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Impact of Arterial Calcification on Cardiovascular and Renal Outcomes in Kidney Transplant Patients

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Keywords
Aortic artery calcification · Cardiovascular disease · Coronary artery calcification · Kidney transplantation · Renal outcome

Abstract
Introduction: Coronary artery calcification score (CACS) and abdominal aortic calcification score (AACS) are both well-established markers of vascular stiffness, and previous studies have shown that a higher CACS is a risk factor for chronic kidney disease (CKD) progression. However, the impact of pretransplant CACS and AACS on cardiovascular and renal outcomes in kidney transplant patients has not been established. ***Methods:*** We included 944 kidney transplant recipients from the KoreaN cohort study for Outcome in patients With Kidney Transplantation (KNOW-KT) cohort and categorized them into three groups (low, medium, and high) according to baseline CACS (0, 0 < and ≤100, >100) and AACS (0, 1–4, >4). The low (0), medium (0 < and ≤ 100), and high (>100) CACS groups each consisted of 462, 213, and 225 patients, respectively. Similarly, the low (0), medium (1–4), and high (>4) AACS groups included 638, 159, and 147 patients, respectively. The primary outcome was the occurrence of cardiovascular events. The secondary outcomes were all-cause mortality and composite kidney outcomes, which comprised of >50% decline in the estimated glomerular filtration rate and graft loss. Cox regression analysis was used to investigate the association between baseline CACS/AACS and outcomes. ***Results:*** The high CACS group (N = 462) faced a significantly higher risk for cardiovascular outcomes (adjusted hazard ratio [aHR], 5.97;

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95% confidence interval [CI], 2.01–17.7) and all-cause mortality (aHR, 2.74; 95% CI, 1.27–5.92) compared to the low CACS group (N = 225). Similarly, the high AACS group (N = 638) had an elevated risk for cardiovascular outcomes (aHR, 2.38; 95% CI, 1.16–4.88). Furthermore, the addition of CACS to prediction models improved prediction indices for cardiovascular outcomes. However, the risk of renal outcomes did not differ among CACS or AACS groups. ***Conclusion:*** Pretransplant arterial calcification, characterized by high CACS or AACS, is an independent risk factor for cardiovascular outcomes and mortality in kidney transplant patients.

Plain Language Summary

Arterial calcification, accumulation of calcium in the arterial walls, vascular stiffness, and loss of elasticity of blood vessels can contribute to the development of cardiovascular diseases. Patients with chronic kidney disease and those undergoing dialysis have a considerably increased risk of vascular calcification. Even after kidney transplantation when kidney function has been restored, the prevalence of vascular calcification and subsequent cardiovascular disease remains high. Coronary artery calcification score and abdominal aortic calcification score are both well-established markers of vascular calcification. However, the impact of pretransplant vascular calcification scores on cardiovascular and renal outcomes in kidney transplant patients has not been established. When we analyzed 944 Korean kidney transplant patients, both vascular calcification scores were significantly associated with cardiovascular outcomes after kidney transplantation, but were not associated with renal outcomes. We also demonstrated that the addition of coronary artery calcification scores led to a modest improvement in the prediction performance for kidney transplant outcomes. Our findings suggest a potential role of pretransplant screening of coronary calcification scores and aortic calcification scores in risk stratification for post-kidney transplant outcomes.

Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality among kidney transplant (KT) patients [1–3]. Arterial calcification, accumulation of calcium in the arterial walls, vascular stiffness, and loss of elasticity of blood vessels can contribute to the development of CVD [4].

Patients with chronic kidney disease (CKD) and those undergoing dialysis have a considerably increased risk of vascular calcification due to various factors, including inflammation, abnormal bone mineral metabolism, and oxidative stress [5, 6]. Chronic imbalances in serum calcium, phosphate, and parathyroid hormone levels in patients with CKD may also play a role by disrupting the equilibrium between bone formation and resorption, leading to ectopic mineralization in the systemic vasculature [7–9]. Notably, coronary artery calcification score (CACS) and abdominal aortic calcification score (AACS) are two well-established markers that can objectively quantify vascular calcification and arterial stiffness [10–14]. Higher CACS is a risk factor for CVD and CKD progression in patients with CKD [15, 16]. Additionally, higher AACS is also a risk factor for CVD and CKD progression in patients with CKD [17, 18].

KT patients are, by definition, a subgroup of CKD patients with a single functional kidney. Even after kidney function has been restored, the presence of traditional and nontraditional risk factors and transplant-related factors, such as immunosuppressive medications, leads to a high prevalence of vascular calcification and subsequent CVD in KT recipients [19]. Therefore, understanding the pathogenic mechanisms that leads to vascular lesions in KT recipients may be crucial for optimizing long-term risk management after KT. However, only a few single-center studies with a small sample size have examined the impact of higher CACS and AACS on CVD, but not on CKD progression in the KT population [20–24]. We aimed to investigate the impact of arterial calcification and vascular stiffness on cardiovascular and renal outcomes in KT patients.

Methods

Study Design and Participants

The KoreaN cohort study for Outcome in patients With Kidney Transplantation (KNOW-KT) is a prospective, multicenter, observational cohort study in Korean KT patients [25]. The study enrolled 1,080 KT patients from 8 transplant centers between 2012 and 2016 who voluntarily provided written informed consent. We excluded 56 patients with no available baseline CACS or AACS. Among the 1,080 patients, 125 were excluded due to withdrawal of consent or a participating center. Additionally, 55 and 11 were excluded due to a lack of CACS and AACS, respectively. The final analyses for CACS and AACS included 900 and 944 patients, respectively (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000538929). This study was conducted in accordance with the principles of the Declaration of Helsinki and

the Declaration of Istanbul. The Regional Ethics Committee and Institutional Review Board of each participating center approved the study protocol.

Data Collection and Measurements

The following baseline clinical characteristics were collected at the time of KT: (1) donor information (age, sex, body weight, height, comorbidities, history of malignancy); (2) recipient information (age, sex, smoking history, cause of end-stage kidney disease, history of malignancy and CVDs, the age-adjusted Charlson Comorbidity Index (CCI), medications); and (3) KT-related information (date of transplantation, prior transplant history, donor-recipient relationship, and desensitization). The CCI is a widely adopted method to assess comorbid conditions, such as myocardial infarction, congestive heart failure, and diabetes mellitus (DM), and its total score can be used to estimate 10-year mortality [26].

The pretransplant cardiovascular evaluations included echocardiography, measurement of pulse wave velocity and ankle brachial index, CACS based on computed tomography, and AACS based on simple radiographs of the lateral lumbar spine using the Kauppila score, a validated scoring system ranging from 0 to 24 points [13]. CACS was measured at baseline and 5-year follow-up, while AACS was measured at baseline, 3-year, and 5-year follow-up. Patients were divided into three groups (low [0], medium [0 < and ≤100], and high [>100]) according to baseline CACS values and were divided into three groups (low [0], medium [1–4], and high [>4]) according to baseline AACS values, which was in accordance with categorization of CACS and AACS in previous studies [16, 27]. Laboratory data and clinical events were collected and documented annually.

Study Outcomes

The primary outcome was the occurrence of cardiovascular events. The secondary outcomes were all-cause mortality and composite kidney outcomes, which comprised of renal function decline and graft loss. Myocardial infarction, coronary revascularization, stroke, and new-onset or aggravation of congestive heart failure were considered cardiovascular events. Renal function decline was defined as a >50% decline in the estimated glomerular filtration rate (eGFR) compared to the baseline value measured <28 days after KT, whereas graft loss was defined as death-censored graft loss requiring maintenance dialysis for more than 3 months or re-transplantation. Serum creatinine levels were measured using an isotope-dilution mass spectrometry-traceable method, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [28].

Statistical Analysis

Demographic and laboratory parameters were summarized using percentages for categorical variables and using mean, median, and standard deviations for continuous variables, as appropriate. The Wilcoxon signed-rank test was used to analyze difference in CACS or AACS between time intervals. Spearman's rank correlation test was used to analyze the correlation of CACS or AACS between the baseline and post-KT 5-year. We used Cox regression analysis to investigate the association between baseline CACS/AACS and post-KT outcomes, including cardiovascular events, composite kidney outcomes, and all-cause mortality. Model 1 was unadjusted, univariate analysis, and model 2 was adjusted for the CCI, smoking status, education level, body mass index, and cause of end-stage kidney disease. Model 3 included KT-specific covariates such as the type of donor (living or deceased), duration of dialysis before KT, desensitization, and immunosuppression medications. All relevant covariates had <10% missingness, and multiple imputations by chained equations were used to fill in the missing values [29]. The results of the multivariate regression analysis are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

Harrell's C-statistics and net reclassification improvement (NRI) were calculated for the prediction models to assess the additive value of the CACS or AACS in the Cox regression models [30]. The bootstrapping method was used to derive 95% CIs. Model 3 was used as the comparator for the base model.

Additionally, risk factors for the progression of vascular calcification during 5 years were analyzed. We defined CACS progression as a binary outcome, which was positive when the square root of the difference between baseline and 5-year follow-up CACS was greater than 2.5, as a previous study reported [31]. Similarly, AACS progression was defined as positive when either 3-year follow-up AACS or 5-year follow-up AACS was numerically greater than the baseline AACS. We then conducted multivariable analyses using the generalized estimating equation and calculated the odds ratios with 95% CIs. Statistical analysis was performed using the statistical software R (R Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ was considered to be statistically significant.

Results

Baseline Clinical Characteristics

The baseline clinical characteristics of the study population are presented according to three CACS and three AACS groups in Tables 1 and 2, respectively. Laboratory findings of the study population are also presented according to three CACS and three AACS groups in online supplementary Table S1 and S2, respectively. In the CACS analysis, the median age was 47 years (interquartile range: 18–71 years), and 62.3% were men. The median CACS value was 0.0 (minimum 0.0, maximum 8,888.0). In the AACS analysis, the median age was 48 years (interquartile range: 17–71 years), and 62.3% were men. The median AACS value was 0.0 (minimum 0.0, maximum 21.0). Patients with higher arterial calcification scores (CACS or AACS) were more likely to be male ($p < 0.001$), older ($p < 0.001$), and more likely to have DM at baseline ($p < 0.001$). Hypertension was more common in patients with a higher CACS ($p = 0.002$). Cardiovascular comorbidities, such as coronary artery disease and cerebrovascular disease, were more common in the groups with higher CACS or AACS than in those with lower CACS or AACS (Tables 1, 2).

Posttransplant Changes in CACS and AACS

CACS and AACS increased slightly in most patients, even after KT (Fig. 1a, b). The mean CACS ($p < 0.001$) and AACS ($p < 0.001$) at 5 years after KT were higher than the pretransplant baseline levels. However, in the

Table 1. Baseline characteristics according to CACS

	Total (*N* = 900)	0 (*N* = 462)	0 <and ≤100 (*N* = 213)	>100 (*N* = 225)	*p* value
CACS	0.0 [0.0, 8888.0]	0.0 [0.0, 0.0]	19.3 [0.1, 99.2]	461.7 [104.0, 8888.0]	<0.001
Type of KT, *n* (%)					<0.001
LDKT	729 (81.0)	415 (89.8)	164 (77.0)	150 (66.7)	
DDKT	171 (19.0)	47 (10.2)	49 (23.0)	75 (33.3)	
Sex (male), *n* (%)	561 (62.3)	248 (53.7)	142 (66.7)	171 (76.0)	<0.001
Age, years	47.0 [18.0, 71.0]	41.0 [18.0, 69.0]	50.0 [27.0, 70.0]	54.0 [31.0, 71.0]	<0.001
BMI, kg/m^2	22.6 [14.7, 35.7]	21.6 [14.7, 34.8]	23.2 [15.9, 34.6]	23.8 [17.2, 35.7]	<0.001
Waist-hip ratio	0.89 [0.70, 1.17]	0.88 [0.70, 1.17]	0.91 [0.74, 1.07]	0.92 [0.75, 1.13]	<0.001
Systolic BP, mm Hg	137 [90.0, 215]	134 [90.0, 210]	142 [100, 215]	139 [99.0, 191]	<0.001
Diastolic BP, mm Hg	83.0 [51.0, 123]	83.0 [54.0, 123]	84.0 [57.0, 115]	80.0 [51.0, 113]	0.007
CCI	2.0 [0.0, 8.0]	2.0 [0.0, 6.0]	2.0 [0.0, 6.0]	3.0 [0.0, 8.0]	<0.001
Etiology of ESKD, *n* (%)					<0.001
DM	184 (20.4)	45 (9.7)	44 (20.7)	95 (42.2)	
Hypertension	197 (21.9)	95 (20.6)	52 (24.4)	50 (22.2)	
Glomerulonephritis	277 (30.8)	190 (41.1)	54 (25.4)	33 (14.7)	
Others	242 (26.9)	132 (28.6)	63 (29.5)	47 (20.9)	
Smoking, *n* (%)					<0.001
Never	475 (52.8)	280 (60.6)	100 (46.9)	95 (42.2)	
Current	67 (7.4)	25 (5.4)	16 (7.5)	26 (11.6)	
Former	358 (39.8)	157 (34.0)	97 (45.5)	104 (46.2)	
Dialysis before KT, *n* (%)					<0.001
HD	589 (65.4)	287 (62.1)	130 (61.0)	172 (76.4)	
PD	110 (12.2)	40 (8.7)	39 (18.3)	31 (13.8)	
KT	15 (1.7)	7 (1.5)	1 (0.5)	7 (3.1)	
Preemptive	186 (20.7)	128 (27.7)	43 (20.2)	15 (6.7)	
DM	225 (25.0)	54 (11.7)	57 (26.8)	114 (50.7)	<0.001
Hypertension	832 (92.4)	405 (87.7)	208 (97.7)	219 (97.3)	0.002
Congestive heart failure	20 (2.2)	9 (1.9)	5 (2.3)	6 (2.7)	0.889
Arrhythmia	13 (1.4)	4 (0.9)	6 (2.8)	3 (1.3)	0.163
Coronary artery disease	50 (5.6)	8 (1.7)	7 (3.3)	35 (15.6)	<0.001
Cerebrovascular disease	37 (4.1)	9 (1.9)	9 (4.2)	19 (8.4)	<0.001

Note: All continuous variables are expressed as median [min, max]. All categorical variables are expressed as number and percentage. CACS, coronary artery calcium score; KT, kidney transplantation; LDKT, living donor kidney transplantation; DDKT, deceased donor kidney transplantation; BMI, body mass index; BP, blood pressure; ESKD, end-stage kidney disease; HD, hemodialysis; PD, peritoneal dialysis.

low CACS (CACS 0) and AACS (AACS 0) subgroups, significant proportions (52% in CACS, 42% in AACS) still had undetectable vascular calcification (CACS 0, AACS 0) at the 5-year after KT. When the progression of CACS/AACS was analyzed according to the subgroups of CACS/AACS, the progression was statistically significant in all of the subgroups, except in the high AACS (AACS >4) subgroup (online suppl. Fig. S2, S3). A significant correlation was observed between pretransplant CACS and 5-year CACS (r^2 = 0.835; p < 0.001; Fig. 1c). The correlation between pretransplant and 5-year AACSs was also significant (r^2 = 0.526; p < 0.001; Fig. 1d).

When risk factors for the progression of vascular calcification were assessed, old age, DM, and high body mass index were significant risk factors for CACS progression. For AACS, old age, DM, and high serum calcium levels were independently associated with the risk of AACS progression (online suppl. Table S3).

Cardiovascular Outcomes and All-Cause Mortality

At a median follow-up of 7.8 years, the incidence of cardiovascular outcomes was 1.5, 11.1, and 20.4 per 1,000 person-years in the low, medium, and high CACS groups, respectively (Table 3). The all-cause mortality

Table 2. Baseline characteristics according to AACS

	Overall (*N* = 944)	0 (*N* = 638)	1–4 (*N* = 159)	>4 (*N* = 147)	*p* value
AACS	0.0 [0.0, 21.0]	0.0 [0.0, 0.0]	2.0 [1.0, 4.0]	9.0 [5.0, 21.0]	<0.001
Type of KT, *n* (%)					<0.001
LDKT	759 (80.4)	540 (84.6)	121 (76.1)	98 (66.7)	
DDKT	185 (19.6)	98 (15.4)	38 (23.9)	49 (33.3)	
Sex (male), *n* (%)	588 (62.3)	372 (58.3)	117 (73.6)	99 (67.3)	<0.001
Age, years	48.0 [17.0, 71.0]	44.0 [17.0, 70.0]	52.0 [26.0, 71.0]	54.0 [26.0, 71.0]	<0.001
BMI, kg/m^2	22.6 [14.7, 39.0]	22.3 [14.7, 39.0]	22.8 [17.1, 33.7]	23.8 [15.5, 34.8]	<0.001
Waist-hip ratio	0.90 [0.70, 1.21]	0.89 [0.71, 1.17]	0.90 [0.74, 1.10]	0.91 [0.70, 1.21]	<0.001
Systolic BP (mm Hg)	136 [90.0, 215]	135 [90.0, 215]	138 [95.0, 191]	140 [100, 187]	0.009
Diastolic BP, mm Hg	82.0 [51.0, 123]	84.0 [54.0, 120]	80.0 [51.0, 123]	80.0 [51.0, 112]	<0.001
CCI	2.0 [0.0, 8.0]	2.0 [0.0, 6.0]	2.0 [0.0, 8.0]	3.0 [1.0, 7.0]	<0.001
Etiology of ESKD, *n* (%)					<0.001
DM	192 (20.3)	77 (12.1)	52 (32.7)	63 (42.9)	
Hypertension	215 (22.8)	152 (23.8)	36 (22.6)	27 (18.4)	
Glomerulonephritis	295 (31.3)	240 (37.6)	34 (21.4)	21 (14.3)	
Others	242 (25.6)	169 (26.5)	37 (23.3)	36 (24.4)	
Smoking, *n* (%)					<0.001
Never	519 (55.0)	373 (58.5)	68 (42.8)	78 (53.1)	
Current	67 (7.1)	31 (4.9)	21 (13.2)	15 (10.2)	
Former	358 (37.9)	234 (36.7)	70 (44.0)	54 (36.7)	
Dialysis before KT, *n* (%)					<0.001
HD	611 (64.7)	395 (61.9)	111 (69.8)	105 (71.4)	
PD	119 (12.6)	78 (12.2)	18 (11.3)	23 (15.6)	
KT	14 (1.5)	7 (1.1)	2 (1.3)	5 (3.4)	
Preemptive	200 (21.2)	158 (24.8)	28 (17.6)	14 (9.5)	
DM	242 (25.6)	100 (15.7)	61 (38.4)	81 (55.1)	<0.001
Hypertension	867 (91.8)	574 (90.0)	153 (96.2)	140 (95.2)	0.483
Congestive heart failure	19 (2.0)	9 (1.4)	5 (3.1)	5 (3.4)	0.196
Arrhythmia	14 (1.5)	10 (1.6)	2 (1.3)	2 (1.4)	0.925
Coronary artery disease	55 (5.8)	16 (2.5)	15 (9.4)	24 (16.3)	<0.001
Cerebrovascular disease	36 (3.8)	16 (2.5)	10 (6.3)	10 (6.8)	0.020

Note: All continuous variables are expressed as median [min, max]. All categorical variables are expressed as number and percentage. AACS, abdominal aortic calcium score; KT, kidney transplantation; LDKT, living donor kidney transplantation; DDKT, deceased donor kidney transplantation; BMI, body mass index; BP, blood pressure; ESKD, end-stage kidney disease; HD, hemodialysis; PD, peritoneal dialysis.

rates were 1.5, 4.6, and 8.9 per 1,000 person-years in the low, medium, and high CACS groups, respectively. The Kaplan-Meier survival analysis showed cumulative incidence curves for each CACS group (Fig. 2). Significant differences were observed in cardiovascular outcomes ($p < 0.001$, Fig. 2a) and all-cause mortality ($p < 0.001$, Fig. 2b) among the different CACS groups according to the log-rank test. In the Cox regression analysis, the risks for cardiovascular events and all-cause mortality in KT recipients increased as CACS increased. Higher CACS as a continuous variable was associated with a higher risk for cardiovascular events (HR: 1.004, 95% CI: 1.004–1.005, $p < 0.001$, model 3) and all-cause mortality (HR: 1.003, 95% CI: 1.002–1.003, $p < 0.001$, model 3, Table 3). The high CACS group (CACS >100) had a higher risk for cardiovascular events (HR: 5.97, 95% CI: 2.01–17.7, $p = 0.002$, model 3) and all-cause mortality (HR: 2.74: 95% CI: 1.27–5.92, $p = 0.009$, model 3) than the low CACS group (Table 3). The medium CACS group (0 <CACS ≤100) also had a higher risk for cardiovascular events (HR: 4.35, 95% CI: 1.52–12.5, $p = 0.007$, model 3) than the low CACS group (Table 3).

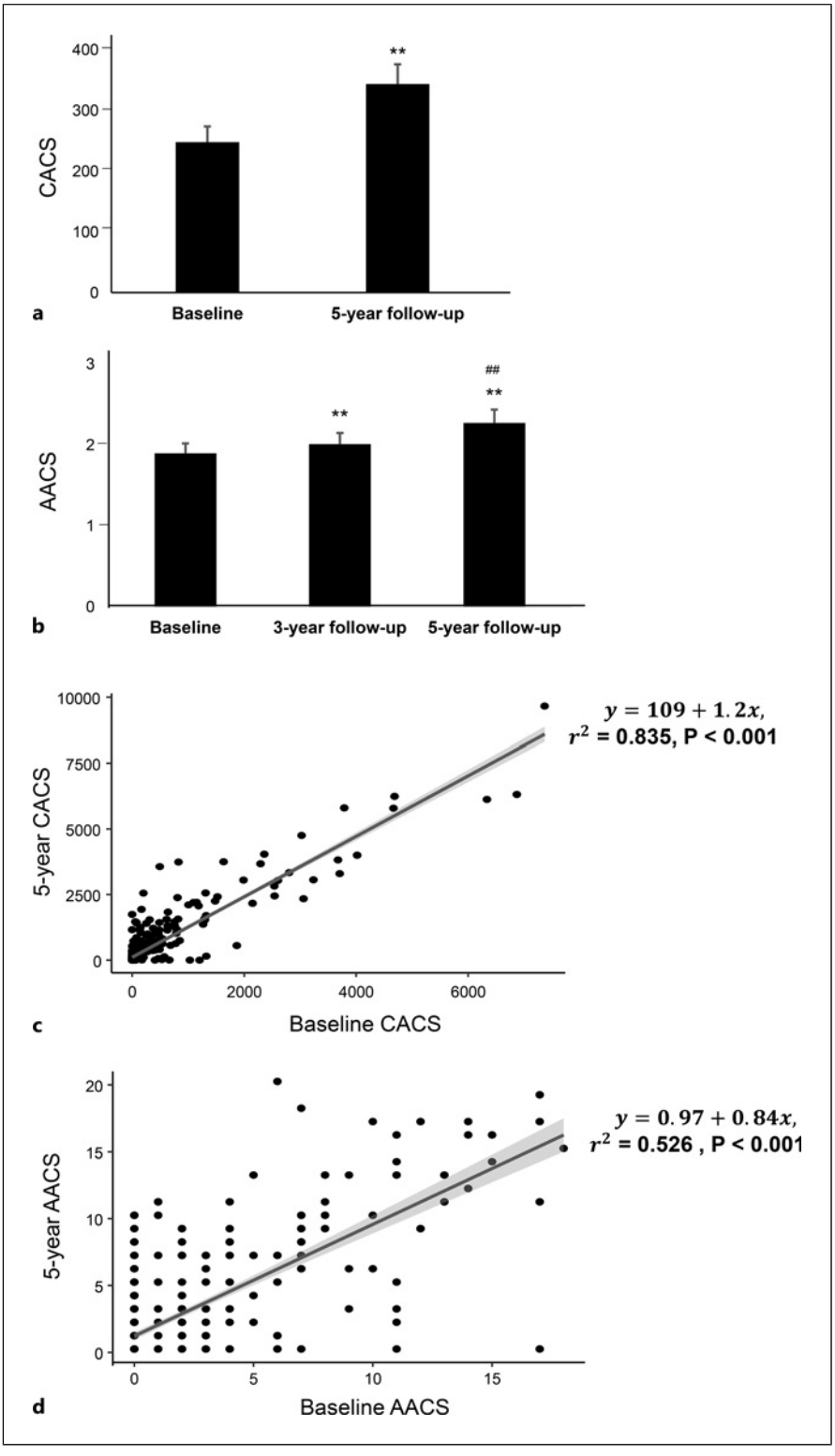

Fig. 1. Changes in CACS and AACS after kidney transplantation. **a** Changes in CACS over 5 years after kidney transplantation. ** indicates $p < 0.001$ compared to the baseline values (Wilcoxon signed-rank test). **b** Changes in AACS over 5 years after kidney transplantation. Each value indicates mean with the standard error of the mean. ** indicates $p < 0.001$ compared to the baseline values. ## indicates $p = 0.007$ between the 3-year and 5-year AACS values (Wilcoxon signed-rank test). **c** Correlation between CACS values at baseline and 5-year follow-up after kidney transplantation. $p < 0.001$ (Spearman's rank correlation test). **d** Correlation between AACS values at baseline and 5-year follow-up after kidney transplantation. CACS, coronary artery calcification score; AACS, aortic artery calcification score. $p < 0.001$ (Spearman's rank correlation test).

Table 3. Incidence and HRs for the outcomes according to CACS

Outcomes	CACS	Events	Person-years	Incidence (/1,000 person-years)	HR Model 1[a]	HR Model 2[b]	HR Model 3[c]	*p* value Model 3[c]
Cardiovascular outcome	0	5	3,395	1.5	Reference	Reference	Reference	–
	0 < and ≤100	16	1,440	11.1	7.37 (2.70–20.1)	4.21 (1.48–12.0)	4.35 (1.52–12.5)	0.007
	>100	29	1,420	20.4	13.25 (5.13–34.2)	5.62 (2.01–15.7)	5.97 (2.01–17.7)	0.002
	HR increase per 1 CACS				1.005 (1.004–1.006)	1.004 (1.004–1.005)	1.004 (1.004–1.005)	<0.001
All-cause mortality	0	5	3,427	1.5	Reference	Reference	Reference	–
	0 < and ≤100	7	1,524	4.6	3.18 (1.01–10.0)	1.88 (0.55–6.45)	1.74 (0.73–4.14)	0.207
	>100	14	1,570	8.9	6.18 (2.23–17.2)	2.99 (0.90–9.88)	2.74 (1.27–5.92)	0.009
	HR increase per 1 CACS				1.004 (1.003–1.005)	1.003 (1.003–1.004)	1.003 (1.002–1.003)	<0.001
Renal outcome	0	70	3,145	22.3	Reference	Reference	Reference	–
	0 < and ≤100	39	1,368	28.5	1.27 (0.86–1.88)	1.17 (0.77–1.80)	1.11 (0.72–1.72)	0.649
	>100	39	1,424	27.4	1.22 (0.83–1.81)	1.04 (0.65–1.66)	0.94 (0.57–1.54)	0.807
	HR increase per 1 CACS				1.001 (0.988–1.013)	1.000 (0.979–1.021)	1.000 (0.994–1.004)	0.166

The HR (95% CI) is reported for each model. The cardiovascular outcome was defined as myocardial infarction, coronary revascularization, stroke and new-onset or aggravation of congestive heart failure. The renal outcome was defined as the first occurrence of a more than 50% decline in eGFR compared to a baseline value measured less than 28 days after kidney transplantation, or death-censored graft loss requiring maintenance dialysis for more than 3 months, or re-transplantation. CACS, coronary artery calcification score; HR, hazard ratio. [a]Model 1: a crude analysis without adjustment. [b]Model 2: adjusted for CCI, smoking status, education levels, body mass index, and cause of end-stage kidney disease. [c]Model 3: Model 2 + type of donor (living or deceased), duration of dialysis before kidney transplantation, desensitization, and immunosuppression medications.

In the AACS analysis, the incidence of cardiovascular outcomes was 4.5, 16.6, and 23.5 per 1,000 person-years in the low, medium, and high AACS groups, respectively (Table 4). The Kaplan-Meier survival analysis showed cumulative incidence curves for each AACS group (Fig. 3). Significant differences were observed in cardiovascular outcomes ($p < 0.001$, Fig. 3a) and all-cause mortality ($p = 0.001$, Fig. 3b) among different AACS groups according to the log-rank test. Higher AACS as a continuous variable was associated with a higher risk for cardiovascular events (HR: 1.08, 95% CI: 1.02–1.14, $p = 0.002$, model 3) and showed a tendency of association with all-cause mortality (HR: 1.05, 95% CI: 0.95–1.18, $p = 0.109$, model 3, Table 4). Both the high AACS group (AACS >4, HR: 2.38, 95% CI: 1.16–4.88, $p = 0.028$, model 3) and the medium AACS group (AACS = 1–4, HR: 2.12, 95% CI: 1.05–4.27, $p = 0.049$, model 3) had a higher risk for cardiovascular events (Table 4). Moreover, the high AACS group (AACS >4, HR: 1.89, 95% CI: 0.70–5.06, $p = 0.179$, model 3) and the medium AACS group (AACS = 1–4, HR: 2.13, 95% CI: 0.82–5.51, $p = 0.163$, model 3) showed a tendency of increased risk for all-cause mortality compared to the low AACS group, despite no statistical significance (Table 4).

Renal Outcomes

The risk of renal outcomes, which we defined as a >50% decline in the eGFR compared to the baseline value measured less than 28 days after the KT operation or graft loss, did not differ significantly among the different CACS groups ($p = 0.403$, Fig. 2c). The HR for the high CACS group compared to the low CACS group was 0.94 (95% CI: 0.57–1.54, $p = 0.807$, model 3, Table 3).

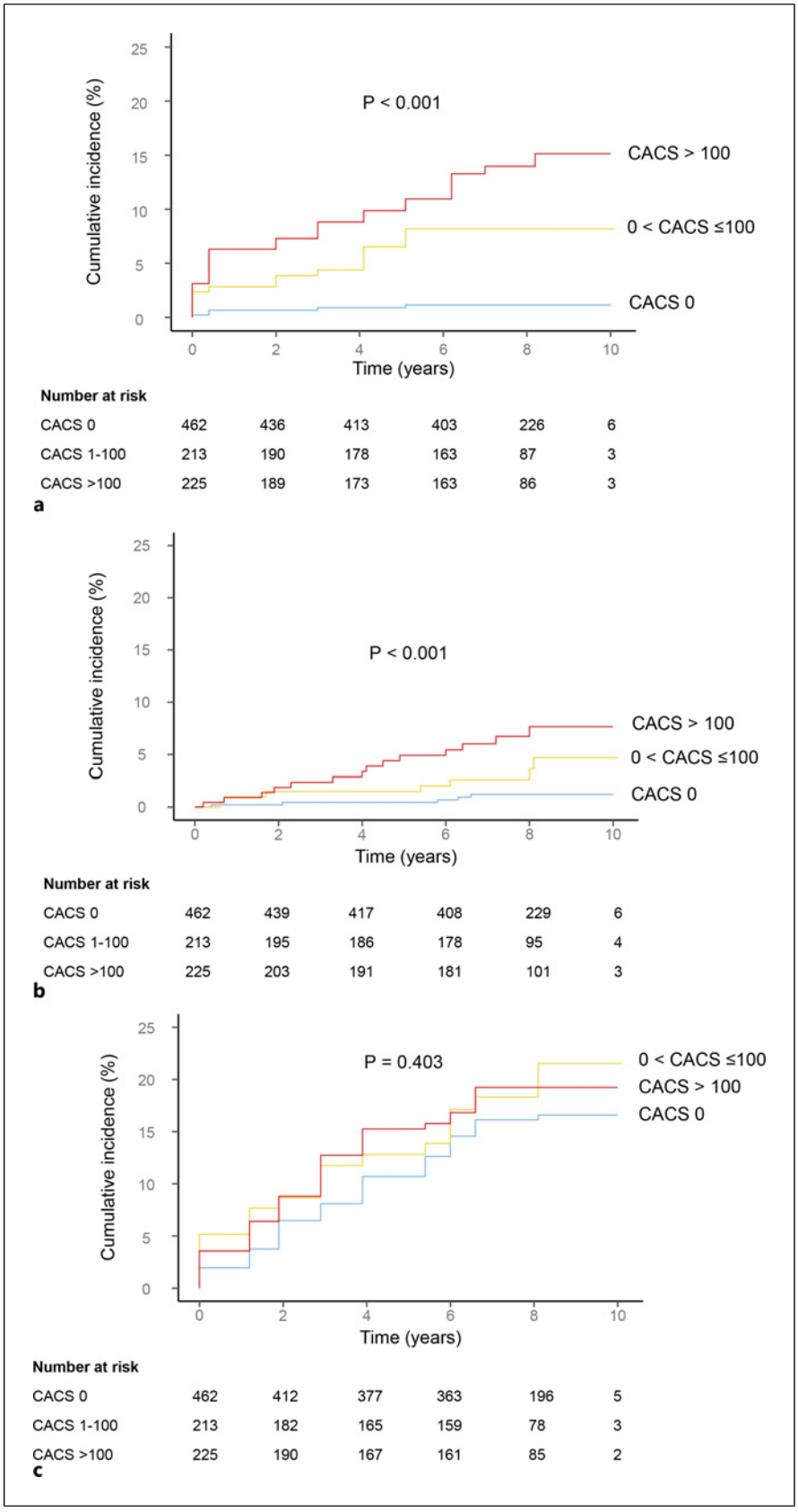

Fig. 2. Kaplan-Meier curves for incidence of cardiovascular outcomes (**a**), all-cause mortality (**b**), and renal outcomes (**c**) according to CACS groups (CACS = 0; 0 < CACS ≤ 100, CACS > 100). p < 0.001, <0.001, and 0.403 for cardiovascular outcomes, all-cause mortality, and renal outcomes, respectively (log-rank test). CACS, coronary artery calcification score.

Table 4. Incidence and HRs for the outcomes according to AACS

Outcomes	AACS	Events	Person-years	Incidence (/1,000 person-years)	HR Model 1[a]	HR Model 2[b]	HR Model 3[c]	*p* value Model 3[c]
Cardiovascular outcome	0	20	4,442	4.5	Reference	Reference	Reference	–
	1–4	17	1,027	16.6	3.61 (1.89–6.88)	2.01 (1.00–4.04)	2.12 (1.05–4.27)	0.049
	>4	21	894	23.5	5.05 (2.73–9.31)	2.38 (1.20–4.73)	2.38 (1.16–4.88)	0.028
	HR increase per 1 AACS				1.13 (1.07–1.20)	1.07 (1.02–1.13)	1.08 (1.02–1.14)	0.002
All-cause mortality	0	12	4,553	2.6	Reference	Reference	Reference	–
	1–4	9	1,121	8.0	3.06 (1.29–7.26)	2.08 (0.81–5.34)	2.13 (0.82–5.51)	0.163
	>4	11	999	11.0	4.18 (1.84–9.47)	2.17 (0.85–5.52)	1.89 (0.70–5.06)	0.179
	HR increase per 1 AACS				1.12 (1.07–1.19)	1.04 (0.95–1.11)	1.05 (0.95–1.18)	0.109
Renal outcome	0	96	4,443	21.6	Reference	Reference	Reference	–
	1–4	30	1,105	27.1	1.23 (0.82–1.85)	1.20 (0.77–1.88)	1.29 (0.81–2.04)	0.282
	>4	33	944	35.0	1.35 (0.91–2.01)	1.17 (0.74–1.83)	1.20 (0.75–1.92)	0.440
	HR increase per 1 AACS				1.04 (0.95–1.11)	1.03 (0.92–1.13)	1.02 (0.96–1.08)	0.569

The HR (95% CI) is reported for each model. The cardiovascular outcome was defined as myocardial infarction, coronary revascularization, stroke, and new-onset or aggravation of congestive heart failure. The renal outcome was defined as the first occurrence of a more than 50% decline in eGFR compared to a baseline value measured less than 28 days after kidney transplantation, or death-censored graft loss requiring maintenance dialysis for more than 3 months, or re-transplantation. AACS, abdominal aortic calcification score; HR, hazard ratio. [a]Model 1: a crude analysis without adjustment. [b]Model 2: adjusted for CCI, smoking status, education levels, body mass index, and cause of end-stage kidney disease. [c]Model 3: model 2 + type of donor (living or deceased), duration of dialysis before kidney transplantation, desensitization, and immunosuppression medications.

Similarly, according to the log-rank test, no significant difference was observed in renal outcomes among the different AACS groups (p = 0.286, Fig. 3c). HR for the high AACS group compared to the low AACS group was 1.20 (95% CI: 0.75–1.92, p = 0.440, model 3, Table 4). When CACS and AACS were treated as continuous variables, the HR increase per 1 CACS was calculated as 1,000 (95% CI: 0.994–1.004, p = 0.166, model 3) in the multivariate model (Table 3). The HR increase per 1 AACS was 1.02 (95% CI: 0.96–1.08, p = 0.569, model 3) in the multivariate model (Table 4).

Prediction Models Based on CACS or AACS

When CACS or AACS was added to the respective base models for major outcomes, significant NRI scores were observed (online suppl. Table S4). NRI was 0.636 (95% CI: 0.067–0.967, p = 0.006) when CCAS was added to the base model to predict cardiovascular outcomes. Moreover, NRI was 0.336 (95% CI: −0.060 – 0.719, p = 0.091) when AACS was added to the base model to predict cardiovascular outcomes. The Cox regression model for the composite outcome of cardiovascular outcome and all-cause mortality showed an NRI of 0.700 (95% CI: 0.085–1.018, p = 0.003) compared to the base model. No statistically significant improvements were observed in C-statistics.

Discussion

This multicenter KT cohort study investigated the association between two well-known vascular calcification markers, CACS/AACS, and posttransplant outcomes. This

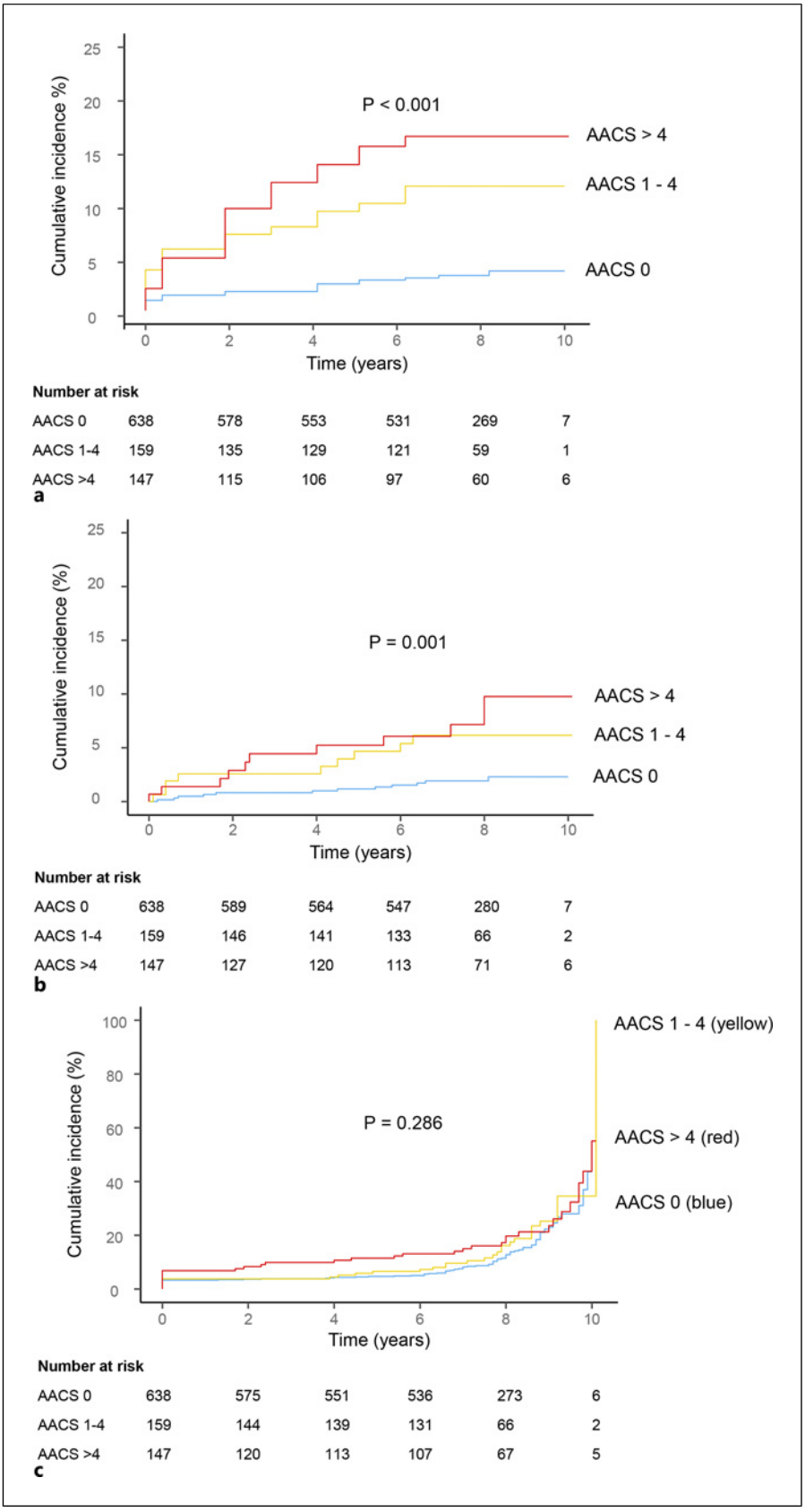

Fig. 3. Kaplan-Meier curves for incidence of cardiovascular outcomes (**a**), all-cause mortality (**b**), and renal outcomes (**c**) according to AACS groups (AACS = 0; AACS = 1–4, AACS > 4). $p < 0.001$, 0.001, and 0.286 for cardiovascular outcomes, all-cause mortality, and renal outcomes, respectively (log-rank test). AACS, aortic artery calcification score.

demonstrates that higher levels of CACS and AACS were associated with an increased risk for cardiovascular events and mortality in KT patients; however, neither was associated with the risk for renal function deterioration in KT patients.

Both CACS and AACS have increased over posttransplant 5 years and progression of vascular calcification seemed to be more prominent in the low and intermediate CACS/AACS subgroups. A previous study showed that old age and high FGF23 levels were common risk factors for CACS and AACS progression in dialysis patients [31], while we found that old age and DM were common risk factors for the progression of CACS and AACS in KT patients.

A Korean multicenter cohort study known as KNOW-CKD showed that high CACS was independently associated with adverse cardiovascular outcomes and all-cause mortality in CKD stages G1–G5 without kidney replacement therapy [15]. A single-center study also showed that high AACS based on CT was associated with an increased risk for CVD in patients with CKD [17]. In the KT population, several small-sized, single-center studies reported that higher CACS or AACS was associated with an increased risk for CVD, similar to the CKD population [20–24]. This multicenter study demonstrated that higher CACS and AACS were associated with an increased risk for CVD, and it strengthened the association of vascular calcification with CVD in KT patients using CACS and AACS simultaneously in a single study. These findings suggest that pretransplant CACS and AACS could be potential prognostic markers for posttransplant CVD in KT patients as well as patients with CKD. Further, we may be able to identify high-risk KT patients that could benefit from receiving better monitoring and intervention using these scores.

The impact of CACS on renal disease progression in patients with CKD has been controversial. Some small-sized studies reported a significant association between CACS and renal function deterioration, whereas other small-sized studies did not show this significant association in patients with CKD [32–34]. Recently, KNOW-CKD, a multicenter study with larger sample size, showed that high CACS was significantly associated with deterioration in kidney function for all stages of CKD without renal replacement therapy [16]. Although there were limited studies on the association between AACS and renal functions, a cross-sectional study reported a significant association between AACS and eGFR in patients with CKD [18]. Several possible mechanisms have been proposed to explain the association between vascular calcification and CKD progression, such as direct renal vascular calcification or renal function decline secondary to cardiorenal syndrome after cardiovascular compromise; however, the dominant mechanism is yet unknown [32, 33].

To the best of our knowledge, our study is the first study to analyze the association of CACS and AACS with renal function progression in KT patients. Contrary to CVD, we found no significant association between vascular calcification scores and renal outcomes. The lack of association with renal outcomes was unexpected, as vascular calcification and CKD progression are known to share many risk factors. One possible explanation for this negative finding is that KT patients have distinct pathophysiological mechanisms from those with CKD, which cause renal function decline and graft loss. Various KT-specific factors, including organ donor quality, human leukocyte antigen matching, sensitization status, and immunosuppressive regimens, may influence graft functional deterioration in KT patients and mitigate the impact of vascular calcification on kidney functional deterioration [35]. However, the statistical power of our study may be insufficient to detect a significant association between arterial calcification and renal outcomes in KT patients. Further studies with larger sample sizes and longer follow-up periods are required to clarify this issue.

CACS improved the predictive performance for cardiovascular outcomes in the CKD population [15, 36]. Because we found that CACS and AACS were significantly associated with cardiovascular outcomes, we investigated whether the addition of CACS or AACS to conventional prediction models can improve the predictive performance for cardiovascular outcomes. This study demonstrated that the addition of CACS led to the modest improvement in the predictive performance for cardiovascular outcomes, and the addition of AACS also showed a trend of improved prediction performance, supporting the clinical usefulness of CACS and AACS in the KT population.

This study has several strengths that contribute substantially to our understanding of the role of CACS and AACS in post-KT CVD and renal outcomes. First, this is the first multicenter cohort study with the largest sample size and relatively long-term follow-up duration in the KT population, in contrast to previous small-sized, single-center studies. Second, although previous studies have analyzed the impact of either CACS or AACS alone on CVD in the KT population, we simultaneously analyzed the impact of both CACS and AACS on renal

outcomes and CVD, providing a more holistic view. Third, we proposed prediction models and performed a risk analysis for CVD and renal outcomes, which was in contrast to previous studies on KT patients. However, this study has several limitations. First, we did not perform a validation study in the external validation group. Second, despite the large sample size and long-term follow-up duration, the number of events was still relatively small, which might have led to failure in detecting significant association between CACS/AACS and renal outcomes. Future studies for other populations could confirm and generalize our findings.

In conclusion, pretransplant arterial calcification, characterized by high CACS or AACS, is an independent risk factor for posttransplant CVD and mortality but not for graft dysfunction in KT patients. Our findings suggest a potential role of pretransplant screening of CACS and AACS in risk stratification for post-KT outcomes.

Acknowledgments

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Statement of Ethics

This study protocol was reviewed and approved by the Regional Ethics Committee and Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (4-2012-0223, 4-2023-0758). This full list of participating sites and ethics committees can be found at Supplementary Information. All patients enrolled in KNOW-KT voluntarily provided written informed consent.

Conflict of Interest Statement

The authors of this manuscript have no conflicts of interest to disclose.

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Author Contributions

Research design and writing: J.H. and J.Y. Data collection: J.H., J.-H.R., M.-G.K., K.H.H., K.W.L., H.-Y.J., K.P.K., H.R., S.H., B.S.K., and J.Y. Data analysis and data interpretation: J.H., J.C.J., and J.Y.

Data Availability Statement

Data supporting the findings of this study are not publicly available due to privacy reasons but are available from the data sharing committee upon reasonable request.

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