


ORIGINAL ARTICLE

Coronary artery calcification progression and long-term cardiovascular outcomes in renal transplant recipients: an analysis by the joint model

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ABSTRACT

Background. Compared with the general population, the risk of death is substantially higher in renal transplant recipients than in age- and sex-matched individuals in the general population. In the general population, coronary artery calcification (CAC) predicts all-cause and cardiovascular mortality. In this study we aimed to analyse these relationships in renal transplant recipients.

Methods. We examined 178 renal transplant patients in this prospective observational cohort study. We measured CAC with multidetector spiral computed tomography using the Agatston score at multiple time points. Overall, 411 scans were performed in 178 patients over an average 12.8 years follow-up. The clinical endpoint was a composite including all-cause death and non-fatal cardiovascular events. Data analysis was performed by the joint model.

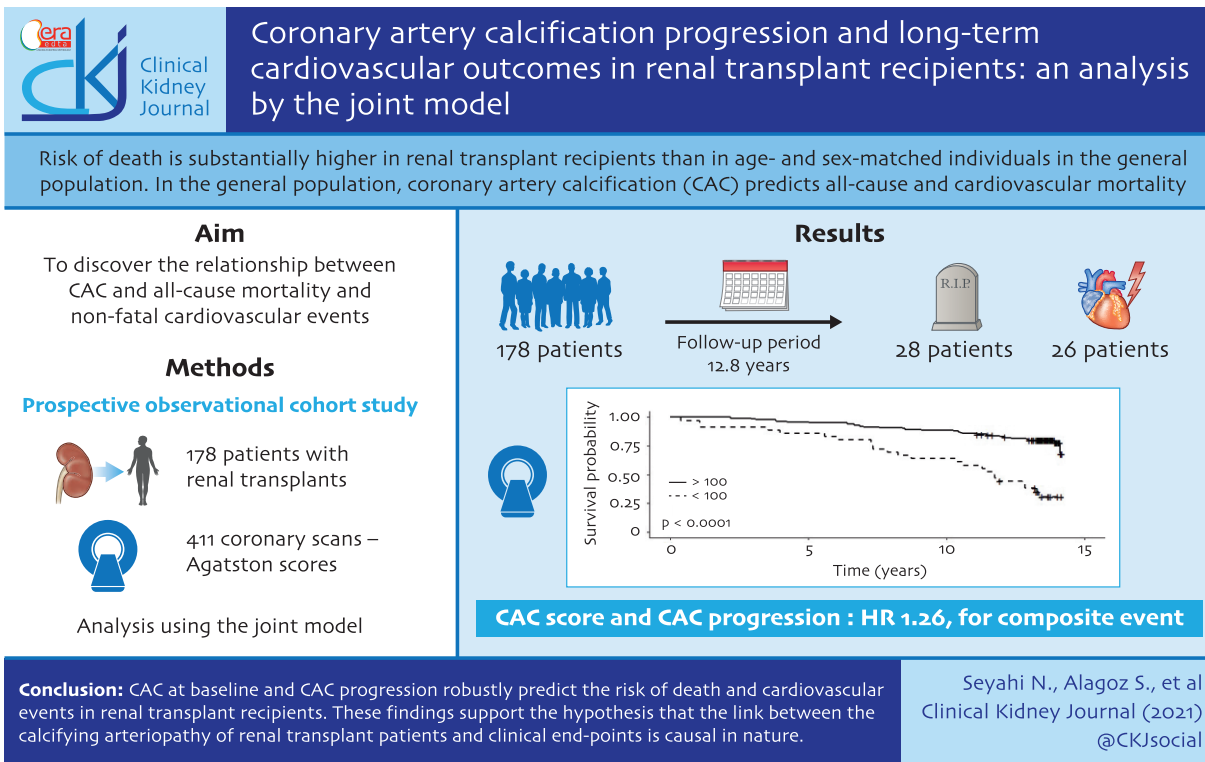
Results. During a follow-up of 12.8 ± 2.4 years, coronary calcification progressed over time ($P < 0.001$) and the clinical endpoint occurred in 54 patients. In the analysis by the joint model, both the baseline CAC score and the CAC score progression were strongly associated with the incidence rate of the composite event [hazard ratio 1.261 (95% confidence interval 1.119–1.420), $P = 0.0001$].

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GRAPHICAL ABSTRACT



Conclusions. CAC at baseline and coronary calcification progression robustly predict the risk of death and cardiovascular events in renal transplant recipients. These findings support the hypothesis that the link between the calcifying arteriopathy of renal transplant patients and clinical end points in these patients is causal in nature.

Keywords: cardiovascular disease, coronary artery calcification, joint model, mortality, renal transplantation

INTRODUCTION

Renal transplantation is indisputably the best renal replacement therapy and provides better survival compared with dialysis therapies [1]. Nevertheless, compared with the general population, life expectancy in renal transplant recipients remains much shorter than in well-matched individuals in the general population [2]. Renal transplant recipients have a much lower cardiovascular risk than haemodialysis patients but they still have a risk for fatal and non-fatal cardiovascular events of 3.5–5% [3], which is substantially higher than that in the general population.

Coronary artery calcification (CAC) is an established prognostic biomarker for cardiovascular events and all-cause mortality in the general population [4, 5] and the 2018 Cholesterol Guideline by the American College of Cardiology and American Heart Association suggests that coronary artery calcium testing may be considered in non-diabetic adults without diabetes at intermediate cardiovascular risk [6]. However, there is a paucity of data about the impact of CAC on the risk of death and cardiovascular events in renal transplant recipients [7]. Furthermore, there is evidence that CAC progression over time may be a more accurate predictor of the future cardiac risk than the baseline

CAC alone [8, 9]. However, to the best of our knowledge, the relationship between repeated measurements of the CAC score and adverse clinical outcomes has not been studied in renal transplant recipients.

We previously examined the association of CAC with coronary ischaemia in renal transplant recipients and studied the short- and long-term progression patterns of CAC in those patients in two separate studies [10–12].

Assessing the link between surrogate prognostic biomarkers like the CAC score and clinical outcomes is fundamental in clinical research. In this study we have therefore investigated in the same database of renal transplant patients the relationship between CAC and a composite endpoint including all-cause mortality and incident non-fatal cardiovascular events by applying the analysis of joint models.

MATERIALS AND METHODS

Study design and subjects

The study design and patient follow-up data are summarized in Figure 1. The study protocol was approved by the local

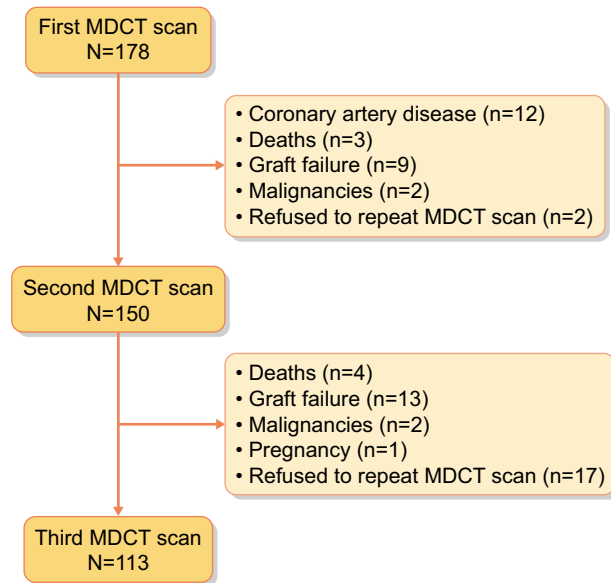


FIGURE 1: Study flow chart.

ethical committee (protocol number 89539, date of approval 6 March 2018).

Data collection

The definitions and methods used during our clinical and laboratory assessments have been previously described in detail [10]. For the collection of outcome data, we used the following approaches. First, we used the data from patient files and in the electronic database of the hospital, along with those collected from the interviews. We recorded the presence and the date of the following cardiovascular events: hospitalization in the coronary intensive care unit, coronary artery disease (myocardial infarction, coronary revascularization procedure or coronary artery disease documented by angiography), peripheral arterial surgical procedure, stroke or transient ischaemic attack diagnosed by a physician. We also collected the mortality data. We contacted the patients or their families by telephone when they did not show up for their regular follow-up visits. In case we could not reach a patient by those means, we also checked the transplantation, dialysis and monitoring systems [Türkiye transplantasyon, diyaliz ve izlem sistemleri (TTDIS)] of the Turkish Ministry of Health to obtain the survival data for that specific patient. The TTDIS is a web-based database that is cross-linked to the national mortality database. Final evaluation, including telephone interviews, was performed during May 2020.

Coronary calcium score measurements

All multidetector computed tomography (MDCT) scans were performed with the same equipment (SOMATOM Sensation version 16 Cardiac; Siemens AG, Erlangen, Germany) using the procedures we described in detail in a previous study [10] and CAC scores were calculated according to the Agatston method.

Outcome measure

The main outcome measure was a combined endpoint including death and/or the following cardiovascular events: myocardial infarction, coronary revascularization procedures including

coronary surgery and coronary angioplasty/stenting, *de novo* coronary artery disease documented by angiography, hospitalization in the coronary intensive care unit, vascular surgery for peripheral vascular disease, transient ischaemic attack and stroke.

Statistical analysis

Data were expressed as mean \pm standard deviation (SD) for the continuous variables and as frequency and percentages for the categorical variables. We made the joint model analysis testing both log-transformed ($\ln [1 + \text{raw CAC score}]$) and raw CAC scores. Given the fact that the data fitting was better with log-transformed CAC scores, we adopted this functional form of the CAC score for assessing the link between this biomarker and the study outcome in the joint model analysis.

In order to determine the longitudinal association between the CAC score and the composite endpoint we used the joint model analysis, which combines the linear mixed model and the Cox model. In this model, longitudinal changes in relevant variables and survival data are modelled simultaneously, using shared random effects. Therefore a more efficient and unbiased parameter estimation is obtained compared with the alternative models that analyse two processes separately. The joint model has two submodels: the linear mixed submodel and the survival submodel. In our study, the linear mixed model was used to compute the changes in the CAC score over the follow-up and the survival submodel was used to estimate the relationship between longitudinal changes in the CAC score and the composite endpoint [13]. In case of multiple events, the last event was considered. The association between the baseline CAC score (as recodified below/above 100) and the cumulative survival free of the combined endpoint was investigated by the Kaplan–Meier survival method.

We performed the joint model analysis in two steps. First, a univariate time-dependent Cox analysis was used to select the variables presented in Table 2. Second, the joint model was constructed by including all the variables significantly associated ($P < 0.05$) with the composite endpoint at the univariate time-dependent Cox analyses. Only 4 of 178 patients had cardiovascular disease at baseline and for this reason we did not include this variable in the joint model.

As a sensitivity analysis, the association between the longitudinal changes of the CAC score and the incidence rate of the composite endpoint was also investigated by a Cox model including the CAC score as a time-dependent covariate.

Parameter estimates were reported as the hazard ratio (HR) with a 95% confidence interval (CI) and P-values for the survival model. In the linear mixed model, data were reported as the regression coefficient, 95% CI and P-value. A P-value < 0.05 was considered statistically significant. The joint model was applied using RStudio version 4.0.2 (RStudio, Boston, MA, USA). The JM package was used to fit the joint model [14].

RESULTS

The cohort of this study is formed by 178 consecutive, adult (≥ 18 years of age) renal transplantation recipients who participated in a study (March 2006 and December 2007) testing the relationship between the CAC score and coronary ischaemia [10]. We also examined the CAC progression in two consecutive follow-up studies [11, 12]. The scope of the previous follow-up studies was that of estimating the risk for *de novo* CAC in patients without coronary artery disease at baseline. Therefore

12 patients who had evidence of coronary artery disease at baseline were not eligible for follow-up MDCT scans [10–12]. In between the first and second scan, three patients died, nine had graft failure, two developed malignancies and two refused to repeat the MDCT scan. A second scan was performed in 150 patients between March 2009 and June 2010. Between the second and third scan, 4 patients died, 13 had graft failure, 2 had malignancies, 1 was pregnant and 17 refused to repeat the MDCT scan. Thus the third scan was performed in 113 patients between April 2013 and July 2014 (Figure 1). Overall, 441 MDCT scans were performed in 178 patients over 12.8 ± 2.4 years of follow-up.

Baseline characteristics of the study population

The demographic characteristics, cardiovascular risk factors and laboratory data of the 178 renal transplant recipients are presented in Table 1. Study participants were predominantly male and mostly young or middle-aged and most of them ($n = 149$) had a living donor transplant. Pre-emptive transplantation was performed in three patients (1.7%). The glomerular filtration rate was >30 mL/min/1.73 m² in 93.8% of the patients, while microalbuminuria was present in 40.4% and overt proteinuria in 19.7%.

Aspirin was used by 16.3% of the patients, statins by 41.0%, antihypertensive medications by 77.5%, bisphosphonates by 19.1%, calcium supplements by 29.2% and vitamin D supplements by 25.8%.

Follow-up data

At the end of the follow-up, of the 178 transplant recipients, 27 were on dialysis and 21 had a functioning second renal graft. The mean eGFR of the patients who had a functional graft ($n = 123$, including second transplantations) at the end of follow-up was 62.0 ± 22.4 mL/min/1.73 m².

During the 12.8 ± 2.4 years of follow-up, 28 patients died and 28 patients had cardiovascular events, which were fatal in 2 cases. Overall, 54 patients experienced the composite endpoint 'death and non-fatal cardiovascular events'. In detail, the combined endpoint included 28 deaths, 15 cases of coronary artery revascularization, 5 cases of strokes, 2 cases of vascular surgery for peripheral arterial disease, 2 cases of hospitalization in the coronary intensive care unit (due to arrhythmia), 1 case of myocardial infarction and 1 case of coronary artery disease documented by angiography. In a Kaplan–Meier survival analysis, patients with a CAC score >100 ($n = 36$) had a significantly lower cumulative survival as compared with those with a CAC score <100 (Figure 2).

CAC progression as tested in the mixed linear submodel of the joint model

In the linear mixed submodel, age, duration of follow-up, systolic blood pressure (BP) and diabetes were significantly related to changes in the CAC score over time, whereas body mass index (BMI) and serum calcium failed to be related with CAC progression ($P = 0.659$ and $P = 0.588$, respectively; Table 2).

In the multiple linear mixed submodel adjusting for variables significantly related with CAC changes over time, including age, duration of follow-up, systolic BP and diabetes, the CAC score progressively increased from baseline (Figure 3).

Table 1. Baseline demographic, clinical and laboratory data and CAC scores

Variable	Values
Age (years)	35 (20–68)
Gender (male), n (%)	120 (67)
Time on transplantation (months)	53.5 (3–295)
Living donor, n (%)	148 (83.1)
Dialysis vintage (months)	16 (0–120)
Current smoker, n (%)	91 (51.1)
BMI (kg/m ²)	25.22 (16.53–38.95)
Diabetes mellitus, n (%)	11 (6.2)
Systolic BP (mmHg)	120.0 (80.0–170.0)
Diastolic BP (mmHg)	80.00 (40.00–115.00)
Creatinine (mg/dL)	1.30 (0.60–6.0)
eGFR ^a (mL/min/1.73 m ²)	61.35 (8.60–144.0)
Total cholesterol (mg/dL)	184(96–387)
Low-density lipoprotein cholesterol (mg/dL)	107.5 (27.0–240.0)
Triglycerides (mg/dL)	132.5 (36.0–581.0)
Calcium (mg/dL)	9.60 (7.90–11.2)
Phosphorus (mg/dL), mean \pm SD	3.36 \pm 0.65
PTH (pg/mL)	76.10 (13.0–856.0)
C-reactive protein (mg/L)	1.60 (0.15–45.6)
Baseline CAC scores ^b	0 (0–1712.0)
All CAC scores ^b	0.60 (0–1876.7)

Data are presented as median (range) until stated otherwise. 'All coronary artery calcification scores' refers to data from all scans performed during the follow-up.

^aModification of Diet in Renal Disease formula was used.

^bAgatston method was used.

Association of the CAC score with the study combined endpoint

On univariate time-dependent Cox regression analyses, the baseline CAC score as well as age, BMI, diabetes, systolic and diastolic BP and serum calcium were significantly associated with the incidence rate of the composite endpoint (Table 3).

In the joint model, adjusting for all univariate correlates of study outcome, a 1-unit increase in the log-transformed CAC score was associated with a 1.26-fold increase of the HR of the composite endpoint (95% CI 1.119–1.420; $P = 0.0001$; Figure 3). In the same joint model, the baseline serum calcium level maintained an independent association with the composite endpoint [HR 0.495 (95% CI 0.287–0.853); $P = 0.011$; Figure 4], whereas age, BMI, systolic BP and a history of diabetes did not after multiple data adjustment (P range 0.092–0.617, Figure 4).

A sensitivity analysis carried out with a time-dependent Cox regression analysis provided similar results regarding the association between the CAC scores and the incidence of the composite outcome [HR 1.236 (95% CI 1.100–1.389); $P = 0.0003$].

DISCUSSION

Our long-term study shows that longitudinal CAC measurements by MDCT predict a composite endpoint including mortality and cardiovascular events in a cohort of renal transplant recipients that were virtually free of cardiovascular disease at baseline [15].

Arterial disease in renal transplant patients is a severe, complex process. Like in patients with Stages 3 and 4 CKD and kidney failure patients on regular dialysis treatment, this process is characterized by an almost unique propensity to calcification [16]. Inflammation is considered a fundamental factor favouring

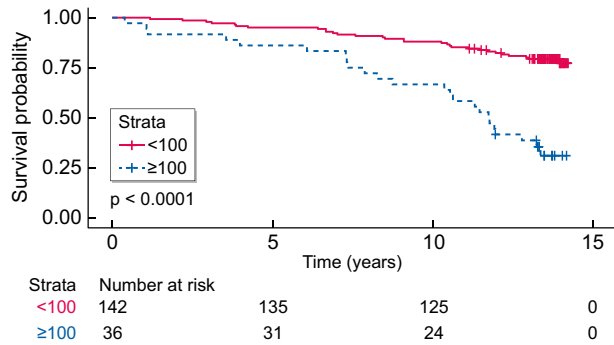


FIGURE 2: Kaplan-Meier survival curve of the composite event in patients stratified according to the baseline CAC score (cut-off: 100).

vascular calcification in these conditions and disturbed bone mineral metabolism occurs to generate arterial damage in these patients [17]. Aortic calcification assessed by a semi-quantitative method predicts cardiovascular events and all-cause mortality in renal transplantation [11, 18, 19]. However, it is still unclear whether a high CAC score predicts a cardiovascular-related or general mortality in renal transplant recipients free of cardiovascular complications and no evidence of coronary calcification at baseline [15]. In the two follow-up studies performed so far, investigators measured the calcium mass score at a single time point to predict cardiovascular mortality in patients with and without background cardiovascular disease at baseline [20, 21]. Ideally the relationship between any purported risk factor and clinical outcomes should be pursued in cohorts of disease-free individuals at baseline [22].

Coronary calcification in patients with coronary heart disease in the general population is mainly a process located in the intima layer of the arteries [23] and both a high CAC score and a high progression rate of this alteration associate with high cardiovascular mortality in the general population [4, 10, 24–30]. Coronary calcification in renal transplant patients differs from that associated with atherosclerosis in the general population. Indeed, coronary calcification in these patients represents the aggregate of both endothelial and medial wall calcification. Medial wall calcification in kidney failure and in renal transplant patients is mainly associated with mineral and bone disorder [11, 23], i.e. a peculiar series of alterations of divalent ions and endocrine factors underlying bone disease in CKD and in kidney failure [31]. In this respect, we found that relatively lower serum calcium was associated with a higher risk for the composite endpoint in these patients. Low serum calcium may underlie vitamin D deficiency and secondary hyperparathyroidism in patients with CKD, like renal transplant patients [32]. On the other hand, low serum calcium may associate with CAC also independent of parathyroid hormone (PTH) levels [33].

Whether the link between coronary calcification and cardiovascular events in renal transplant patients is causal in nature is unknown. The gold standard for assessing causality is the randomized clinical trial, i.e. a design testing whether an intervention reducing coronary calcification reduces the risk for cardiovascular events. Until now, no such trial has ever been performed in renal transplant patients. Sevelamer and cinacalcet, two drugs that mitigate secondary hyperparathyroidism in patients with kidney failure on dialysis, reduce the progression of vascular calcification in various arterial districts, including the coronary artery. However, randomized clinical trials with these drugs in the dialysis population failed to show a benefit of

Table 2. Parameter estimation for longitudinal linear mixed submodel

Variable	Estimation (95% CI)	P-value
Intercept	-2.673 (-7.176–1.829)	0.245
Follow-up duration (years)	0.122 (0.083–0.161)	0.0001
Age (years)	0.084 (0.065–0.104)	0.0001
Body mass index (kg/m ²)	0.012 (-0.044–0.069)	0.659
Systolic BP (mmHg)	0.018 (0.006–0.030)	0.003
Diabetes	1.411 (0.663–2.161)	0.0002
Calcium (mg/dL)	-0.1410 (-0.651–0.369)	0.588

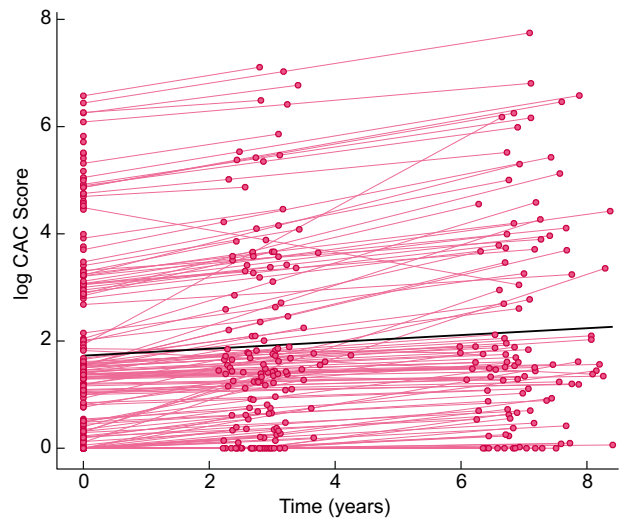


FIGURE 3: Black line represents population mean for CAC score evolution with a fixed effect for time. Red lines represent individual CAC score evaluations with random intercept and random slope for time (linear mixed model).

these interventions on mortality and cardiovascular outcomes [34, 35]. In renal transplant patients, there has been just one trial testing the hypothesis that drug treatment may regress coronary calcification [36]. This trial that evaluated the effect of fluvastatin on CAC progression largely failed to document a benefit of this drug over 1 year of treatment. In another trial in the same population, fluvastatin failed to reduce the risk for cardiac death and non-fatal myocardial infarction [37].

Coronary calcification in renal transplant patients was studied in at least six cross-sectional studies [10, 38–42]. However, this study design is inherently inadequate for assessing causality. Longitudinal studies have several advantages over cross-sectional studies for exploring causation. Indeed, these studies provide information about individual changes in the variables of interest, exclude between-subject variations from error and allow investigation of the relationship between predictor variables with relevant study endpoints [43]. Several longitudinal studies in renal transplant patients [11, 12, 44–50], including one by us [12], focused on the progression of CAC after renal transplantation. The results of these longitudinal studies are

Table 3. Univariate time-dependent Cox analysis for endpoint

Variable	Composite endpoint (cardiovascular events and all-cause mortality)	
	HR (95% CI)	P-value
Age (years)	1.054 (1.031–1.076)	0.0001
Gender (male)	0.699 (0.380–1.285)	0.245
Living donor	1.796 (1.201–2.447)	0.066
Dialysis vintage (months)	0.999 (0.988–1.011)	0.894
Smoker	1.337 (0.796–2.294)	0.291
Body mass index (kg/m ²)	1.070 (1.011–1.136)	0.024
Family history of cardiovascular disease	1.345 (0.575–3.144)	0.494
Diabetes mellitus	3.646 (1.649–8.092)	0.002
Systolic BP (mmHg)	1.027 (1.011–1.043)	0.001
Diastolic BP (mmHg)	1.043 (1.007–1.059)	0.013
Creatinine (mg/dL)	0.956 (0.615–1.487)	0.845
GFR (mL/min/1.73 m ²) ^a	1.001 (0.988–1.014)	0.925
Total cholesterol (mg/dL)	1.005 (0.999–1.011)	0.076
Low-density lipoprotein cholesterol (mg/dL)	1.003 (0.995–1.010)	0.496
Triglycerides (mg/dL)	1.001 (0.997–1.004)	0.719
Calcium (mg/dL)	0.561 (0.331–0.951)	0.032
Phosphorus (mg/dL)	1.090 (0.727–1.635)	0.675
PTH (pg/mL)	1.001 (0.82–1.002)	0.753
C-reactive protein (mg/L)	1.006 (0.957–1.057)	0.805
CAC score ^b	1.311 (1.185–1.456)	0.0001

CAC data changed over time, the other variables are baseline values.

^aModification of Diet in Renal Disease formula was used.

^bAgatston method was used.

disparate. Indeed, some of these showed a slowing of the process starting 6 months after transplantation [44] or a global slowing [45], while the majority of long-term studies documented an unrelented progression of CAC [11, 12, 46–50]. However, in none of these studies was the relationship between CAC progression and death and cardiovascular events investigated. So far, just two follow-up studies have investigated the predictive power of baseline CAC score for clinical events in renal transplant patients. In the first, the CAC score was a powerful predictor of major adverse cardiovascular events, including cardiovascular death, myocardial infarction, stroke and transient ischaemic attack [20]. In the second, the baseline CAC score predicted all-cause death and cardiovascular events, but the number of events in this study was very small (just 21

events) and preclusive to multivariate analyses [21]. Given the lack of randomized clinical trials, longitudinal analyses combining repeated measurements of the CAC score with cardiovascular endpoints are provisionally important to better appraise the nature of the link between coronary calcification and cardiovascular outcomes in renal transplant patients.

In this respect, the joint model is a robust method for analysing the relationship between repeated measurements of the CAC score and cardiovascular outcomes. Indeed, in this model longitudinal changes in relevant variables and survival data are modelled simultaneously, using shared random effects. Thus the joint model allows testing the relationship between the longitudinal evolution over time of CAC estimated by the linear mixed model with major cardiovascular events and death estimated by the Cox model. This approach was not applied in the three studies focusing on cardiovascular events that had either a simple follow-up design with the CAC score measured just at baseline [7, 20] or twice with an interstudies interval of 1.7 years [21]. As alluded to before, the number of events in the study by Roe et al. [21] was just 21, and even lower in the subgroup (87 patients of an initial cohort of 112 patients) who repeated the CAC score measurement. In this study we performed 441 MDCT scans in 178 patients over a median follow-up of 12.8 years. In this analysis we found that baseline CAC and CAC progression over time were strongly associated with the combined endpoint. Overall, our data support the interpretation that the process of arterial damage underlying calcification in the coronary arteries in renal transplant patients is causally linked to adverse health outcomes in renal transplant patients.

Our study has limitations. First, despite the long follow-up duration, the number of events was still relatively small. Second, the majority of the patients in our unit were living donor transplant recipients and might not be representative of the general transplant population, including cadaveric kidney transplantation. On the other hand, the fact that we focused on a population without coronary calcification at baseline and the application of the joint model to analyse the incidence and evolution of this alteration and its relationship with clinical endpoints is a strength.

In conclusion, CAC and CAC progression both predict death and cardiovascular events (the combined endpoint of this study) over long-term follow-up in renal transplant recipients. These findings provide circumstantial evidence that the link between the calcifying arterial disease and the high risk for cardiovascular events in renal transplant patients is causal in nature. Overall, our data further underscore the need for intervention trials aimed at mitigating the calcification process in this population. New drugs interfering with vascular calcification are under development. A recent randomized trial in patients with kidney failure reported that a selective inhibitor of hydroxyapatite formation and growth effectively reduces coronary calcification in this population [51]. Future studies of this or other drugs [52] will assess whether slowing the calcification process may translate into cardiovascular risk reduction in renal transplant patients.

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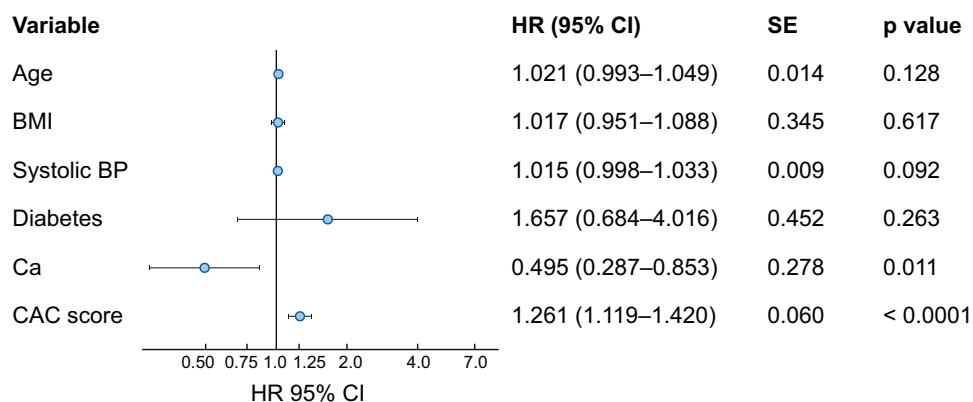


FIGURE 4: Cox regression submodel showing the association of the composite endpoint with selected variables.

AUTHORS' CONTRIBUTIONS

N.S., S.A., Z.A., S.G.O., G.T., A.B. and C.Z. were involved in the conception or design of the study and/or the analysis and interpretation of data. N.S., Z.A., S.G.O., G.T., S.T. and C.Z. were responsible for drafting or revising the manuscript. N.S., Z.A., G.T. and C.Z. provided intellectual content of critical importance to the work described. N.S., S.A., Z.A., G.T., S.P. and C.Z. provided final approval of the version to be published.

CONFLICT OF INTEREST STATEMENT

CZ is a member of the CKJ editorial board.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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