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Abdominal Arterial Calcification Score Association with Patients' Survival Post Kidney Transplant

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Abstract:	**Background** Abdominal arterial calcification (AAC) is a common comorbidity in patients with End Stage Kidney Disease (ESKD) and a predictor of cardiovascular events post-kidney transplant. However, prior studies lacked a standardized approach to evaluate AAC and its impact on post-transplant outcomes. This study aimed to correlate AAC score values with post-kidney transplant outcomes using a modified scoring system traditionally applied to coronary artery calcification. **Methods** This retrospective study included 14,339 adult patients listed for kidney transplant between 2002 and 2023 at three transplant centers. Among them, 3,683 patients met the criteria of undergoing a kidney transplant and an abdominal computed tomography (CT) scan pre-transplant. We modified coronary calcium score software by adjusting intake data points to quantify calcification in the abdominal aorta, common iliac, external iliac, and internal iliac arteries. Outcomes focused on post-transplant mortality. **Results** In 3,683 kidney transplant recipients, higher AAC scores were significantly associated with increased mortality. Each 1,000-

	unit increase in AAC score elevated hazard ratios (HRs) across arterial regions, including 1.116 for the aorta and 1.389 for the internal iliac (all $p<0.001$). Adjusted analyses confirmed AAC as an independent risk factor for mortality. Kaplan-Meier curves demonstrated lower survival with increasing AAC quartiles. **Conclusions** Abdominal arterial calcification, measured by a standardized score, is a significant mortality risk factor in kidney transplant recipients. Integrating AAC scores into pre-transplant evaluations could enhance risk stratification and improve outcomes. Prospective studies are needed to validate these findings and explore interventions to reduce AAC and improve survival.

Abdominal Arterial Calcification Score Association with Patients' Survival Post Kidney Transplant

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Running Head: Abdominal Arterial Calcification and Survival Post-Kidney Transplant

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Abbreviations: Abdominal Arterial Calcification (AAC), Chronic Kidney Disease (CKD), End Stage Kidney Disease (ESKD), Coronary Artery Disease (CAD), Diabetes Mellitus (DM).

Abstract:

Background

Abdominal arterial calcification (AAC) is a common comorbidity in patients with End Stage Kidney Disease (ESKD) and a predictor of cardiovascular events post-kidney transplant. However, prior studies lacked a standardized approach to evaluate AAC and its impact on post-transplant outcomes. This study aimed to correlate AAC score values with post-kidney transplant outcomes using a modified scoring system traditionally applied to coronary artery calcification.

Methods

This retrospective study included 14,339 adult patients listed for kidney transplant between 2002 and 2023 at three transplant centers. Among them, 3,683 patients met the criteria of undergoing a kidney transplant and an abdominal computed tomography (CT) scan pre-transplant. We modified coronary calcium score software by adjusting intake data points to quantify calcification in the abdominal aorta, common iliac, external iliac, and internal iliac arteries. Outcomes focused on post-transplant mortality.

Results

In 3,683 kidney transplant recipients, higher AAC scores were significantly associated with increased mortality. Each 1,000-unit increase in AAC score elevated hazard ratios (HRs) across arterial regions, including 1.116 for the aorta and 1.389 for the internal iliac (all $p<0.001$). Adjusted analyses confirmed AAC as an independent risk factor for mortality. Kaplan-Meier curves demonstrated lower survival with increasing AAC quartiles.

Conclusions

Abdominal arterial calcification, measured by a standardized score, is a significant mortality risk factor in kidney transplant recipients. Integrating AAC scores into pre-transplant evaluations could enhance risk stratification and improve outcomes. Prospective studies are needed to validate these findings and explore interventions to reduce AAC and improve survival.

Introduction:

Long-term survival following kidney transplant is impacted by cardiovascular disease, which remains a leading cause of death in patients with functioning kidney allografts and significantly limits their survival[1]. Studies have shown that transplant recipients with pre-existing, undiagnosed, or poorly managed coronary artery disease (CAD) face significantly higher risks of major adverse cardiac events post-transplant[2], including myocardial infraction, heart failure, and sudden cardiac death within the first few years after transplant. These elevated cardiac risks impact both short- and long-term survival rates[3], highlighting the critical need for comprehensive CAD evaluation and management prior to transplant approval.

In addition to the risk of coronary artery disease, AAC is the next important vascular change to consider and a common comorbidity in patients with ESKD [4, 5]. Previous studies have identified arterial calcification as a predictor of cardiovascular events following kidney transplant[6-8]. However, varying methods used to assess arterial calcification in these studies have led to inconsistent results, making it hard to link calcification scores directly with post-transplant outcomes[9].

To address this, we modified the coronary calcium score software, by changing the intake data points, and applied it to the abdominal aorta, common iliac, external iliac, and internal iliac arteries. With this approach we developed an AAC score system to quantitate the severity of the abdominal arterial calcification. In a previous study, we highlighted the role of AAC, as a predictor of patients' survival and kidney allograft function following transplant based on a single center patients population transplanted between 2010 and 2013 and included 227 kidney transplant recipients[10]. In this study, we expanded the modified AAC score system to include patients transplanted at three transplant centers and enrolled 3,683 patients.

This study aimed to: (1) provide a standardized quantitative measurement of abdominal and pelvic arterial calcification using a computed tomography-based scoring system, and (2) to assess the association of the AAC score with patient survival after transplant. By standardizing the evaluation of AAC, we aim to improve pre-transplant risk stratification and potentially enhance post-transplant outcomes for kidney transplant recipients.

Materials and Methods:

Study Population

The kidney transplant evaluation protocol at our centers requires that all patients with diabetes, regardless of their age, and all patients aged 50 years or older undergo a non-contrast abdominal and pelvic CT scan at the start of their transplant evaluation. This retrospective cohort study involved 14,339 adult patients who were listed for kidney transplant at three different Mayo Clinic Transplant Centers (Mayo Rochester, Mayo Arizona, and Mayo Florida) between 2002 and 2023. Out of these, 3,683 patients met the criteria to be included in the study. All the included patients were 18 years and older, had a kidney transplant, and had a non-contrast abdominal and pelvic CT scan performed within two years before or after their transplant listing date. Patients who underwent combined kidney and pancreas transplants, combined liver and kidney transplants, or combined heart and kidney transplants, as well as those who had a CT scan performed more than two years before or after being listed for kidney transplant, or did not have a CT scan available, were excluded from the study. Additionally, patients who were still on the waitlist until our end date on 15 July 2024 were also excluded. (Figure 1).

Data Collection

Data collected for this study included patient demographics (age, sex, race, and smoking history), the presence of diabetes mellitus (DM), a history of CAD defined as a history of coronary artery bypass surgery and/or percutaneous coronary artery interventions before the kidney transplant evaluation (Table 1).

Abdominal Arterial Calcification (AAC) Score System

For analysis, non-contrast abdominopelvic CT scans, performed within two years before or after the transplant listing date, were selected. The images were retrieved from the picture archiving and communication system, Visage (version 7.1.14, Visage Imaging, Inc, San Diego, CA). Arterial calcification was identified and quantified using a semiautomated software package (syngo.via Client 5.1, Siemens Healthcare, Erlangen, Germany, or TeraRecon Aquarius iNtuition ver 4.4.13.P6, Durham, North Carolina) designed to assess coronary artery calcium using the Agatston method. The software automatically detected calcifications by applying a density threshold of 130 Hounsfield units (HU) or higher and measured the area of each calcification. The AAC score was calculated by multiplying the area of each calcification by a weighted value, determined based on the maximum HU within that calcification. Since the software could not determine the specific anatomical location of the calcifications, four study researchers manually assigned each scored calcification to the appropriate anatomical region, and this assignment was subsequently reviewed by two study radiologists to ensure accuracy. The total calcium score was calculated by summing the calcium scores from the abdominal aorta (from the origin of the celiac artery to the iliac bifurcation), the bilateral common iliac arteries, the bilateral internal iliac arteries (from the iliac bifurcation to the first branch), and the external iliac arteries (from the iliac bifurcation to the inferior epigastric artery). This approach allowed for a comprehensive and standardized assessment of AAC, facilitating the analysis of its association with post-transplant outcomes.

Statistical analysis

Kidney transplant patient's characteristics and outcomes were described as counts and percentages for categorical variables, while sample medians and interquartile ranges were reported for continuous variables. Kaplan–Meier survivorship curves were utilized to demonstrate the association of patient survivorship (death or cardiac-related death) with total calcification score quartiles. Additionally, to visualize the casual effect of the total calcification score on mortality, other survival curves were created using g-computation methods as previously described. Adjusted and multivariable Cox proportional hazard regression models were used to investigate AAC scores as potential risk factors for mortality (death and cardiac-related death). Multivariable models were adjusted for age at transplant, tobacco use, diabetes, and coronary artery disease. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Forest plots were also created to visualize the HR estimates of the AAC predictors. All statistical analyses were conducted using R Statistical Software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria), and significance was set at 0.05.

Results:

Patient Characteristics

The study included 3,683 kidney transplant recipients who met the inclusion criteria (Table1). The median age at the time of listing was 57 years (interquartile range [IQR]: 47-65 years), and the median age at transplant was 59 years (IQR: 49-67 years). The cohort was predominantly male, with 60% of the patients being male and 40% female. The racial distribution was 71% White, 16% Black, 5% Asian, and 7% classified as Other/Unknown/Choose not to disclose. Most patients (83%) were not Hispanic or Latino, while 13% identified as Hispanic or Latino, and 4% were of unknown ethnicity. The patients were distributed across three Mayo Clinic centers: Arizona (44%), Florida (32%), and Rochester (24%) (Table 1).

The median body mass index (BMI) was 28.9 (IQR: 25.0-33.1). Among the cohort, 32% had a history of diabetes mellitus (DM), 13% had CAD, and 91% had hypertension. The median AAC score for the cohort was 968.7 (IQR: 44.9-5015.9), with the median aorta calcification score being 414.7 (IQR: 0.0-2491.1), common iliac calcification score being 189.1 (IQR: 0.0-1454.8), external iliac calcification score being 0.0 (IQR: 0.0-0.0), and internal iliac calcification score being 58.8 (IQR: 0.0-549.0) (Table 1).

Association of AAC Scores with Mortality

The unadjusted Cox proportional hazards model demonstrated that higher AAC scores were significantly associated with increased mortality (Figure 2A). Specifically, each 1000-unit increase in the calcification score was linked to hazard ratios (HRs) for mortality of 1.116 (95% CI: 1.100-1.132, $p<0.001$) for the aorta, 1.122 (95% CI: 1.104-1.141, $p<0.001$) for the common iliac bilateral, 1.285 (95% CI: 1.225-1.349, $p<0.001$) for the external iliac bilateral, 1.389 (95% CI: 1.322-1.460, $p<0.001$) for the internal iliac bilateral, and 1.057 (95% CI: 1.050-1.064, $p<0.001$) for the total calcification score.

After adjusting for potential confounders, including age at transplant, tobacco use, diabetes, and coronary artery disease, the multivariable analysis continued to show a significant association between higher AAC scores and increased mortality (Figure 2B). The adjusted hazard ratios were 1.047 (95% CI: 1.029-1.067, $p<0.001$) for the aorta, 1.051 (95% CI: 1.029-1.073, $p<0.001$) for the common iliac bilateral, 1.138 (95% CI: 1.075-1.204, $p<0.001$) for the external iliac bilateral, 1.126 (95% CI: 1.056-1.201, $p<0.001$) for the internal iliac bilateral, and 1.025 (95% CI: 1.016-1.034, $p<0.001$) for the total calcification score.

Survival Curves

Kaplan-Meier (KM) survival curves show that overall survival decreases as total calcification score quartiles increase (Supplementary Figure 1). This relationship is further highlighted by the survival curves, which display the causal effects of total calcium score on survival probability (Figures 3A and 3B).

The unadjusted model shows a strong inverse relationship between calcium scores and survival rates, with patients having higher calcium levels experiencing a steeper decline in survival probability. This trend is visually emphasized by a color gradient from red (high calcium) to blue (low calcium) across the 20-year follow-up period (Figure 3A).

After adjusting for covariates such as age at transplant, tobacco use, diabetes, and coronary artery disease, the association remains significant. Patients with lower calcium scores continue to exhibit superior survival outcomes compared to those with higher scores, confirming that calcium levels are a strong and independent predictor of survival (Figure 3B).

Discussion:

Using a modified method to calculate the calcification score in the abdominal arteries [9, 11], our study demonstrated that among patients who underwent kidney transplant, those with higher AAC scores had lower survival rates compared to patients with lower AAC scores, even after adjusting for other cardiovascular risk factors such as CAD, smoking, and diabetes. The association between higher AAC scores and decreased survival was consistent across all arterial locations studied, including the aorta, common iliac, external iliac, and internal iliac. These findings align with previous studies that have linked arterial calcification with cardiovascular risk and mortality[12], providing new insights into the role of AAC in post-transplant outcomes.

Despite significant advancements in kidney transplant as a life-saving intervention for patients with ESKD [13], cardiovascular complications continue to pose a substantial challenge, adversely impacting long-term survival in this population [14]. In addition, nearly 50% of all kidney transplant failures result from recipient deaths with a functioning graft [15], representing a significant loss of organs that could have provided long-term benefits to other patients [16]. Established contributors to post-transplant mortality, including ischemic and non-ischemic cardiomyopathy [17], hypertension[18], smoking, and a history of diabetes[19] have been extensively investigated. However, the contribution of AAC has been relatively underexplored [20].

Most published studies have assessed AAC using metrics such as the measured length of calcification, the presence or absence of calcification, and a 24-point scoring system [21]. In this study, we developed a modified adaptation of the existing coronary calcification scoring system, generating a quantitative scoring system specifically for abdominal arteries, including the aorta, common iliac, external iliac, and internal iliac arteries. We further evaluated the association between this calcification score and clinical outcomes in patients with ESKD who underwent kidney transplants. A recent meta-analysis, and multiple clinical studies, have demonstrated that increased AAC is a significant risk factor for reduced survival in both the general population and patients with chronic kidney disease [12]. However, these studies often lacked standardized methods for reporting AAC and utilized varying assessment modalities. Benjamens et al. reported similar findings, showing decreased overall survival among kidney transplant recipients with substantial arterial calcifications [7, 22].

A recent study conducted at our center also demonstrated an association between AAC scores and patient survival following kidney transplant [10]. The current study evaluated a larger cohort of kidney transplant recipients utilizing the modified calcification scoring system, reinforcing the significance of AAC as a potential predictor of mortality in this population. These results contribute to the development of a comprehensive biomarker profile aimed at identifying kidney transplant recipients who are likely to derive the greatest survival benefit.

Despite the strengths of our study, including the large sample size and the use of a standardized, quantitative AAC scoring system, there are several limitations to consider. First, the retrospective nature of the study may introduce selection bias, as patients with more severe calcification may have been more likely to be included. However, we believe that this bias does not significantly affect our conclusions, as we demonstrated that higher AAC scores were consistently associated with worse outcomes across the study population. Additionally, due to referral patterns to our transplant program, some patients' data preceding their kidney transplant evaluation were missing, which may have limited the completeness of our analysis. Furthermore, data on CKD-related complications such as secondary hyperparathyroidism, which could influence calcium metabolism, were not included in our study.

In conclusion, our study highlights the significant impact of AAC on both patient survival and kidney allograft function following transplant. The AAC score should be considered a valuable addition to the pre-transplant evaluation of patients with ESKD. Future prospective studies are needed to further validate the AAC score's role in clinical practice and to explore potential interventions aimed at reducing arterial calcification and improving outcomes in kidney transplant recipients.

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Statement of Ethics:

I confirm that the research described in this manuscript has been conducted in accordance with ethical principles outlined in the Declaration of Helsinki and has received approval from the institutional review board at our institution.

Study approval statement:

The study was approved by Mayo Clinic IRB.

Consent to participate statement:

The Mayo Clinic Internal Review Board approved and waved the requirement for informed consent.

Conflict of interests:

The authors have no conflicts of interest to report.

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Data Availability Statement:

Data is available on request.

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Table 1. Patient Characteristic

Variable	Overall (N=3683)
Age at listing (years)	57 (47, 65)
Sex	
Male	2211 (60%)
Female	1470 (40%)
Race	
White	2624 (71%)
Black	607 (16%)
Asian	201 (5%)
Other/Unknown/Choose not to disclose	251 (7%)
Ethnicity	
Not Hispanic or Latino	3068 (83%)
Hispanic or Latino	481 (13%)
Unknown	134 (4%)
Mayo center	
Arizona	1608 (44%)
Florida	1185 (32%)
Rochester	890 (24%)
BMI	28.9 (25.0, 33.1)
Tobacco use at time of listing	
Never smoker	2269 (62%)
Former smoker	1351 (37%)
Current smoker/chewer	60 (2%)
CAD	473 (13%)
Diabetes	1195 (32%)
Hypertension	3362 (91%)
Age at transplant (years)	59 (49, 67)
CT before or after listing	
Before	2611 (71%)
After	1072 (29%)
Time between listing and CT (days)	124.0 (48.0, 286.8)
Aorta calcification score	414.7 (0.0, 2491.1)
Bilateral Common iliac calcification score	189.1 (0.0, 1454.8)
Bilateral External iliac calcification score	0.0 (0.0, 0.0)
Bilateral Internal iliac calcification score	58.8 (0.0, 549.0)
Total calcification score	968.7 (44.9, 5015.9)
The sample median (Q1, Q3) is given for continuous variables.	

BMI = Body mass index; CAD = coronary artery disease; CT = Computed Tomography.

Table Legends:

Table 1.

This table summarizes the baseline characteristics of the study population (N = 3,683). The variables listed include demographic data (age, sex, race, and ethnicity), clinical data (body mass index [BMI], medical history (CAD, diabetes, dialysis), and details related to the timing of medical procedures (time between listing and CT). The table also includes the use of tobacco, and calcium scores for various vascular regions. Continuous variables are presented as median values with interquartile ranges (Q1, Q3), and categorical variables are presented as counts and percentages.

Figure 1. Flowchart of Patient Selection and Exclusion Criteria

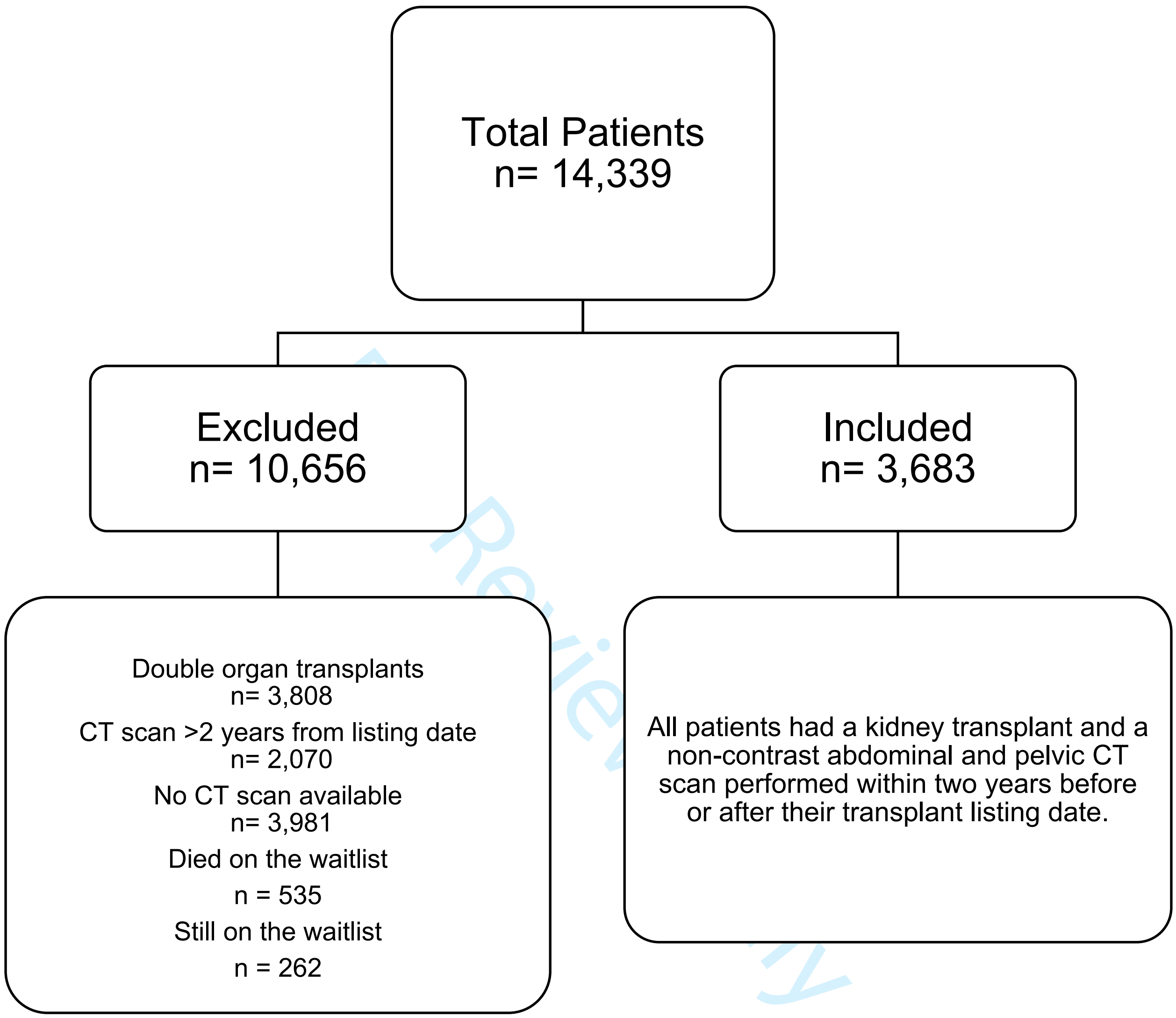


Figure 2A. Forest Plots of Cox Unadjusted Models (Per 1,000-unit change in score)

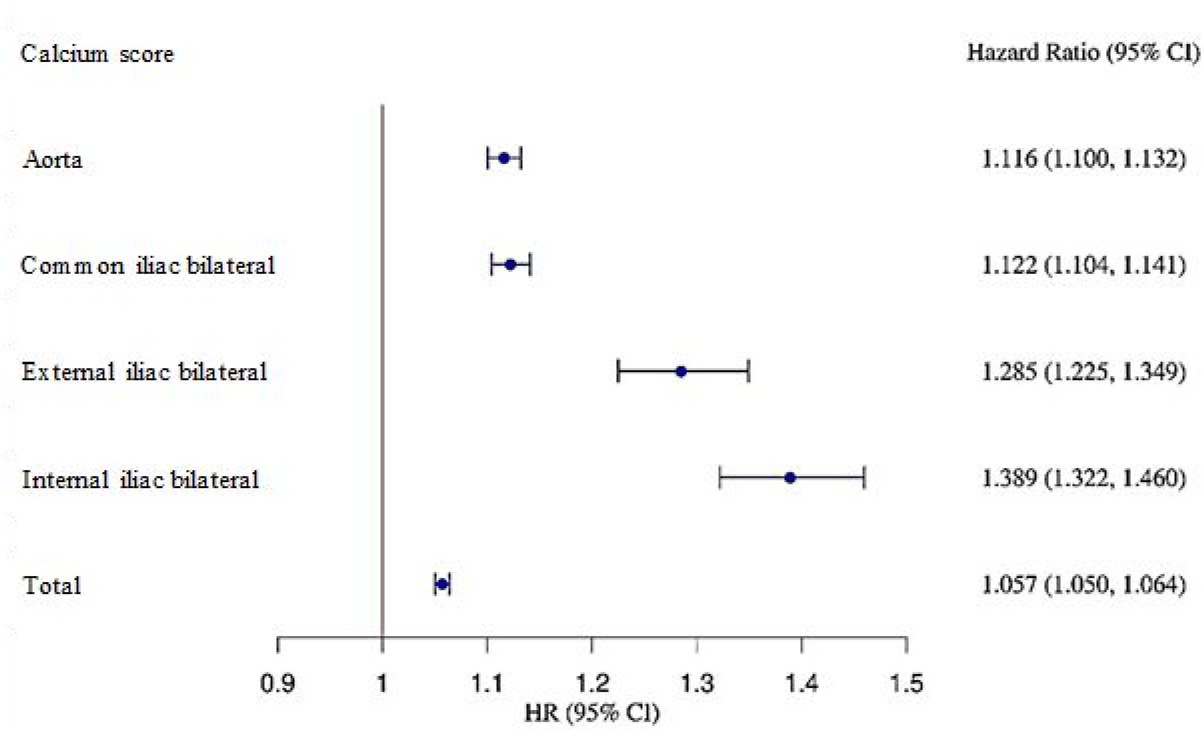


Figure 2B. Forest Plots of Cox Multivariable Models (Per 1,000-unit change in score)

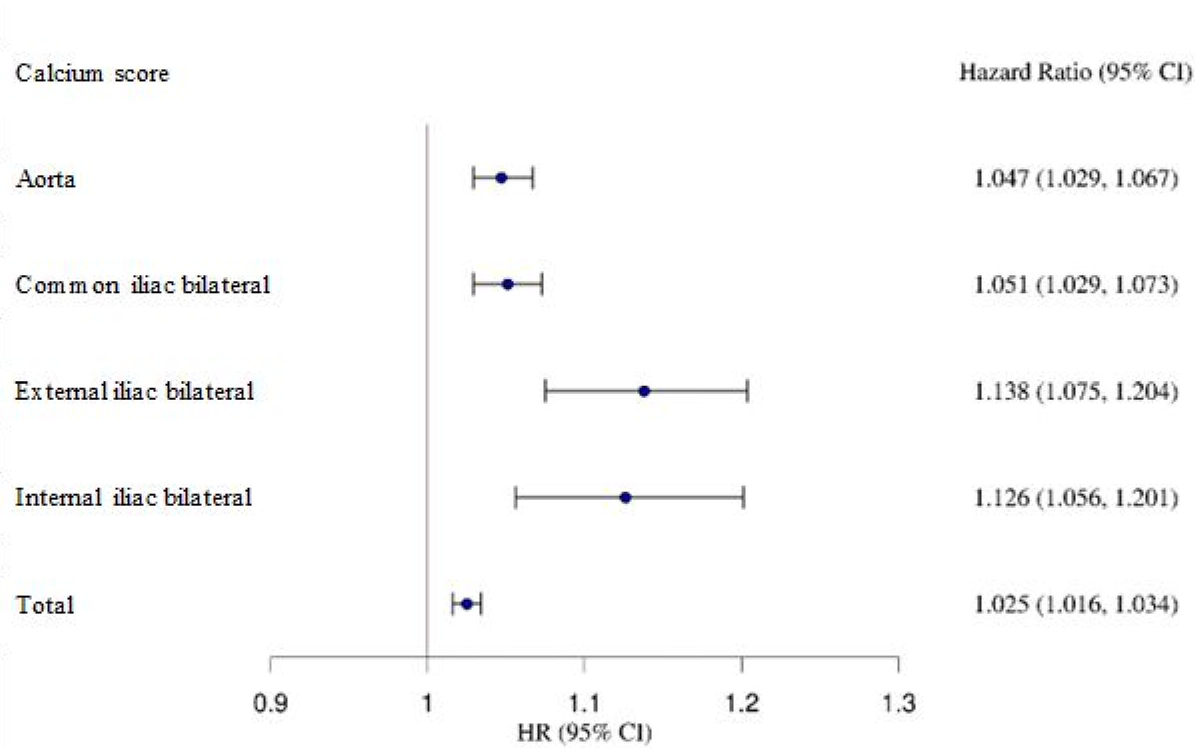


Figure 3A. Casual Effect of Total Calcium Score Survival Area Plot (unadjusted model)

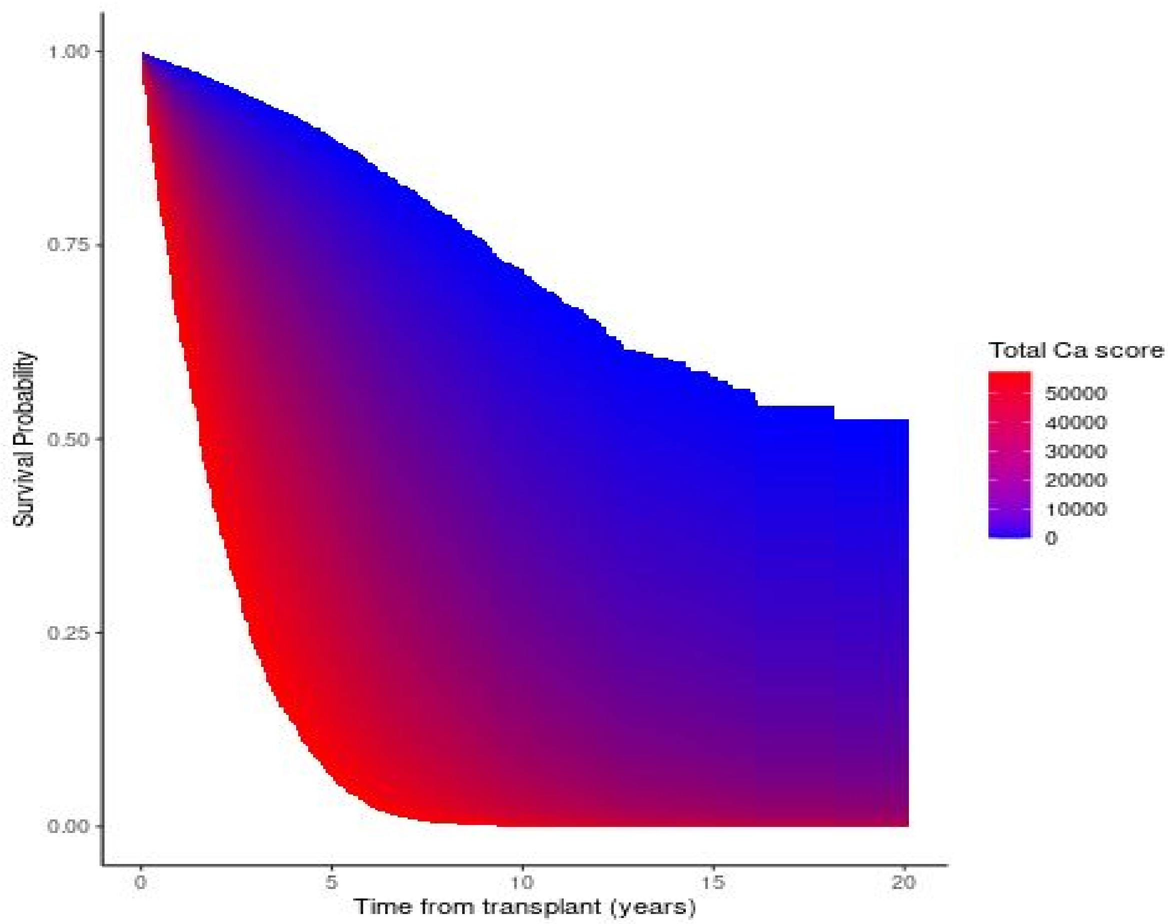


Figure 3B. Casual Effect of Total Calcium Score Survival Area Plot (multivariable model, adjusted for age at transplant, tobacco use, diabetes, and coronary artery disease.)

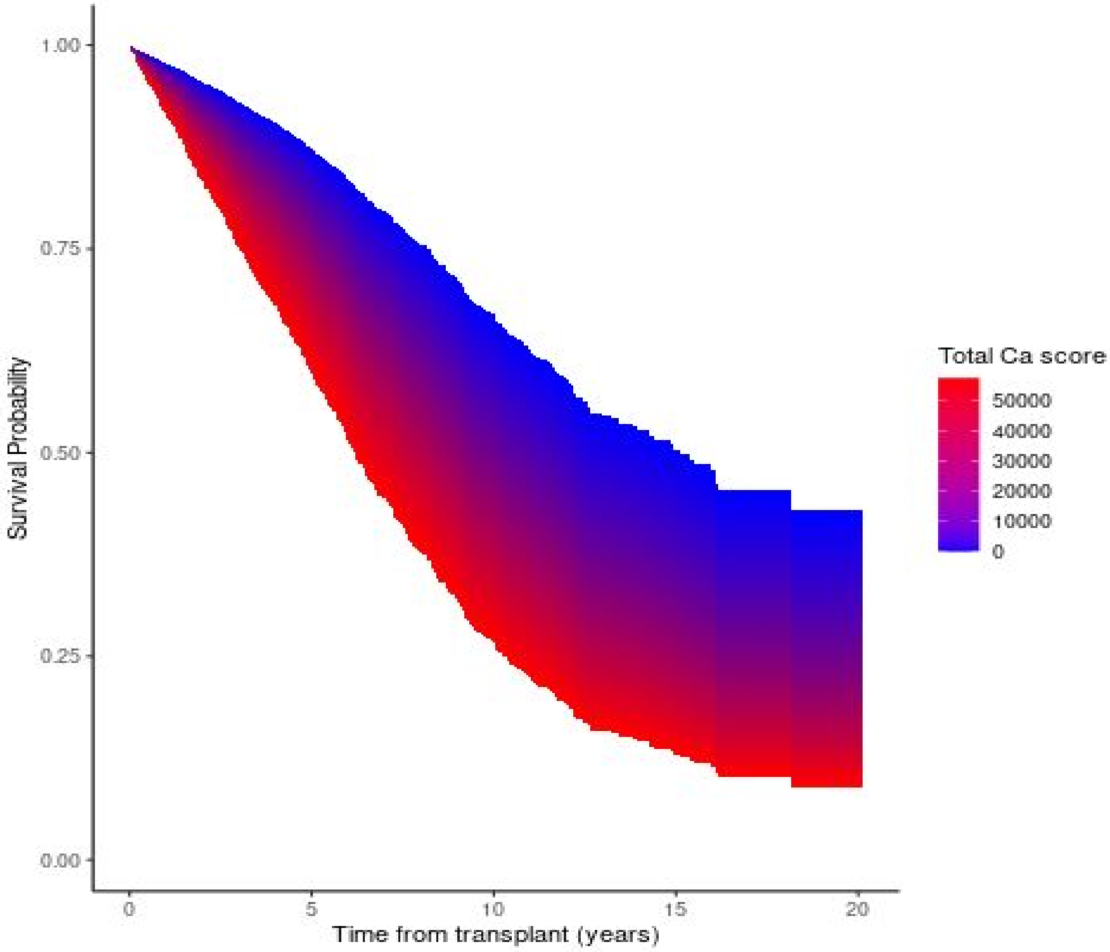


Figure legends:

Figure 1.

This flowchart outlines the selection and exclusion criteria for the study cohort. Out of 14,339 total patients, 10,656 were excluded based on the following criteria: 3,808 patients had double organ transplants, 2,070 had CT scans performed more than two years from the listing date, 3,981 had no available CT scan, 535 patients died on the waitlist, and 262 patients were still on the waitlist. The final study cohort included 3,683 patients, all of whom underwent kidney transplant and had a non-contrast abdominal and pelvic CT scan performed within two years before or after their transplant listing date.

Figure 2A.

This figure displays forest plots for unadjusted Cox regression models. HRs and their 95% CIs are reported for each calcium score predictor. HR estimates are interpreted as per 1,000-unit change in score.

Figure 2B.

This figure shows the forest plot results for multivariable Cox regression models. These models were adjusted for potential confounders (age at transplant, tobacco use, DM, and CAD). HRs and their 95% CIs are reported for each calcium score predictor. HR estimates are interpreted as per 1,000-unit change in score.

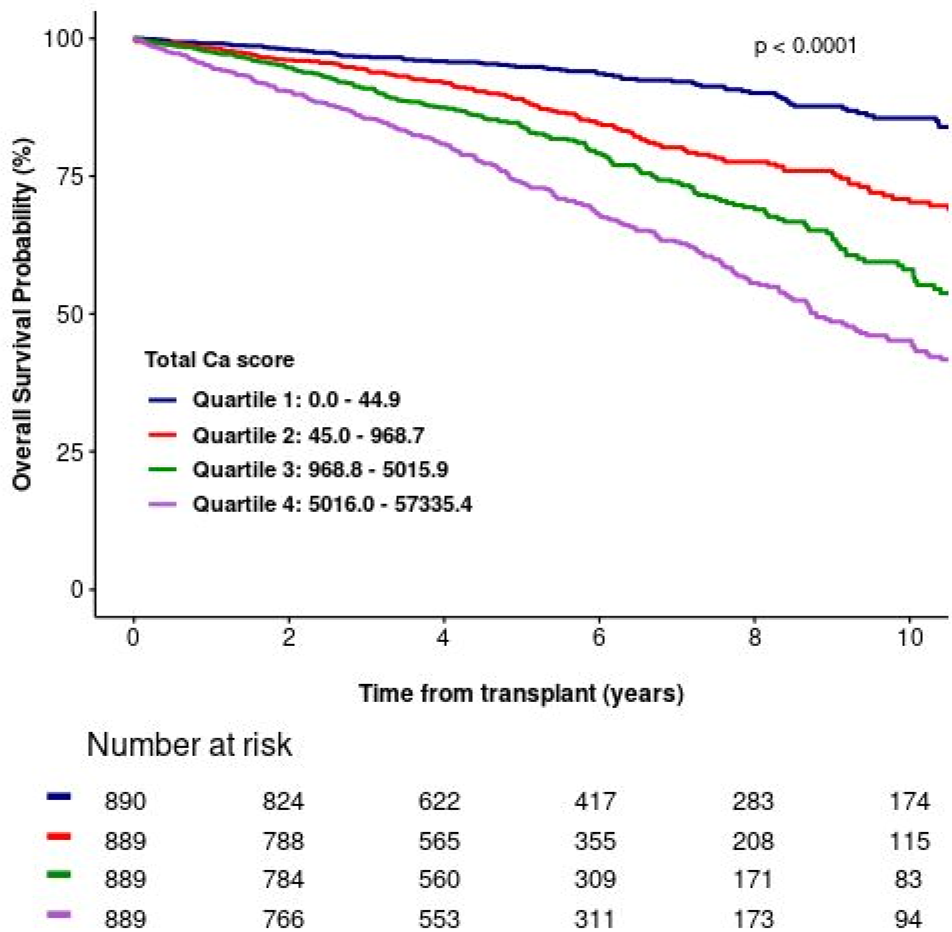
Figure 3A.

This figure illustrates the unadjusted relationship between total calcium scores and survival probability over a 20-year period following transplant. The gradient color scale represents different calcium score levels, ranging from low (blue) to high (red). The plot demonstrates that patients with higher calcium scores have significantly lower survival probabilities, indicating a steeper decline in survival rates over time compared to those with lower calcium scores.

Figure 3B.

This figure shows the survival probability over 20 years, adjusted for age at transplant, tobacco use, diabetes, and coronary artery disease. The color gradient, from low (blue) to high (red) calcium scores, indicates the adjusted impact of calcium levels on survival rates. Even after adjusting for key confounders, higher calcium scores are associated with significantly lower survival probabilities, confirming that elevated calcium levels are an independent predictor of reduced long-term survival post-transplant.

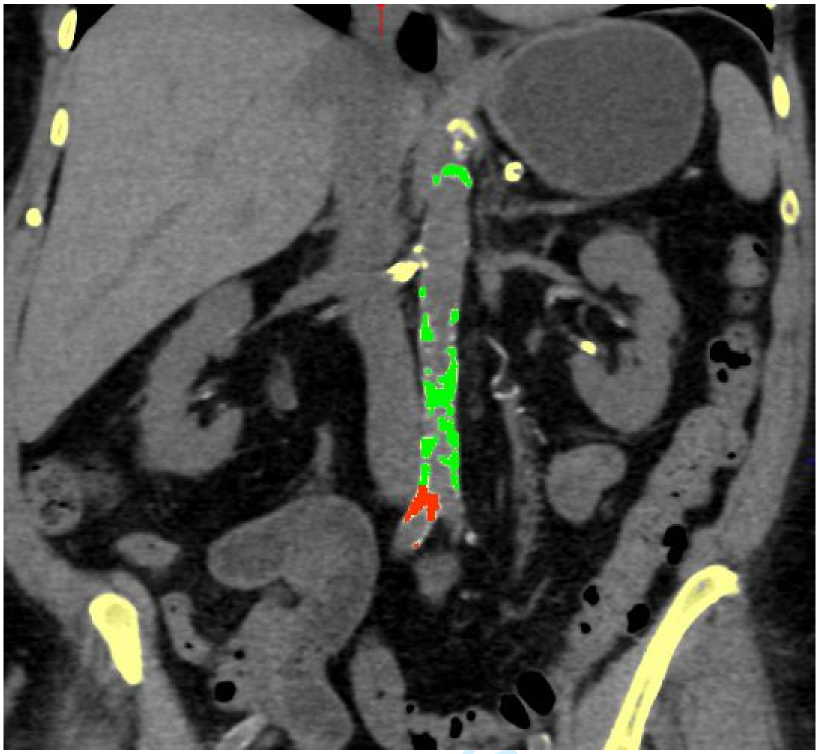
Supplementary Figure 1. Overall Survival KM Curve for Total Calcium Score by Quartiles



Supplementary Figure 1 Legend:

This figure shows KM survival curves according to total calcification score quartiles. Overall survival decreases with increasing total calcification score quartile.

Supplementary Figure 2. Sample calcification score measurement



Supplementary Figure 2.

The semiautomatic software package detects any calcium above the Agatston threshold of 130 Hounsfield (purple). The reader then assigns calcium in interest to an anatomic category (aorta, common iliac, external iliac, internal iliac) to calculate the score for that artery (green = abdominal aorta, red = common iliac)