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Atherosclerosis and Intrarenal Resistance Index in Kidney Transplant Recipients

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Background. Atherosclerosis of the aortoiliac vessels can adversely affect kidney perfusion after kidney transplantation. Atherosclerosis severity can be determined using the calcium score (CaScore). Potential problems with posttransplantation kidney perfusion can be determined using the intrarenal resistance index (RI). This study investigated the association between aortoiliac CaScore and RI in kidney transplant recipients. **Methods.** Kidney transplant recipients (2004–2019), for whom the CaScore and RI were determined, were included in this dual-center cohort study. CaScore was measured in 3 aortoiliac segments using noncontrast CT imaging. RI was determined using Doppler ultrasound. Multivariable linear regression analyses were performed between the CaScore and RI, adjusted for confounding variables. **Results.** The mean age of the 389 included patients was 59 (±13) y. The mean RI (unitless) was 0.71 (±0.09), and the median CaScore (unitless) was 3340 (399–7833). In univariable linear regression analyses with RI as the dependent variable, CaScore ($\beta = 0.011$; $P < 0.001$) was positively associated with RI. Moreover, recipient age ($\beta = 0.014$; $P < 0.001$), history of diabetes ($\beta = 0.029$; $P = 0.003$), recipient history of vascular interventions ($\beta = 0.032$; $P = 0.002$), prior dialysis ($\beta = 0.029$; $P = 0.003$), deceased donor transplantation ($\beta = 0.042$; $P < 0.001$), donation after cardiac death ($\beta = 0.036$; $P = 0.001$), an increase in cold ischemia time ($\beta = 0.011$; $P < 0.001$), and the Comprehensive Complication Index ($\beta = 0.006$; $P = 0.002$) were also positively associated with RI, whereas preoperative recipient diastolic blood pressure ($\beta = -0.007$; $P = 0.030$) was inversely associated. In multivariable analyses, CaScore and RI remained significantly ($P = 0.010$) associated, independent of adjustment for potential confounders. Furthermore, in univariable linear regression analyses, multiple graft function characteristics were associated with RI. **Conclusions.** A significant association was found between CaScore and RI, independent of adjustment for multiple potential confounding factors, leading to a better insight into the development and interpretation of RI. Aortoiliac atherosclerosis should be considered when interpreting the RI and determining the possible cause of malperfusion and graft failure after kidney transplantation.

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INTRODUCTION

Various donor and recipient factors are influential in determining successful kidney transplantation outcomes. In particular, hemodynamic factors such as pulse pressure, arterial stiffness, aortic stiffness, and pulse wave velocity can negatively impact transplant outcomes in terms of survival and graft failure.[1-3] Atherosclerosis predisposes patients to arterial stiffness and, subsequently, decreases arterial compliance. At the time of transplantation, atherosclerosis can lead to undesirable hemodynamic conditions, such as higher pulse pressure, pulse wave velocity, and

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higher pulsatility, resulting in a worse outcome or early graft failure in severe cases.[4-6] Increased arterial stiffness is associated with an increased risk of cardiovascular disease in patients with end-stage renal disease patients.[7] The degree of atherosclerosis in the iliac artery appears to have a negative impact on both graft and patient survival.[8-10] Nonenhanced CT-based quantification of aortic atherosclerosis using the aortoiliac calcium score (CaScore) has proven to be a feasible and reliable technique for cardiovascular risk stratification.[11]

Doppler ultrasound is part of the armamentarium used to assess the quality of kidney perfusion posttransplantation. Through utilization of the intrarenal resistance index (RI), corticomedullary differentiations and grayscale median, perfusion, and tissue characteristics can be extrapolated posttransplantation.[12,13] RI indicates the resistance of blood flow through the renal artery and cortex and is considered normal within the range of 0.50 to 0.70.[14-16] Abnormal RI values are generally considered an indication of malperfusion and can be utilized as a prognostic indicator for graft failure.[17-20] A previous study determined that an elevated RI (>0.70), measured shortly after kidney transplantation, was associated with the occurrence of postoperative cardiovascular events (CVEs).[14] Therefore, a high RI may be considered a predictor of CVE and a basic proxy for the cardiovascular burden of the recipient. Although both atherosclerosis and increased RI appear to be important determinants of vascular compliance, an association between RI and atherosclerosis in kidney transplant recipients has not yet been established. The aim of this study was to investigate whether an independent association exists between aortoiliac atherosclerosis, as measured by the CaScore, and RI in kidney transplant recipients.

MATERIALS AND METHODS

This study was part of a larger cohort study on kidney transplantation, medical imaging, and atherosclerosis.[11,14] All kidney transplants performed in adults (≥18 y) between December 2004 and September 2019 at the University Medical Center Groningen and Erasmus University Medical Center, where the CaScore and RI were available or could be determined, were consecutively included in this dual-center study. In line with the pretransplant screening protocol in both transplant centers, a CT scan was performed if either of the following were present: age >50 y, dialysis vintage >2 y, a history of peripheral artery disease or signs and symptoms of peripheral artery disease, diabetes, or prior surgery in the iliac fossa. Patients were not included for further analysis if Doppler ultrasound data were insufficiently reported or stored for reanalysis or if patients underwent a combined liver–kidney or kidney–pancreas transplantation.

Aortoiliac Atherosclerosis

The aortoiliac CaScore, principles, and techniques have been previously published by Benjamens et al.[11,21] In short, the CaScore was extrapolated for 3 different segments of the aortoiliac axis, consisting of the infrarenal aorta and the common and external iliac arteries on the transplant side (Figure 1).

Unenhanced low-dose CT was analyzed using the CaScoring software (Syngo, Siemens Healthineers, Erlangen, Germany) to determine the extent of aortoiliac atherosclerosis. Subsequently, the Agatston score was calculated based on the weighted density score given to the highest attenuation value in Hounsfield units (HU) multiplied by the area of the atherosclerosis speck.[22] The Agatston score was adjusted for the aortoiliac trajectory according to the methodology published by Benjamens et al and applied to the 3 vascular segments.[11,23,24]

Doppler Ultrasound and RI Measurement

The RI was measured as the "(peak systolic velocity – end-diastolic velocity)/peak systolic velocity" and has been previously published by van de Kuit et al.[14]

In short, the RI was measured in an interlobar artery at 3 locations, the upper pole and interpolar and lower pole, approximately 3 h posttransplantation. The sum of these results was obtained, and the mean value was calculated. The mean of these 3 values provides an accurate representation of the overall arterial intrarenal RI and is therefore the value referred to as RI in this study. RI was measured using a curved array transducer (multifrequency, 1–6 MHz) on a Toshiba Aplio MX (Tokyo, Japan), Philips Medical Systems (Bothell, WA), and Zonare ZSe (Shenzhen, China) ultrasound system.

Statistical Analyses

Baseline characteristics are presented as the mean (±SD) or median (interquartile range) for nonskewed and skewed continuous variables, respectively. The distribution of the data was determined by visual inspection using histograms and Q–Q plots. Univariable linear regression analyses were applied with RI as the dependent variable to determine potential associations with recipient-related characteristics, including recipient age (per 10 y), sex (male/female), Body Mass Index (per 10 kg/m^2), smoking history (yes/no), diabetes (Y/N), history of vascular interventions, preoperative systolic and diastolic blood pressure (per 10 mm Hg), prior dialysis (Y/N), hypercholesterolemia defined as >5.2 mmol/L (Y/N), use of antihypertensive drugs (Y/N), use of betablockers (Y/N), use of calcium channel blockers (Y/N), use of statins (Y/N); donor variables, including donor age (per 10 y), sex (m/f), status (deceased, living), and type (donation after circulation death, donation after brain death); and perioperative and postoperative variables, such as warm and cold ischemia time (min) and the Comprehensive Complication Index (unitless).[25] Furthermore, a univariable linear regression analysis was applied with the Comprehensive Complication Index as the dependent variable and the CaScore as the independent variable to assess whether atherosclerosis and a higher rate of complications were associated. For these regression analyses, skewed variables were transformed by means of natural logarithm or square root transformation, depending on the optimal achievement of the normal distribution. The assumptions for linear regression, that is, linearity, normality, and homoscedasticity, were checked to be met. To provide a well-interpretable outcome of univariable linear regression, the original units of the variables CaScore (HU), recipient age (y), Body Mass Index (kg/m^2), preoperative systolic and diastolic blood pressure (mm Hg), preoperative total cholesterol (mmol/L), and donor age (y) were converted to CaScore (per 100 HU), recipient age (per 10 y), Body Mass Index (per 10 kg/m^2), preoperative systolic and diastolic blood pressure (per 10 mm Hg), preoperative total cholesterol (per 10 mmol/L), and donor age (per 10 y).

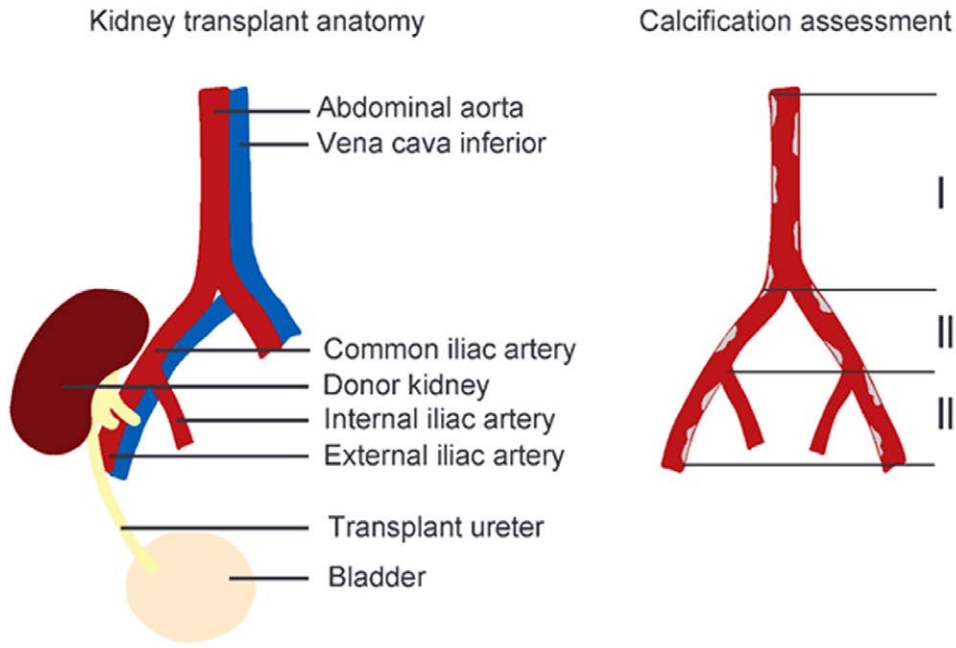

FIGURE 1. Graphical image of the kidney transplant anatomy and the aortoiliac calcium score (CaScore) assessment performed in 3 vascular segments, being (I) the abdominal aorta inferior of the renal arteries, (II) the common iliac artery, and (III) the external iliac artery on the side of the subsequent transplant (originally published by Benjamens et al[11]).

Multivariable linear regression analyses, with RI as the dependent variable, were performed for the variables that were associated with RI in preexisting literature, including the donor variables age and sex, perioperative variable cold ischemia time, and recipient variables such as age, Body Mass Index, current smoking status, diabetes, diastolic blood pressure, systolic blood pressure, and prior dialysis.[26-32] Additionally, potential confounding variables identified in the univariable analyses were included in the model.

These variables were added to the model for each group. First, donor variables were added to the model, followed by perioperative variables, and finally, recipient variables were added.

After adding all variables known to be associated with RI or as determined by univariable analysis, the CaScore was added to the multivariable analyses to determine the association between the CaScore and RI. Significant confounders detected by multivariable analyses were further investigated using Pearson correlation analysis.

Finally, to access the clinical benefit of the presented data, graft function characteristics are presented as the mean (±SD) or median (interquartile range) for nonskewed and skewed continuous variables, respectively. Univariable linear regression analyses were applied with RI as the dependent variable to determine potential associations between RI and graft function characteristics including delayed graft function (DGF, Y/N), acute rejection (Y/N); acute rejection within 1 y after transplantation (Y/N); graft failure (Y/N); graft loss (Y/N); patient mortality (Y/N); estimated glomerular filtration rate (eGFR, mL/min) after 3 mo, 6 mo, and 1 y; and multiple blood and urine biomarkers 1 y after transplantation, including serum creatinine (μmol/L), serum calcium (mmol/L), serum phosphate (mmol/L), serum albumin (g/L) serum glucose (mmol/L) serum hemoglobin (mmol/L), and proteinuria (g/L). To provide a well-interpretable outcome of univariable linear regression, the original unit of eGFR (mL/min) was converted to eGFR (mL/s). The tests were considered significant at a P value of <0.05. Statistical analyses were performed using SPSS Statistics, version 23 (SPSS Inc, Chicago, IL).

RESULTS

A total of 389 kidney transplant recipients for whom preoperative CT scans and postoperative RI measurements were available were included. The median recipient age of the study population was 61 (51–69) y, and 235 (60%) patients were male. The mean RI score (unitless) of the study population was 0.71 ± 0.09, and the median CaScore (unitless) was 3340 (399–7833). The additional baseline characteristics are summarized in Table 1.

Independent Variables on the RI

In the univariable linear regression analysis, RI was presented as a dependent variable and the baseline variables as independent predictors. CaScore (β = 0.011; 95% confidence interval, 0.006-0.017; P < 0.001) was positively associated with RI. Moreover, recipient age (β = 0.014; 0.007-0.021; P < 0.001), history of diabetes (β = 0.029; 0.010-0.049; P = 0.003), recipient history of vascular interventions (β = 0.032; 0.011-0.053; P = 0.002), prior dialysis (β = 0.029; 0.010-0.048; P = 0.003), deceased donor transplantation (β = 0.042; 0.024-0.059; P < 0.001), donation after cardiac death (β = 0.036; 0.015-0.056; P = 0.001), and an increase in cold ischemia time (β = 0.011; 0.006-0.016; P < 0.001) and the Comprehensive Complication Index (β = 0.006; 0.002-0.009; P = 0.002) were also positively associated with RI. Preoperative recipient diastolic blood pressure (β = −0.007; −0.014 to −0.001; P = 0.030) was inversely associated with RI. The additional linear regression outcomes are summarized in Table 2.

TABLE 1.

Baseline characteristics of the kidney transplantation patients

Characteristics	Baseline statistics
RI	n = 389, 0.71 ± 0.09
CaScore (HU)	3340 (399–7833)
Recipient	
Age (per 10 y)	5.9 ± 1.3
Sex (female)	154 (40)
BMI (per 10 kg/m^2)	2.7 ± 0.5
History of diabetes	120 (31)
History of vascular interventions	101 (26)
Preoperative systolic blood pressure (per 10 mm Hg)	14.6 ± 2.3
Preoperative diastolic blood pressure (per 10 mm Hg)	8.0 ± 1.4
Hypercholesterolemia (>5.2 mmol/L)	105 (27)
Preoperative total cholesterol (per 10 mmol/L)	0.47 ± 0.13
Prior dialysis	250 (64)
Smoking history	
Never	87 (22)
Smoked (stopped >1 y)	263 (68)
Smoking	39 (10)
Medication	
Use of antihypertensive drugs	319 (82)
Use of betablockers	250 (64)
Use of calcium channel blockers	165 (42)
Use of statins	212 (55)
Donor	
Age (per 10 y)	5.7 (4.6–6.5)
Sex (male)	219 (56)
Donor status	
Deceased	178 (46)
Living	211 (54)
Donor Type	
DCD	102 (26)
DBD	76 (20)
Perioperative and postoperative	
Cold ischemia time (min)	222 (163–682)
Warm ischemia time (min)	40 (32–46)
CCI	20.9 (0.0–29.6)

Data are presented as n (%), mean ± SD, or median (interquartile range).
BMI, Body Mass Index; CaScore, calcium score; CCI, Comprehensive Complication Index; DBD, donation after brain death; DCD, donation after circulatory death; HU, Hounsfield units; RI, resistance index.

CaScore and the Comprehensive Complication Index

In the univariable linear regression analysis, CaScore (β = 0.152; 0.002-0.302; P = 0.046) was positively associated with the Comprehensive Complication Index.

Multivariable Linear Regression

In the multivariable linear regression analyses, the CaScore was significantly associated with RI, independent of donor type, donor sex, donor age, prior dialysis, cold ischemia time, Comprehensive Complication Index, recipient history of diabetes, recipient history of vascular interventions, recipient Body Mass Index, recipient current smoking status, and recipient systolic and diastolic blood pressure (P = 0.010, model 7; Table 3). When we adjusted for recipient age, the CaScore was no longer significantly associated with RI (P = 0.163, model 8; Table 3).

Correlation Analysis Between CaScore and Recipient Age

Using Pearson's r, CaScore and recipient age had a significantly strong correlation (r = 0.661, P < 0.001).

Graft Function Characteristics

A total of 109 (28%) patients were diagnosed with DGF, and 61 (15.7%) patients were diagnosed with acute rejection. The mean eGFR 1 y after transplantation (mL/min) was 51.50 ± 20.61. The additional graft function characteristics are summarized in Table 4.

Potential Associations Between RI and Graft Function Characteristics

In univariable linear regression analyses, RI was presented as a dependent variable and graft function characteristics as independent predictors. DGF (β = 0.031; 0.011-0.051; P = 0.003) was positively associated with RI. Moreover, graft failure (β = 0.041; 0.010-0.072; P = 0.010), graft loss (β = 0.037; 0.013-0.060; P = 0.002), and mortality (β = 0.051; 0.022-0.080; P < 0.001) were also positively associated with RI. Both eGFR 6 mo after transplantation (β = –0.032; –0.063 to –0.002; P = 0.037) and eGFR 1 y after transplantation (β = –0.033; –0.061 to –0.006; P = 0.018) were inversely associated with RI. The additional linear regression outcomes are summarized in Table 5.

DISCUSSION

This study identified a positive association between RI and aortoiliac CaScore in kidney transplant recipients, independent of important confounders despite interaction with recipient age. Recipient age was strongly correlated with CaScore, which counteracted other confounders and significant associations. Generally, from a surgical perspective, an abnormal RI is considered an indicator of malperfusion and is associated with graft failure and postoperative CVE.[14,17-20] With the current study, we hope to provide more insights into the development of the RI and the role of the recipient (ie, atherosclerotic burden) when confronted with an abnormal RI. Although the RI value, especially during follow-up, can be an interplay between macrovasculature and parenchymal complications, the CaScore can support further diagnostics. Because of the association between the CaScore and RI, atherosclerosis should be considered when interpreting the RI and the subsequent reduced or absent graft function. By demonstrating this association, important evidence is obtained regarding the development and interpretation of RI after kidney transplantation, such as the pathophysiological association between the macro- and microcirculation and the significance of RI and arterial stiffness in this context.[33] An abnormal RI is determined not only by intrarenal abnormalities or complications but also by the atherosclerotic burden of the recipients. This new knowledge can contribute to the treatment strategy or be considered when considering a retransplantation, either by optimizing the aortoiliac flow or in the shared decision-making process regarding expectations. This association can also be used as an assessment tool for the quantification of atherosclerotic burden and expected effects on transplant outcomes.

In addition, our study confirms the strong dependence of RI on various recipient variables (recipient age, history of diabetes, history of vascular interventions, diastolic blood pressure, and prior dialysis), a perioperative variable (cold ischemia time), and donor variables (donor status).[26-32]

Given the positive association between CaScore and the Comprehensive Complication Index, atherosclerotic burden appears to lead to a perioperative and postoperative complication risk. In turn, the Comprehensive Complication Index

TABLE 2.

Univariable linear regression with patient characteristics as the independent variable and the RI as the dependent variable

Characteristics	Univariable linear regression with RI			
	Unstandardized β-coefficient	95% CI	t-value	*P*
RI	–	–	–	–
CaScore (per 100 HU)[a]	0.011	0.006-0.017	4.261	**[<0.001]**
Recipient				
Age (per 10 y)	0.014	0.007-0.021	3.785	**[<0.001]**
Sex (female)	0.006	−0.013 to 0.025	0.630	0.529
BMI (per 10 kg/m^2)	−0.012	−0.032 to 0.008	−1.190	0.235
History of diabetes	0.029	0.010-0.049	2.956	**[0.003]**
History of vascular interventions	0.032	0.011-0.053	3.058	**[0.002]**
Preoperative systolic blood pressure (per 10 mm Hg)	0.002	−0.002 to 0.006	0.797	0.426
Preoperative diastolic blood pressure (per 10 mm Hg)	−0.007	−0.014 to −0.001	−2.175	**[0.030]**
Hypercholesterolemia (>5.2 mmol/L)	−0.010	−0.030 to 0.011	−0.929	0.354
Preoperative total cholesterol (per 10 mmol/L)	0.034	−0.038 to 0.105	0.927	0.354
Prior dialysis	0.029	0.010-0.048	3.036	**[0.003]**
Smoking history				
Never	−0.011	−0.033 to 0.011	−0.978	0.329
Smoked (stopped > 1 y)	0.004	−0.016 to 0.023	0.354	0.723
Smoking	0.012	−0.018 to 0.043	0.804	0.422
Medication				
Use of antihypertensive drugs	0.013	−0.011 to 0.037	1.071	0.285
Use of betablockers	0.005	−0.014 to 0.024	0.486	0.627
Use of calcium channel blockers	0.002	−0.017 to 0.020	0.209	0.835
Use of statins	0.010	−0.008 to 0.029	1.122	0.263
Donor				
Age (per 10 y)	0.005	−0.002 to 0.011	1.458	0.146
Sex (male)	0.014	−0.004 to 0.032	1.510	0.132
Donor status				
Deceased	0.042	0.024-0.059	4.574	**[<0.001]**
Living	–	–	–	–
Donor Type				
DCD	0.036	0.015-0.056	3.420	**[0.001]**
DBD	0.022	−0.001 to 0.045	1.868	0.063
Perioperative and postoperative				
Cold ischemia time (min)	0.011	0.006-0.016	4.383	**[<0.001]**
Warm ischemia time (min)	0.021	−0.043 to 0.085	0.637	0.525
CCI (unitless)	0.006	0.002-0.009	3.074	**[0.002]**

[a]CaScore: The normal unit HU is converted to per 100 HU to generate an interpretable unstandardized β-coefficient and 95% CI.
Statistically significant values are shown in bold.
BMI, Body Mass Index; CaScore, calcium score; CCI, Comprehensive Complication Index; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; HU, Hounsfield units; RI, resistance index.

is found to be positively associated with RI, which resulted in the Comprehensive Complication Index being a potential confounding variable. Nevertheless, a positive association between RI and aortoiliac CaScore remained after we added the Comprehensive Complication Index to the multivariable regression models.

This study also showed the clinical benefit of the presented data by identifying RI to be positively associated with various outcome variables such as DGF, graft failure, graft loss, and patient mortality. Furthermore, RI was inversely associated with eGFR 6 mo and 1 y after transplantation, which even further enhances the clinical benefit.

The positive association found between RI and the incidence of DGF in kidney transplant recipients corresponds with a meta-analysis from Bellos et al.[34] Moreover, our baseline differences correspond with those of previous studies on cardiovascular risk stratification in kidney transplantation.[35] In line with preexisting literature, our study shows that atherosclerosis is more common in patients with diabetes, elevated blood pressure, elevated cholesterol, and older recipient age.[4,35-37] After adding recipient age to the final multivariable linear regression model, the association between the CaScore and RI was no longer significant ($P = 0.130$). Recipient age is a predictor of CaScore. CaScore and recipient age were found to have a significant strong correlation ($r = 0.661$, $P < 0.001$), causing the effect of these variables to be canceled out in the multivariable regression analyses. Emphasizing recipient age influences the association between CaScore and RI because recipient age has been proven to be significantly associated with atherosclerosis,

TABLE 3.

Multivariable linear regression with patient characteristics as the independent variables and the resistance index as the dependent variable

	Unstandardized β-coefficient	95% CI	R^2-value	*P*
Model 1	0.011	0.006-0.017	0.045	**[<0.001]**
Model 2	0.010	0.004-0.015	0.083	**[0.001]**
Model 3	0.010	0.004-0.016	0.093	**[<0.001]**
Model 4	0.010	0.004-0.015	0.102	**[0.001]**
Model 5	0.008	0.002-0.014	0.114	**[0.006]**
Model 6	0.009	0.003-0.015	0.123	**[0.004]**
Model 7	0.008	0.002-0.014	0.127	**[0.010]**
Model 8	0.005	–0.002 to 0.012	0.132	0.163

Model 1: crude (calcium score)
Model 2: adjusted for deceased donation and donor age
Model 3: adjusted for model 2 + donor sex and prior dialysis
Model 4: adjusted for model 3 + cold ischemia time and the comprehensive complication index
Model 5: adjusted for model 4 + recipient history of diabetes and recipient history of vascular interventions
Model 6: adjusted for model 5 + recipient Body Mass Index and recipient current smoking
Model 7: adjusted for model 6 + recipient systolic blood pressure and recipient diastolic blood pressure
Model 8: adjusted for model 7 + recipient age

Statistically significant values are shown in bold.
CI, confidence interval.

strengthening our statistical approach and outcome.[37] The association between RI and atherosclerosis has been studied before, showing that RI, in accordance with our study, is positively associated with atherosclerosis.[38,39] But next to these similarities, our study has also important differences. Our study provides a better understanding of the etiology of the RI buildup, with emphasis on atherosclerosis in the aortoiliac tract, with the aim of understanding how the intrarenal RI is constructed, whereas both Köger et al and Heine et al associated RI with traditional cardiovascular risk factors and subclinical atherosclerosis. Köger et al also stated that a greater understanding of the theoretical basis of RI might help the RI to live up to its promise as a parameter for measuring changes in renal status, which we think we have contributed to this theoretical basis. In addition, unlike Köger et al and Heine et al, our study demonstrates the clinical value of the use of RI, which will aid clinicians in understanding the RI and hopefully support clinical decision-making.

TABLE 4.

Graft function characteristics of the kidney transplantation recipients

Graft function characteristics	Descriptive statistics
DGF	109 (28)
Acute rejection	61 (15.7)
Acute rejection within 1 y posttransplantation	53 (13.6)
Graft failure	37 (9.5)
Graft loss	70 (18)
Mortality	42 (10.8)
eGFR	
eGFR 3 mo after transplantation (mL/min)	49.00 ± 18.17
eGFR 6 mo after transplantation (mL/min)	49.70 ± 18.29
eGFR 1 y after transplantation (mL/min)	51.50 ± 20.61
Blood and urine biomarkers	
Serum creatinine 1 y after transplantation (μmol/L)	121.0 (99.0–149.0)
Serum calcium 1 y after transplantation (mmol/L)	2.44 ± 0.13
Serum phosphate 1 y after transplantation (mmol/L)	0.93 ± 0.20
Serum albumin 1 y after transplantation (g/L)	43.34 ± 3.00
Serum glucose 1 y after transplantation (mmol/L)	5.8 (5.1–7.3)
Serum hemoglobin 1 y after transplantation (mmol/L)	8.13 ± 1.14
Proteinuria 1 y after transplantation (g/L)	0.17 (0.10–0.27)

Data are presented as n (%), mean ± SD, or median (interquartile range).
DGF, delayed graft function; eGFR, estimated glomerular filtration rate.

This study had a few limitations that need to be addressed. Owing to the retrospective study design, not all confounding factors could be accounted for. For example, serum lactate and heart rate have been reported to affect RI but were unfortunately not available for analysis in our cohort.[29,30] However, we combined data from 2 prospective studies from 2 high-volume transplant centers, which resulted in a large nearly complete data file with >150 variables available, thus minimizing the effect of missing data. Second, the measurement and interpretation of the RI were performed by different radiologists, which can be considered a minor limitation given the low intraobserver and interobserver variability (<5%).[14,17,20] Third, for this study, we only selected patients who underwent both unenhanced low-dose CT and Doppler ultrasound. All patients underwent Doppler ultrasound posttransplantation, but the aforementioned criteria for a CT scan resulted in a selection bias. In any event in which selection has been applied, the results cannot simply be extrapolated to other cohorts. However, given that the majority of the patients in our hospital underwent a CT scan and that all patients underwent Doppler ultrasound posttransplantation, the degree of selection was limited, adding to the generalizability of our results. Moreover, all remaining necessary recipient data were prospectively collected and fully available; therefore, no further selection was made, adding to the consistency and reliability of our analysis. Lastly, RI has been demonstrated to be increased in native kidneys from patients with both hypertension and normal kidney function.[40] Furthermore, an increased RI has been demonstrated to be correlated with mild albuminuria.[40] Therefore, donor data regarding donor history of hypertension and diabetes would be of great benefit. These data were not available within the current study but should be included in future studies to further solidify the clinical use of RI in kidney transplantation.

TABLE 5.

Univariable linear regression with graft function characteristics as the independent variable and the resistance index as the dependent variable

Graft function characteristics	Univariable linear regression with resistance index			
	Unstandardized β-coefficient	95% CI	t-value	*P*
DGF	0.031	0.011-0.051	2.992	**[0.003]**
Acute rejection	−0.008	−0.033 to 0.017	−0.614	0.539
Acute rejection within 1 y posttransplantation	0.000	−0.027 to 0.026	−0.033	0.974
Graft failure	0.041	0.010-0.072	2.599	**[0.010]**
Graft loss	0.037	0.013-0.060	3.068	**[0.002]**
Mortality	0.051	0.022-0.080	3.435	**[<0.001]**
Estimated glomerular filtration rate (eGFR)				
eGFR 3 mo after transplantation (mL/s)[a]	0.000	−0.051 to 0.010	−1.352	0.177
eGFR 6 mo after transplantation (mL/s)[a]	−0.032	−0.063 to −0.002	−2.091	**[0.037]**
eGFR 1 y after transplantation (mL/s)[a]	−0.033	−0.061 to −0.006	−2.381	**[0.018]**
Blood and urine biomarkers				
Serum creatinine 1 y after transplantation (μmol/L)	0.010	−0.054 to 0.075	0.320	0.749
Serum calcium 1 y after transplantation (mmol/L)	0.033	−0.039 to 0.105	0.901	0.368
Serum phosphate 1 y after transplantation (mmol/L)	0.063	0.015-0.110	2.593	**[0.010]**
Serum albumin 1 y after transplantation (g/L)	−0.003	−0.006 to 0.000	−2.035	**[0.043]**
Serum glucose 1 y after transplantation (mmol/L)	0.093	0.031-0.154	2.946	**[0.003]**
Serum hemoglobin 1 y after transplantation (mmol/L)	−0.011	−0.019 to −0.003	−2.560	**[0.011]**
Proteinuria 1 y after transplantation (g/L)	−0.012	−0.035 to 0.012	−0.962	0.337

[a]eGFR: The normal unit mL/min is converted to mL/s to generate an interpretable unstandardized β-coefficient and 95% CI.
Statistically significant values are shown in bold.
CI, confidence interval; DGF, delayed glomerular function; eGFR, estimated glomerular filtration rate.

The strengths of the current study are as follows: The significant association found between the CaScore and RI in our study is more robust and reliable, compared with preexisting literature, given our stepped approach and model building with correction for statistically substantiated confounding variables.[36] The large number of patients included in this study provided us with an extensive amount of patient information and the opportunity to perform multivariable regression analyses without the risk of overfitting the models. Furthermore, the primary outcome variables of CaScore and RI are both means of repeated measurements, providing a more accurate interpretation and increasing reliability. Despite the similarities regarding cardiovascular risk stratification, our study cohort was much larger (n = 389) than the previously published, nontransplant paper (n = 77), and it is generally acknowledged that large populations yield the most reliable estimates.[36] Furthermore, it should be taken into account that, in our study, atherosclerosis was measured over the aortoiliac segment, in contrast to just the abdominal aorta in the other nontransplant study. Also, our patient cohort included only kidney transplant patients, whereas the other study included patients with chronic kidney disease (eGFR <0.60 mL/min/1.73 m^2).

In conclusion, this study identified an independent significant association between RI and aortoiliac CaScore in kidney transplant recipients despite interaction with recipient age.

This knowledge provides more insights into the development of RI and its clinical benefit. The presence of aortoiliac atherosclerosis should be considered when using the RI, which leads to a more reliable interpretation of RI in clinical decision-making.

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Ethical approval was not required for this study because all the required data were obtained from preexisting retrospective databases. Data from the 2 previous projects were compiled into a new merged database. Protocols from both projects were approved by our center's medical ethics committee (University Medical Center Groningen) in 2017 and 2018 (ILIAC study, research registry 201700698; RI Doppler study, research registry 201800363).

The data underlying this article will be shared upon reasonable request with the corresponding author.

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