic calcification; BP=blood pressure; CI=confidence interval

Table 4. Univariate and multivariate cox proportional hazard analysis of risk factors associated with cardiovascular mortality in CKD patients

Risk	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age ≥60	2.037	0.473 to 8.775	0.34			
Male	1.756	0.392 to 7.807	0.463			
Diabetes mellitus	0.096	0.011 to 0.819	0.032	0.160	0.018 to 1.447	0.103
Dyslipidemia	0.302	0.058 to 1.587	0.157			
Coronary artery disease	2.20	0.225 to 21.55	0.498			
Stroke	2.20	0.225 to 21.55	0.498			
ACEI/ARBs	0.856	0.161 to 4.548	0.854			
AAC ≥1	10.963	1.285 to 93.126	0.029	6.718	0.745 to 60.590	0.05
Serum phosphate ≥4.5	0.578	0.110 to 3.045	0.518			
Systolic BP ≥140	1.241	0.278 to 5.544	0.777			
Diastolic BP ≥90	0.694	0.079 to 6.094	0.742			
Hb ≥10	0.464	0.108 to 2.003	0.304			

ACEI=angiotensin-converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; AAC=abdominal aortic calcification; BP=blood pressure; CI=confidence interval

understanding of the pathogenesis of vascular calcification in CKD. AAC is associated with the risk for congestive heart failure[14]. Diabetes mellitus, a common comorbidity in CKD, is known to accelerate vascular calcification through mechanisms such as advanced glycation end-product formation, oxidative stress, and dysregulation of mineral metabolism[15]. Hyperlipidemia, another frequently observed condition in CKD patients, has been linked to the promotion of vascular calcification through inflammatory pathways and endothelial dysfunction[16].

The authors' observation that AAC progression is associated with more RRT initiation is supported by the evidence suggesting a bidirectional relationship between vascular calcification and the progression of CKD[17]. Several potential mechanisms have been proposed to explain this association:

1. Hemodynamic effects: AAC contributes to increased arterial stiffness and reduced vascular compliance, leading to elevated afterload and impaired renal perfusion. This hemodynamic stress on the kidneys may accelerate the deterioration of renal function overtime[18].

2. Inflammation and oxidative stress: The process of vascular calcification is accompanied by chronic inflammation and oxidative stress, which can exacerbate renal injury and contribute to progression

of CKD[19].

3. Endothelial dysfunction: AAC is often associated with endothelial dysfunction, which can impair renal autoregulation and microvascular function, leading to a decline in renal function[20].

4. Shared risk factors: Traditional and non-traditional risk factors, such as hypertension, diabetes, dyslipidemia, and dysregulation of mineral metabolism, are common to both vascular calcification and the progress of CKD. The presence of these risk factors may simultaneously accelerate both processes[21,22].

The finding of this study has important clinical implications. Regular monitoring and early detection of AAC in CKD patients may aid in risk stratification and guide the implementation of targeted interventions to manage risk factors and potentially slow the progression of vascular calcification. Vascular calcification assessment by plain lateral abdominal X-ray should be considered in CKD stage 3 to 5D and the frequency of assessment may depend on baseline AAC score and individual risk factors. Strategies such as optimal blood pressure control, glycemic control in diabetic patients, lipid-lowering therapy, and management of mineral metabolism imbalance may help mitigate the development and progression of AAC[23,24].

Furthermore, the association between AAC progression and the need for RRT initiation underscores the importance of monitoring vascular calcification in CKD patients as a potential marker of disease progression. Early identification of AAC progression may prompt more intensive monitoring and management to delay the progression to end-stage renal disease and the associated cardiovascular complications.

The limitation of the present study is the retrospective cohort study design, the causality between AAC and mortality or the need for RRT that cannot be definitely established due to the observation nature of the study. Furthermore, there are potential confounding factors that could influence the observed association. Due to the small sample size, larger prospective studies would be needed to confirm and further validate the results. Moreover, patients who have undergone kidney transplantation and were lost to follow up were excluded from the analysis, which might affect the outcome.

In conclusion, AAC is the important risk-factor for cardiovascular and all-mortality and the need for RRT in CKD patients. The presence of AAC should be considered as a significant prognostic indicator, and patients with AAC might benefit from more intensive monitoring and management of risk factors associated with vascular calcification and CVD.

What is already known on this topic?

Plain lateral abdominal radiograph to assess AAC in CKD patient stage 3 to 5 is a safe and cost-effective technique to predict cardiovascular outcome and risk of progression to ESKD require RRT.

What does this study add?

Due to high cardiovascular mortality in CKD patients and the burden of CKD patient who have a progressive decline in renal function to ESKD, AAC by plain lateral abdominal radiograph might be used as a guide to classify this high- risk group to intensive therapy and better outcome.

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Conflicts of interest

The authors declare no conflict of interest.

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