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Association of the donor's calcification score of the abdominal aorta, common iliac and renal arteries with outcomes in kidney recipients

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Artigo Original

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Abstract

Introduction: Kidney transplantation is the best treatment for end-stage renal disease and offers improved survival rates and quality of life. Portugal has witnessed a significant number of kidney transplants, with 429 renal transplants performed in 2021. However, organ shortage remains a critical issue, with 1,890 patients on the waiting list at that date. To address this, expanding donor criteria have been explored. This study aimed to investigate the association between vascular calcification in living kidney donors and recipient outcome.

Methods: In this retrospective study, we analysed the clinical records of living kidney donors and their recipients at a transplantation centre over a 9-year period. A total of 210 donor-recipient pairs were included in the study. Donor and recipient characteristics including age, sex, smoking habits, and medical history were recorded. Calcification Score of the Abdominal Aorta, Common Iliac, and Renal Arteries were calculated using the Agatston method in pre-transplant donors CT. The primary parameter of interest was the donor's total calcification score (TCaScore) at donation, which classified the pairs into absent to minimal calcification (<100 TCaScore) and moderate to severe calcification (≥100 TCaScore). Outcome parameters, such as estimated glomerular filtration rate (eGFR) and proteinuria, were assessed during a 5-year follow-up period.

Results: In our study, we analysed the characteristics and outcomes of 210 donor-recipient pairs undergoing kidney transplantation. Donor characteristics revealed that 30.95% of donors had calcification in the studied arteries, with 18.1% having moderate-to-high calcification (TCaScore ≥100). Donor age and creatinine clearance in 24-hour urine sample were significant predictors of TCaScore. Among recipients, there were no significant differences between the groups based on donor TCaScores in pre-transplant characteristics. No significant differences were found in the mean estimated glomerular filtration rate (eGFR) or proteinuria between the two TCaScore groups during the 5-year follow-up period. The risk factors for reduced eGFR included male sex, diabetes mellitus, and hypertension. However, the TCaScore was not a significant predictor of reduced eGFR or proteinuria. Linear and logistic regression models showed that donor age and creatinine clearance were significant predictors of eGFR during the 1st year of follow-up. Similar associations were observed during the 5th year of follow-up. Surgical vascular complications were not associated with the TCaScore. Our findings suggest that donor calcification scores do not significantly impact post-transplant outcomes, such as eGFR and proteinuria.

Conclusion: We found that the presence of arterial calcification in donors is not significantly associated with worse GFR and proteinuria in kidney transplant recipients during the 5-year follow-up period. These findings indicate that arterial calcification may be prevalent in older donors; however, it did not appear to have a significant effect on transplant outcomes in this specific population in this time period. However, additional research is needed to validate these results and to identify other potential risk factors that may affect transplant outcomes.

Keywords: kidney transplantation; vascular calcification; Agatston score; expanded criteria donors, recipients' outcomes.

Resumo

Introdução: O transplante renal é o melhor tratamento para a doença renal em fase terminal e oferece melhores taxas de sobrevivência e qualidade de vida. Portugal tem registado um número significativo de transplantes renais, com 429 transplantes renais realizados em 2021. No entanto, a escassez de órgãos continua a ser um problema crítico, com 1890 doentes em lista de espera. Para resolver isso, a expansão dos critérios de dadores foi explorada. Este estudo teve como objetivo investigar a associação entre a calcificação vascular em dadores vivos renais e possíveis repercussões nos recetores.

Métodos: Neste estudo retrospetivo, analisámos os registos clínicos de dadores vivos de rim e respetivos recetores num centro de transplantação durante um período de 9 anos. Um total de 210 pares dador-recetor foram incluídos na coorte do estudo. Foram registadas as características do dador e do recetor, incluindo idade, sexo, hábitos tabágicos e antecedentes médicos. O Score de calcificação arterial da aorta abdominal, das artérias renais e das artérias ilíacas comuns foram calculadas utilizando o método de Agatston nas CT dos dadores pré-transplante. O parâmetro de interesse foi a pontuação de calcificação total do dador (TCaScore) na doação, que classificou os pares em calcificação ausente a mínima (<100 TCaScore) e calcificação moderada a grave (≥100 TCaScore). Os parâmetros de resultado, como a taxa de filtração glomerular estimada e a proteinúria, foram avaliados anualmente durante um período de 5 anos.

Resultados: As características dos dadores revelaram que 30,95% dos dadores tinham calcificação nas artérias estudadas, sendo que 18,1% tinham calcificação moderada a alta (TCaScore ≥100). A idade do dador e a clearance de creatinina numa amostra de urina de 24 horas foram preditores significativos do TCaScore. Entre os recetores, não houve diferenças significativas entre os grupos com base nos TCaScores dos dadores nas características pré-transplante. Não foram encontradas diferenças significativas na taxa média de filtração glomerular estimada ou proteinúria entre os dois grupos TCaScore durante o período de acompanhamento de 5 anos. Os fatores de risco para a redução da taxa de filtração glomerular estimada incluíram o sexo masculino, a *diabetes mellitus* e a hipertensão. No entanto, o TCaScore não foi um fator de previsão significativo da redução da taxa de filtração glomerular estimada ou da proteinúria. Os modelos de regressão linear e logística mostraram que a idade do dador e a clearance de creatinina foram fatores de previsão significativos da taxa de filtração glomerular estimada durante o primeiro ano de seguimento. Associações semelhantes foram observadas durante o 5º ano de seguimento. As complicações cirúrgicas vasculares não foram associadas ao TCaScore. Os nossos resultados sugerem que o score de calcificação do dador não tem um impacto significativo nos resultados pós-transplante, tais como a taxa de filtração glomerular estimada e a proteinúria.

Conclusão: Os nossos resultados demonstram que a presença de calcificação arterial nos dadores não está significativamente associada a uma pior taxa de filtração glomerular estimada e proteinúria nos recetores de transplante renal durante o período de seguimento de 5 anos. Estes resultados indicam que a calcificação arterial pode ser prevalente em dadores mais velhos; no entanto, não parece ter um efeito significativo nos resultados do transplante nesta população específica para o período estudado. No entanto, é necessária investigação adicional para validar estes resultados e para identificar outros potenciais fatores de risco que possam afetar os resultados do transplante.

Palavras-chave: transplante renal; calcificação vascular; score de Agatston; dadores com critérios expandidos; prognóstico recetores de transplante renal.

Abbreviations and Acronyms List

AAC	Abdominal Aortic Calcification
BMI	Body Mass Index
CaScore	Calcification Score
CHUdSA	Centro Hospitalar Universitário de Santo António
CKD	Chronic Kidney Disease
ClCrU24h	Creatinine clearance in 24-hour urine sample
CT	Computer Tomography
CV	Cardiovascular
eGFR	Estimated Glomerular Filtration Rate
ESDR	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
HTA	Arterial Hypertension
HU	Hounsfield Units
ICBAS	Instituto De Ciências Biomédicas Abel Salazar
OR	Odd Ratio
PWV	Aortic Pulse Wave Velocity
SD	Standard Deviation
TCaScore	Total Calcification Score
UPCR	Urine Protein:Creatinine Ratio

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Introduction

Kidney transplantation is considered the most effective treatment for patients with end-stage renal disease. This procedure has been proven to enhance survival rates and significantly improve the overall quality of life of patients (1–3). Portugal, similar to other countries, has witnessed a substantial number of kidney transplant cases (4). In 2021, the country performed 429 renal transplants, resulting in an average of 42.06 transplants per million people (4). Additionally, during that period, 707 individuals per million people had a functioning renal graft, with 10.6% of them being living donors. Despite these achievements, the persistent shortage of organs available for transplantation remains a critical issue. By the end of 2021, the waiting list for kidney transplants in Portugal had accumulated 1,890 patients eagerly awaiting a suitable donor organ.

However, the number of donors is limited and the number of chronic kidney patients on the transplant list is increasing. In response to this increase, other solutions have been sought, including expanding donor criteria for kidney transplantation.(5)

The donor eligibility criteria have been expanded, which means that people who were previously excluded due to medical or anatomical issues may now be accepted to donate. However, the full impact of transplants from these donors is not yet fully understood, which could potentially affect both the donor and the recipient.(5–8)

Studies have suggested that donor age influences long-term prognosis of recipients. Other characteristics such as donor obesity, smoking, and kidney size have also been the subject of research (9,10). A score that can predict the risk of graft failure is sought, such as the Kidney Donor Risk Index (KDRI), which considers 10 donor parameters (age, height, weight, ethnicity, history of arterial hypertension, history of diabetes, cause of death, serum creatinine level, HCV status, and death after cardiac arrest) and parameters related to recipient pairing (HLA compatibility, duration of cold ischemia, or double transplantation). This score, already tested

for deceased donors and with a risk of proportional failure, has a reduced prognostic value, which reveals the complexity of the choice of donor-recipient pairs (11).

Additionally, the Living Kidney Donor Profile Index (LKDPI) considers various donor factors, such as age, glomerular filtration rate, body mass index, race, smoking history, blood pressure, ABO incompatibility, biological relationship with the recipient, HLA mismatches, and donor/recipient weight ratio (12). It was developed using data from over 100,000 kidney transplants from the US registry and it is externally validated in several populations. The predictive ability of LKDPI for graft failure was relatively low. (13–15)

Another model, developed by Ashby et al.(16), used data from the US registry and included donor and recipient characteristics to predict graft loss. This model provided estimated overall and censored graft failure rates, as well as recipient risk of death. The discriminative ability of this model was moderate, and there were no external validations.

The iPREDICTLIVING tool was developed for a European population and has different tools for predicting donor mortality, recipient death, and graft loss. The models considered various factors such as age, smoking habits, cholesterol values, and serum creatinine for donor mortality prediction, and factors such as age, sex, primary renal disease, and HLA mismatch for recipient mortality prediction. The tool showed good performance in internal validation, but lacked external validation. (17)

Overall, these models and tools provide some predictive ability for outcomes in living kidney transplantation, but their clinical use may be limited due to their moderate discriminative ability and potential variations in healthcare systems and ethnicities. It is critical to continue studying the different parameters that may have an influence. In fact, knowing how to choose donors with the best potential within this group of donors with expanded criteria may be the key to achieving better long-term results.

The parameter that we decided to study in greater depth in this study was vascular disease in living donors, manifested by calcification of the aorta, iliac, and renal arteries. Cardiovascular and renal diseases are closely linked (18,19).

Bahous et al. conducted a study to investigate the factors influencing a composite outcome comprising doubling of serum creatinine, development of end-stage renal disease (ESRD), myocardial infarction, stroke, or cardiovascular (CV) death. The study found that a personal history of previous CV events and the recipient's eGFR at the beginning of the study were the main determinants of the composite outcome. Additionally, the pulse wave velocity (PWV) of the donor's aorta showed a significant association with the outcome. When renal and cardiovascular outcomes were analysed separately, recipient eGFR and donor PWV were significant determinants of the renal outcome, while a previous history of CV events was the only significant determinant of the CV outcome. Multiple regression analysis did not establish a significant association between donor aortic PWV and recipient eGFR at the end of the study, except in the lower tertile of eGFR. After accounting for potential confounders, the study identified three key factors associated with the outcome: pre-inclusion CV events and a low baseline eGFR, which were recipient-related and significantly associated with the outcome, and a high PWV level at inclusion, which depended on the donor and had a borderline significant association with the outcome. This study is the first to suggest an independent association between a donor vascular factor (PWV) and the occurrence of adverse outcomes in the recipient, although this finding was not confirmed in the multiple regression analysis for eGFR determinants.(20)

We know that cardiovascular diseases are associated with important risk factors such as age, hypertension, CKD and osteoporosis (21–23). A number of other clinical, imaging and blood markers have also been associated with abdominal aortic calcification (AAC), including diabetes;

hypertension; smoking; aortic stiffness; circulating phosphate, osteoprotegerin, homocysteine, c reactive protein, fibroblast growth factor-23 and osteoprogenitor cells. (22)

According to Leckstroem et al., mild calcification of the abdominal aorta can be detected in approximately one-third of healthy, non-hypertensive, non-diabetic kidney donors without cardiovascular comorbidities and with normal renal function (21). This finding suggests that AAC may be the first sign of silent cardiovascular disease.(24)

Some studies have reported the influence of pre-transplant recipient arterial calcification and outcomes, further supporting the importance of arterial calcification in renal function. A 2020 meta-analysis investigating pre-transplant aortoiliac calcification found two associations: one between pre-transplant calcification in recipients and reduced overall survival, and another with increased rates of graft failure. The association between graft failure, censored by death, and graft function was not statistically significant. This lack of statistical power regarding renal graft outcomes may be attributed to the limited number of studies available, the various methods used for the identification of calcification, and the small sample sizes of the existing publications (25). In a 2021 study, the impact of the recipient aortoiliac CaScore, measured as an agatston-adjusted pre-transplant computed tomography (CT) score, on renal graft function at one-year post-transplant, graft failure censored by death, overall graft failure (including death), death with a function graft, and decline in graft function were identified (26).

Arterial calcification, particularly in the abdominal aorta, has also been linked to surgical outcomes in patients undergoing both general elective and vascular surgeries. Studies have shown that AAC may be associated with the progression of cardiovascular disease and increased morbidity rates, even in patients without known cardiovascular risk factors (27). Multivariate logistic regression analyses have confirmed the significance of AAC as a predictor of morbidity, with an odds ratio of 1.35 ($P = 0.017$). Vascular surgical complications in renal transplantation can significantly impact the success and outcomes of the procedure. Several risk factors have

been identified in relation to these complications. Age, deceased kidney donors, and prolonged operative time have been found to be associated with a higher incidence of surgical complications following kidney transplantation (28). Renal arterial stenosis, the most frequent vascular surgical complication, has a complex etiology. Multiple factors contribute to the development of stenosis, including anastomotic suturing technique, renal artery trauma during graft harvesting or implantation, kinking or twisting of the renal artery, vascular-type rejection, atherosclerosis of donor or recipient arteries, and cytomegalovirus infection (29). Studying the potential impact of donor arterial calcification on surgical vascular complications is crucial for surgeons and healthcare professionals to minimize the occurrence of adverse events and to optimize patient outcomes.

In a clinical study carried out at the CHUdSA (Centro Hospitalar Universitário de Santo António), a correlation was found between the vascular calcification score in the living donor pre-transplant and the glomerular filtration rate 1 year after transplantation and a reduction in renal function at 5 years in the donor. Another study suggested that the aortic calcification index indicates pre-existing kidney damage in living donors(30).

The impact of donor arterial calcification score on graft function and recipient prognosis remains unclear. Previous studies have reported a prevalence of abdominal aortic calcification (AAC) in living kidney donors ranging from 31% to over 40% (21,31). Interestingly, AAC severity did not appear to be associated with donor glomerular filtration rate (GFR) or systolic blood pressure. In a recent study (31), researchers found no significant differences in the eGFR between donors with and without AAC. Similarly, the presence or severity of donor AAC was not correlated with recipient eGFR or urinary protein-to-creatinine ratio up to 36 months after transplantation, although the impact on graft outcomes may take longer to manifest. However, at the 6-month protocol biopsy, allografts from donors with AAC were found to have a five-fold higher incidence of vascular fibrous intimal thickening and arteriolar hyaline thickening

compared to those without. Additionally, the presence of donor AAC was an independent predictor of these two histologic findings. There was no significant difference in the incidence of interstitial fibrosis or tubular atrophy between the donors with and without AAC.

The main objective of this study was to investigate a possible association between the calcification score of the abdominal aorta and common iliac and renal arteries of living kidney donors and the evolution of the recipient's Glomerular Filtration Rate (GFR) and proteinuria.

Materials and Methods

Subjects and Study Design

This was a retrospective study of a transplantation centre that analysed the clinical records of living donors with nephrectomies performed at the Centro Hospitalar Universitário de Santo António and their respective recipients who underwent surgery between January 2008 and December 2017. The study was approved by the Ethics Committee and Department for Education, Training, and Research of CHUdSA/ICBAS, as the data for the study were retrieved from the patients' electronic and paper medical records, and their anonymity was maintained. Of the 235 living donor transplantations performed in this 9-year timeframe, 25 patients were excluded because their CT scans were unavailable for examination. Thus, the remaining 210 donor-recipient pairs defined our study cohort. The institutional Review Board at Centro Hospitalar Universitário de Santo António (CHUdSA) approved this retrospective observational study, conducted according to Helsinki Declaration.

Donor characteristics such as age, sex, smoking habits, previous diagnoses of hypertension, dyslipidaemia, and creatinine clearance in 24h urine pre-donation, as well as the following recipient characteristics: age, sex, previous diagnoses of hypertension, diabetes mellitus, and laboratory tests during the period up to 5 years of post-transplantation follow-up were recorded. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl or the use of insulin and/or other hypoglycaemic agents. Hypertension was classified as a prescription for antihypertensive medications or a registered blood pressure of ≥ 140/90 mmHg during visits. Dyslipidaemia was considered present when patients either used hypolipidemic agents, had total cholesterol >200 mg/ dL, LDL >130 mg/dL, triglycerides >150 mg/dL or HDL.

The CT scans were performed according to the pre-transplant screening protocol, with one of the two multidetector-row CT scans available at our institution (a 64-detector GE VCT LightSpeed® or a 16-detector GE BrightSpeed®) and were examined using the 3D Slicer software,

version 4.11, which allows for the calculation of the calcification score of the abdominal aorta, from the branch of the celiac trunk to the branch of the common iliac artery, and of the common iliac and renal arteries, along their entire length.

Agatston Method

As described in our previous study (32), calcification scores were calculated using the Agatston method, with a 5 mm CT slice thickness and a detection threshold ≥130 Hounsfield units (HU) involving an area ≥ 1 mm2 or three adjacent pixels. The individual Agatston scores were calculated by multiplying each area of interest by a weighted score assigned to the highest density of calcification (1–130-199 HU, 2–200-299 HU, 3–300-399 HU and 4, >400 HU) within the individual area. The total calcification score (TCaScore) is the cumulative sum of the Agatston scores of all the calculated areas: abdominal aorta (celiac axis to aortic bifurcation), common iliac arteries and renal arteries.(33)

The parameter of interest was the donor's total calcification score (TCaScore) at donation. Each pair of donor recipients was stratified into two groups according to their donor's baseline TCaScore: absent to minimal calcification, <100 TCaScore; and moderate to severe calcification, ≥100TCaScore.

Outcome Parameters

Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration equation (CDK-EPI). An eGFR <60 ml/min/1.73 m^2 was considered to be decreased, according to the KDIGO classification of CKD stage 3 and was assessed at the 1st and 6th month and annually during the 5-year follow-up. Proteinuria was defined as the presence of random urine protein >15 mg/dL and was measured at the same time as that described for the GFR.

Arterial surgical complications were also recorded. The following incidents were taken into account: renal artery stenosis, arterial kinks, renal artery thrombosis, and arterial rupture.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. Categorical data were compared using Pearson's chi-square test, and continuous variables were compared using Student's t-test or Mann–Whitney U-test, as appropriate.

Correlations between recipients eGFR values during follow-up and donor total calcification scores (TCaScore) were assessed using Spearman's correlation test.

Linear prediction of eGFR at 1 year of follow-up were analysed through a univariate and multivariable linear regression model, and risk factors for an eGFR < 60 ml/min per 1.73m2 at 1 year were calculated through a univariate multivariable logistic regression.

Risk predictors of first measurement with an eGFR < 60 ml/min/1.73 m2 (as defined above) were analysed using univariate and multivariate Cox regression models. Previous outcomes-free survival curves, between donors with TCaScore<100 and TCaScore ≥100, were depicted by Kaplan-Meier curves and comparisons were made by log-rank test. The risk predictors of the first measurement with proteinuria> 15 mg/dL were analysed in the same manner.

Statistical analysis was performed using IBM SPSS Statistics 27.0.1 software for Windows. A 2-sided P-value of < 0.05 was considered as statistically significant.

Results

Excluded pairs

An analysis of the excluded patients was performed (Tables 1). Statistically significant differences were identified in the percentage of donors who smoked (p=0.020) and recipients who smoked (p=0.015). No other statistically significant differences were identified between the 2 groups.

	Excluded	**Included**	**p**
Donors' age, mean±SD	45,4±2,0	47,7±0,7	0,277
Female donors, n (%)	17 (68)	150 (71)	0,721
Donors' BMI, mean±SD	25,9±0,7	25,1±0,2	0,343
Donors with hypertension, n (%)	3 (13)	31 (14)	0,818
Smoking Donors, n (%)	7 (29)	25 (12)	0,02
Donors' ClCrU24h, mean±SD	142,3±8,9	131,7±2,6	0,263
Recipients' age, mean±SD	39,5±2,5	40,8±0,9	0,612
Female recipients, n (%)	7 (29)	66 (31)	0,726
Recipients' BMI, mean±SD	23,1±0,6	24,0±0,3	0,191
Recipients with hypertension, n (%)	15 (71)	155 (74)	0,813
Smoking Recipients, n (%)	1 (4)	54 (25,7)	0,015
Recipients with diabetes mellitus, n (%)	1 (4)	12 (5,7)	0,723

Table 1 – Comparison of Donors' and Recipients' Characteristics: Excluded vs. Included

Donors

Of the 210 donors in our sample, 150(71.4%) were women, 25(11.9%) were active smokers at the time of donation, and 31(14.8%) had been diagnosed with hypertension before nephrectomy. The mean age of the donors was 47.74 (±10.68) years (range 21-68) and the mean BMI was 25.15 (±0.23) kg/m^2. Mean creatinine clearance in 24-hour urine sample was 131.73 (±35.79) ml/min/1.73 m^2.

Calcification was detected in the arteries of 65 (30.95%) donors; 38 (18.1%) had a TCaScore considered moderate to high (≥100) according to the measurement made in the pre-transplant CT scan. The highest TCaSore value was 2222.17. The minimum age of donors with

calcification was 38 years. Three donors had calcification of their renal arteries. 38 donors had calcification of iliac arteries.

Donors	**Without or Mild Calcification**	**Moderate/High Calcification**	**p**
Age at donation, mean±SD	45,8 ± 0,8	56,64±1,0	0,009
Female donor, n (%)	127 (74)	23 (61)	0,100
BMI at donation, mean±SD	24,9±0,3	26,2±0,5	0,777
Hypertension at donation, n (%)	18 (11)	13 (34)	<0,001
Smoking donors, n (%)	19 (11)	6 (16)	0,421
ClCrU24h, mean±SD	129,5±2,4	141,1±8,9	0,589

Table 2 – Donors' baseline characteristics

There were significant differences in the mean age of the TCaScore groups (p=0,009): the group of donors with absence or slight calcification presented a mean of 45.78 (±0.80), and the group with moderate to high calcification presented a mean of 56.64 (± 1.05). There was also an association between a previous diagnosis of hypertension and a TCaScore >100 (p<0.001) (Table 2).

Recipients

Of the 210 recipients in our sample, 144(68.6%) were men, 12(5.7%) had diabetes mellitus diagnosed at the time of transplantation, 155(73.8%) had a previous diagnosis of hypertension, and 54(25.7%) were active smokers at the time of transplantation. Mean age among recipients was 40.86 (±13.5) years and mean BMI 23.89(±3.96) kg/m^2.

We divided the recipients according to the donors' TCaScores. We found a significant difference between age at transplantation in the two groups (p=0,015). No other significant differences were identified between the pre-transplant characteristics of the two groups. (Table 3)

Recipients	Without or Mild Calcification N=145	Moderate/High Calcification N=65	p
Age at transplantation, mean±SD	40±1	46±2	0,015
Recipients BMI, mean±SD	23,9±0,3	24,1±0,6	0,786
Female recipients, n (%)	45 (31)	21 (32)	0,716
Recipients with hypertension, n (%)	102 (70)	53 (81)	0,426
Recipients with diabetes mellitus, n (%)	7 (5)	5 (8)	0,522
Smoking recipients, n (%)	37 (25)	17 (26)	0,925

Table 3 – Recipients' baseline characteristics

Recipients' outcomes

Comparing the outcomes of recipients in the two defined groups, we did not identify statistically significant differences in the mean eGFR in the studied period (measured at 1st and 6th months, 1st, 2nd, 3rd, 4th and 5th years post-transplant) or for the mean proteinuria in the same period. (Table 4)

Similarly, we found no statistically significant differences between the two TCaScore groups for proteinuria >15 mg/dL during the study period. For an eGFR<60 ml/min/1.73 m^2, there was an isolated difference in measures in the 2nd year post-transplant (p=0,044) and no other changes in the study period. (Table 5)

Comparing the risk of reduced GFR measurement over the 5-year follow-up period in recipients who received donor kidneys with or without moderate-to-severe calcification in the aorta, iliac, and renal arteries, no significant differences were identified. No significant differences were identified between the risk of proteinuria and risk of proteinuria. (Graphs 1 and 2).

Linear regression showed that the only variables with statistical significance for the calculation of TCaScore were donor age and ClCrU24h. For each additional donor year, the TCaScore increased by 9.398 (p<0.001), and for each ml/min/1.73 m^2, ClCrU24h increased, the TCaScore increased by 2.295 (p<0.001) (Table 6). Logistic regression showed similar results;

donor age was associated with a 17.6% (p<0,001) increased risk of moderate-to-high calcification, and ClCrU24h was associated with a 1.9% (p=0,011) increased risk. Additionally, donor smoking was associated with a 4-fold increased risk of moderate-to-high calcification (p=0,040) (Table 7).

Model		B	p	95,0% Intervalo de Confiança para B	
				Limite inferior	Limite superior
1	(Constante)	-628,360	<0,001	-943,802	-312,918
	Age at donation	9,398	<0,001	5,827	12,970
	BMI_donor	-0,853	0,881	-12,104	10,398
	ClCreatU24hpre_donor	2,295	<0,001	1,260	3,331

Table 6 – Linear Regression: TCaScore and donors'characteristics

	p	OR	OR 95% C.I.	
			Inferior	Superior
Age at donation	<0,001	1,176	1,105	1,252
sex_donor	0,144	0,482	0,181	1,282
smoker_donor	0,04	4,098	1,07	15,699
BMI_donor	0,581	1,039	0,907	1,19
HTApre_Donor	0,155	2,141	0,75	6,109
ClCreatU24hpre_donor	0,011	1,019	1,004	1,033
Constante	<0,001	0		

Table 7 – Logistic Regression: TCaScore and donors'characteristics

There was no association between a TCaScore>100 and surgical complications or vascular reconstruction (p=0.744). (Table 8)

		Without/Mild Calcification	Moderate/High Calcification	Total	p
Vascular surgical complication	None N (%)	164 (95,3)	36 (94,7)	200 (95,2)	0,873
	Arterial Complication N(%)	8 (4,7)	2 (5,3)	10 (4,8)	

Table 8 – Comparison of Surgical Vascular Complications in Groups with Without/Mild Calcification vs. Moderate/High Calcification

After linear regression and logistic regression for eGFR and eGFR<60mL/min/1.73 m^2, there was no statistical significance with TCaScore and TCaScore>100 either in the first or fifth year of follow-up.

Discussion

Based on our study's findings, there were no significant differences observed between donors with a TCaScore >100 and those without in our main recipient outcomes. Interestingly, while Wu et al. did not find any correlation between AAC and recipient eGFR or UPCR up to 36 months following transplantation (31), our study did not find any association between donors with moderate-to-high calcification and recipient eGFR or proteinuria. It should be noted that in this other article, GFR was not estimated with the same formula, and our other criterion was proteinuria when they used UPCR. In addition, we did not observe any statistically significant differences in the TCaScore prevalence between men and women.

Regarding the link between a TCaScore>100 and ClCrU24h, no association was found in the multivariable analysis. This result is consistent with that of the study by Wu et al., who found no differences in eGFR between donors with and without AAC. In contrast, in multivariable analysis, ClCrU24h showed an association with a TCaScore>100. However, this association proved to be minimal (OR 1.019), suggesting that it does not have a strong impact or substantial influence on the TCaScore.

We detected calcification in 30.95% of donors, a result similar to that obtained by Leckstroenm et al (31%) in their study "Prevalence and predictors of abdominal aortic calcification in healthy living kidney donor"(21).

Donors with calcified arteries were older on average. This association has already been described for arterial calcification in renal transplant recipients (34). In fact, it has already been

described that recipients from donors 'aged over 60 years' at the time of transplantation had a decreased transplant survival (9). However, this result is not consensual in all studies (7,8,35).

In our study, we found no association between active smoking at the time of nephrectomy and calcification or outcomes in univariate analysis. However, in our logistic regression smoking was associated with a 4-fold increased risk of moderate-to-high calcification (p=0,040). Leckstroem et al. reported that those who smoked cigarettes had no more AAC than did non-smokers (21). In contrast, Heldt et al. reported a dose-dependent relationship between tobacco exposure and kidney graft function. They showed a direct correlation between high tobacco exposure and reduced kidney graft function by measuring the post-transplant glomerular filtration rate at one and six months after transplantation in organ recipients (36). It is important to draw attention to note that in our study, the smoking burden of donors and previous habits were not considered, which may have an impact on graft quality (37).

We also described an association between a previous diagnosis of hypertension and a TCaScore of >100. This was surprising, as Leckstroem found no relationship between AAC and blood pressure.(21)

Our study on kidney transplantation revealed that surgical arterial complications occurred in 4.8% of the transplant cases. These findings are consistent with the results of a study conducted by Carvalho et al. at another renowned Portuguese reference center for kidney transplantation, where they reported a similar incidence rate of 4.5% (38). Furthermore, our results are consistent with the existing literature, which reported a frequency range of 5-15% for vascular complications in renal transplantation (39).

We did not find a direct association between arterial complications and donor calcification in kidney transplantation. While some studies have explored the correlation between arterial calcification in transplant recipients and surgical complications (28), to our knowledge, this is the first study to specifically investigate the relationship between donor

arterial calcification and surgical complications. Further research is warranted to comprehensively assess the impact of donor arterial calcification on the surgical outcomes of kidney transplantation.

In this study, we focused on potential vascular diseases in donors. It is important to keep in mind that vascular disease in recipients has already been studied and also impacts on outcomes with atheroma being a risk factor for thrombosis, renal failure and recipient mortality (40). Similarly, we suspect several factors with potential effects on the long-term outcomes of recipients, such as lifestyle factors including diet and exposure to toxic contaminants, as well as persistent disease mechanisms after renal transplantation (i.e., inflammation, redox imbalance, and vascular calcification) (41).

Given the number and complexity of both donor and recipient factors that may affect the outcomes of kidney transplants, incorporating dynamic predictive models into electronic health records may allow for timely mitigation of the risk of graft failure and/or facilitate the planning of renal replacement therapies (37). We must not forget that these models will always be tools for clinicians to discuss and adapt the best strategy for the patient.

These findings suggest that, while arterial calcification may be prevalent in older living renal donors, it may not have a significant impact on transplant outcomes in our patient population in the five-year post-transplantation. In fact, longer follow-up may be needed to truly evaluate outcomes that may take longer to manifest. Further research is needed to confirm these findings and determine whether other factors are more important predictors of transplant outcomes in this population.

This study has several limitations that must be considered. First, the study was retrospective and observational in nature, which means that it is subject to selection bias and confounding factors. Additionally, the quantification of vascular calcification was performed by a single examiner, which could introduce bias or measurement error, even though the Agatston

method used is considered reliable and reproducible. Furthermore, the study cohort was relatively small, with only 210 donor-recipient pairs, and a follow-up period of 5 years was limited. Finally, this study was conducted at a single centre, which may limit the generalizability of the findings to other populations. While this is the longest follow-up period reported in CT-based studies on vascular calcification, larger registry studies are needed to fully understand the association between donor calcification scores and outcomes in kidney recipients.

Conclusion

We investigated the presence of arterial calcification in living kidney donors and its effect on transplantation outcomes. The presence of arterial calcification in donors was not significantly associated with worse GFR and proteinuria in kidney transplant recipients during the 5-year follow-up period. These findings indicate that arterial calcification may be prevalent in kidney donors; however, it did not appear to have a significant effect on transplant outcomes in this specific population. It should be noted that our main objective was to determine whether arterial calcification of the donor was associated with worse outcomes in the recipient; according to our results, no relationship was found. Therefore, we may consider that transplantation of kidneys from living donors with calcified arteries is not associated with worse GFR and proteinuria outcomes in recipients within five years after the procedure.

However, additional research is needed to validate these results and to identify other potential risk factors that may affect transplant outcomes. A better understanding of these associations is crucial for optimizing clinical decisions related to donor selection and improving long-term outcomes in kidney transplant recipients.

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Appendix

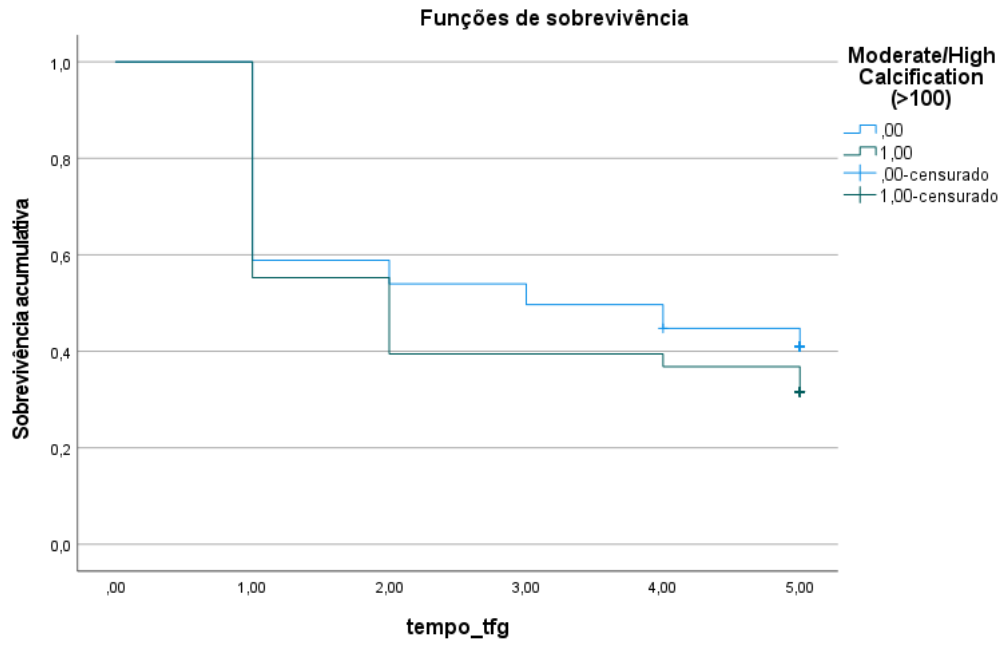
	Without/Mild Calcification		Moderate/High Calcification		
	Mean	SD	Mean	SD	p
eGFR_1M	65,56	1,70	61,77	2,72	0,401
eGFR_6M	65,04	1,57	61,11	2,53	0,430
eGFR_1A	67,50	1,57	60,76	2,31	0,102
eGFR_2A	68,40	1,61	62,28	2,75	0,044
eGFR_3A	67,24	1,55	60,80	3,00	0,124
eGFR_4A	65,77	1,51	62,39	2,84	0,310
eGFR_5A	64,69	1,67	60,25	2,91	0,154
ProtR_1M	0,25	0,03	0,24	0,04	0,781
ProtR_6M	0,24	0,04	0,14	0,02	0,848
ProtR_1A	0,48	0,34	0,20	0,05	0,846
ProtR_2A	0,19	0,03	0,23	0,09	0,241
ProtR_3A	0,21	0,03	0,79	0,56	0,489
ProtR_4A	0,48	0,28	0,11	0,02	0,261
ProtR_5A	0,21	0,03	0,20	0,06	0,321

Table 4 – Comparison eGFR and proteinuria mean in Groups Without/Mild Calcification vs. Moderate/High Calcification

		Without or Mild calcification		Moderate/High Calcification		
		Count	Column N %	Count	Column N %	p
tgf60_1m	,00	96	57,5%	21	55,3%	0,401
	1,00	71	42,5%	17	44,7%	
tgf60_6m	,00	94	57,3%	21	55,3%	0,430
	1,00	70	42,7%	17	44,7%	
tgf60_1a	,00	97	59,5%	21	55,3%	0,102
	1,00	66	40,5%	17	44,7%	
tgf60_2a	,00	102	68,5%	17	47,2%	0,044
	1,00	47	31,5%	19	52,8%	
tgf60_3a	,00	108	67,5%	22	57,9%	0,124
	1,00	52	32,5%	16	42,1%	
tgf60_4a	,00	104	65,8%	23	62,2%	0,310
	1,00	54	34,2%	14	37,8%	
tgf60_5a	,00	100	62,9%	18	48,6%	0,154
	1,00	59	37,1%	19	51,4%	
Proteinuria_1M	,00	33	39,3%	9	36,0%	0,781
	1,00	51	60,7%	16	64,0%	

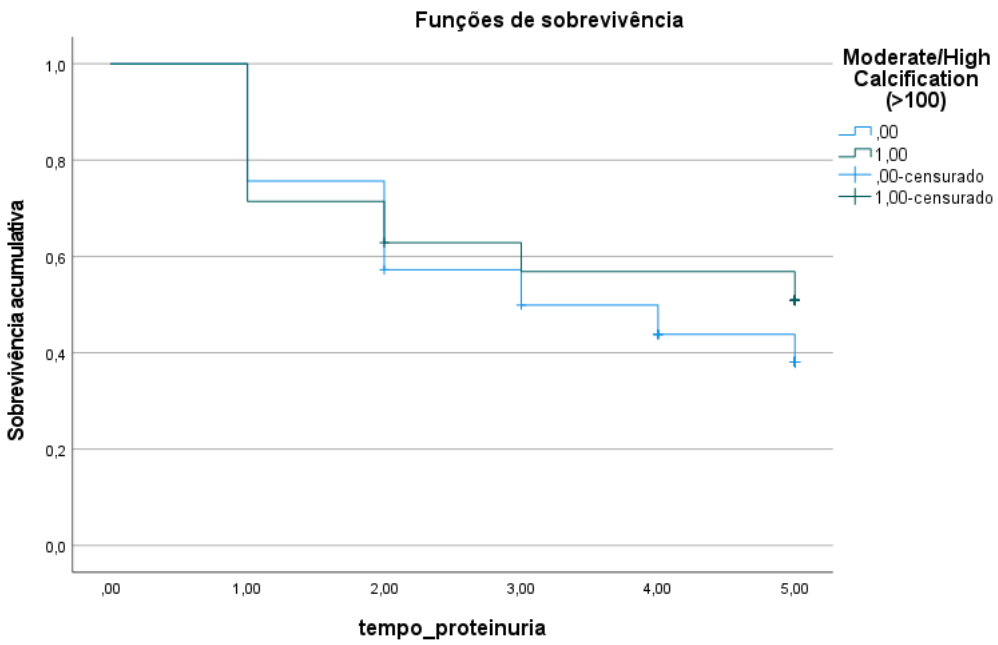
Proteinuria_6M	,00	51	62,2%	12	63,2%	0,848
	1,00	31	37,8%	7	36,8%	
Proteinuria_1A	,00	79	72,5%	20	74,1%	0,846
	1,00	30	27,5%	7	25,9%	
Proteinuria_2A	,00	67	62,6%	19	70,4%	0,241
	1,00	40	37,4%	8	29,6%	
Proteinuria_3A	,00	88	69,3%	18	66,7%	0,489
	1,00	39	30,7%	9	33,3%	
Proteinuria_4A	,00	93	72,1%	22	78,6%	0,261
	1,00	36	27,9%	6	21,4%	
Proteinuria_5A	,00	93	71,0%	22	71,0%	0,321
	1,00	38	29,0%	9	29,0%	

Table 5 – Comparison of eGFR<60 and Proteinuria in Groups Without/Mild Calcification vs. Moderate/High Calcification



Arterial Calcification	Median				
	Estimate	Std. Error	95% Confidence Interval		p
			Lower Bound	Upper Bound	
Without or Mild calcification	3,000	,833	1,368	4,632	0,268
Moderate/High Calcification	2,000	,502	1,016	2,984	
General	3,000	,708	1,612	4,388	

Graph 1 – Risk of one measurement of decreased eGFR, < 60 ml/min/1.73m^2, over the course of the 5-year of follow-up in recipients with and without moderate to severe abdominal aortic, iliac and renal calcification



	Median				
	Estimate	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound	p
Without/Mild Calcification	3,000	,607	1,811	4,189	0,268
Moderate/High Calcification	.	.	.	.	
Geral	4,000	,617	2,791	5,209	

Graph 2 – Risk of one measurement of proteinuria (presence of random urine protein >15 mg/dL), over the course of the 5-year of follow-up in recipients with and without moderate to severe abdominal aortic, iliac and renal calcification

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