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par

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TITRE

INDICE DE RESISTANCE INTRA-RENAL, DIABETE ET RISQUE DE DECES APRES TRANSPLANTATION RENALE

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« Un homme savant a compris un certain nombre de vérités.
Un homme cultivé a compris un certain nombre d'erreurs. »

Propos, Alain

Résumé

Introduction L'indice de résistance rénal (RI) prédit la mortalité chez les receveurs de transplantation rénale. Cependant sa valeur varie avec le temps et selon le statut diabétique du receveur. L'objectif de cette étude était d'analyser les variations de l'indice de résistance entre 1 mois et 3 mois après la transplantation rénale chez les patients diabétiques et non diabétiques, et sa valeur prédictive pour le décès avec greffon fonctionnel (DCGF).

Méthodes Nous avons réalisé une étude rétrospective chez les patients transplantés rénaux à Tours (France) entre 1985 et 2017. Les caractéristiques du donneur et du receveur ont été recueillies au moment de la transplantation et à 3 mois.

Résultats 1800 patients à 3 mois, et 1685 patients à 1 mois et 3 mois avaient une mesure de RI disponible. RI $\geq$ 0.75 était associé au décès chez les patients non diabétiques (hazard ratio (HR) = 3.33, [intervalle de confiance à 95% 2.46–4.36], $p < 0.001$), mais pas chez les patients diabétiques (HR = 1.32, [0.80–2.20], $p = 0.28$). Le risque de décès augmentait de manière continue avec l'indice de résistance à 1 mois et 3 mois, mais pas chez les patients diabétiques. La meilleure survie était observée chez les patients avec RI < 0.70 à 1 mois et 3 mois, et la moins bonne survie chez les patients avec RI $\geq$ 0.70 à 1 mois et 3 mois (HR = 3.77, [2.71–5.24], $p < 0.001$). Le risque était intermédiaire chez les autres patients. Chez les patients diabétiques, seul le RI < 0.70 à 1 mois et $\geq$ 0.70 à 3 mois était associés à une augmentation du risque de décès (HR = 4.69, [1.07-20.52], p=0.040).

Conclusion Le RI mesuré précocement et son évolution à court terme après la transplantation prédit le risque de décès à long terme chez les receveurs non diabétiques, mais son interprétation est différente chez les receveurs diabétiques, chez qui seule l'élévation du RI entre 1 mois et 3 mois semble associée à un mauvais pronostic.

RENAL RESISTIVE INDEX, DIABETES AND MORTALITY RISK AFTER RENAL TRANSPLANTATION

Abstract

Introduction Renal resistive index (RI) predicts mortality in renal transplant recipients. However, RI may change overtime, and this change may provide useful information on the risk of death. The objective of this study was to analyse RI changes between 1 month and 3 months after transplantation and its predictive value for death with a functioning graft.

Methods We conducted a retrospective study in renal transplant recipients in Tours (France) between 1985 and 2017. Donor and recipient characteristics at time of transplantation and at 3 months were reviewed.

Results 1800 patients at 1 month and 1685 patients at 1 month and 3 months had RI measurement available. RI $\geq$ 0.75 was associated with death in nondiabetic patients (hazard ratio (HR) = 3.33, [2.46–4.36], $p < 0.001$), but not in diabetic patients (HR = 1.32, [0.80–2.20], $p = 0.28$). The risk of death increased continuously with RI at 1 month and 3 months, but not in nondiabetic patients. Best survival was observed in patients with RI < 0.70 both at 1 and 3 months, and the worst survival was found in patients with RI $\geq$ 0.70 both at 1 and 3 months (HR = 3.77, [2.71–5.24], $p < 0.001$). The risk of death was intermediate for other patients. In diabetic patients, only RI < 0.70 at 1 month and $\geq$ 0.70 at 3 months was associated with increased risk of death (HR = 4.69, [1.07-20.52], $p = 0.040$).

Conclusion High RI at different time points early after transplantation is a strong predictor of death in nondiabetic patients, but must not be interpreted the same way in diabetic patients, in whom only RI elevation between 1 and 3 months is associated to an increased risk of death.

Mots-clés

Indice de résistance rénal

Transplantation rénale

Diabète

Echographie- doppler

Résistances vasculaires

Keywords

Renal resistive index

Kidney transplantation

Diabetes mellitus

Ultrasonography-doppler

Vascular resistance

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Serment d'Hippocrate

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les moeurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

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Abréviations

ANOVA: analysis of variance

BMI: body mass index, IMC: indice de masse musculaire

CI: confidence interval, IC: intervalle de confiance

CICR: cumulative incidence competing risk

DBP: diastolic blood pressure, PAD: pression artérielle diastolique

DSA: donor specific antigen

DWFG : death with a functioning graft, DCGF: décès avec greffon fonctionnel

eGFR : estimated glomerular filtration rate, DFGe : débit de filtration glomérulaire estimé

ESRD: end-stage renal disease

HR: hazard ratio

MMF: mycophenolate mofetyl

M-TOR: mammalian-target of rapamycin

NODAT: new onset diabetes after transplantation

PP: pulse pressure

PSV: peak systolic velocity, VPS: vitesse de pic systolique

EDV: end-diastolic velocity, VTD: vitesse télé-diastolique

RI: renal resistive index/indice de résistance rénal

RTR: renal transplant recipients

SBP: systolic blood pressure, PAS: pression artérielle systolique

Préambule

Cette thèse est basée sur l'étude rétrospective des patients transplantés rénaux à Tours depuis 1985. Nous avons montré dans un premier travail que l'indice de résistance rénal était associé au diabète chez les receveurs, mais pas chez le donneur, entérinant l'idée que cet indice était plus lié à l'environnement vasculaire systémique qu'aux caractéristiques rénales à proprement parler. Ce premier travail avait donnée lieu à un mémoire de DES et à une publication (de Freminville et al., "Impact on Renal Resistive Index of Diabetes in Renal Transplant Donors and Recipients.", *Journal of Clinical Hypertension*, 2019) (1).

Ce travail de thèse constitue la suite de la réflexion sur la signification de l'indice de résistance rénal chez les transplantés rénaux diabétiques ou non. Il a fait l'objet de 2 articles en premier auteur (un article publié (2) et un article soumis pour publication (NDT-01336-2019)). L'objectif principal était l'étude de l'indice de résistance rénal et de sa valeur pronostique chez les transplantés rénaux ainsi que l'impact du diabète sur cette valeur pronostique. Nous allons donc présenter successivement les deux articles issus de ce travail de recherche.

Introduction

La transplantation rénale est considérée comme le meilleur traitement de la maladie rénale chronique terminale, aussi bien en terme de qualité de vie que d'espérance de vie. Les receveurs de transplantation rénale ont toutefois une mortalité supérieure à la population générale (3).

L'indice de résistance rénal (RI) est une mesure doppler réalisée partir des vitesses sanguines systoliques (vitesse de pic systolique, VPS) et diastoliques (vitesse télé-diastolique, VTD) dans les artères rénales interlobaires.

$$RI = \frac{VPS - VTD}{VPS}$$

Les mesures doppler sont beaucoup plus aisées à réaliser sur les greffons rénaux que sur les reins natifs, du fait du positionnement plus superficiel de ces derniers. L'indice de résistance rénal est ainsi mesuré en routine dans de nombreux centres de transplantation rénale pour l'évaluation des greffons rénaux et de leurs receveurs. Leur signification clinique est ainsi un grand sujet d'intérêt.

Il a été montré au début des années 2000 que le RI élevé était associé chez les transplantés rénaux à une augmentation du risque de décès (4). D'autres études ont confirmé cette valeur prédictive dans la maladie rénale athéromateuse (2,5)

Pourtant, la signification clinique de l'indice de résistance n'est pas bien comprise. En effet ce paramètre était autrefois considéré comme un reflet des résistances vasculaires rénales et associé à la diminution de la surface du lit vasculaire d'aval (6). Il a aussi été montré qu'il était associé à la pression interstitielle rénale, ou à l'artériolosclérose. Mais il s'est finalement avéré que les deux principaux déterminants de l'indice de résistance étaient l'âge du receveur et la pression pulsée (PP) (7–10). De plus, il a été récemment montré que chez les receveurs de greffons rénaux, l'indice de résistance reflète plutôt la rigidité artérielle que les caractéristiques du donneur (8,11–13).

Les patients diabétiques et notamment les patients souffrant de néphropathie diabétique ont habituellement un indice de résistance élevé. Ainsi, si la transplantation d'un rein chez un receveur diabétique modifie l'indice de résistance, on peut se demander si cela modifie aussi sa valeur prédictive sur le risque de décès.

De plus, le moment de la mesure de l'indice de résistance en tant que prédicteur du risque de décès n'est pas bien déterminé. En effet, certaines études montrent une association entre RI mesuré précocement après la transplantation et risque de décès, quand d'autres ne retrouvent pas cette association lorsque le RI est mesuré moins de 12 mois après la transplantation (6,14). Une seule mesure pourrait ne pas être suffisante pour évaluer efficacement le risque de décès.

Lors de ce travail, nous avons analysé l'indice de résistance rénal à 1 mois et à 3 mois après la transplantation, afin de confirmer sa valeur prédictive du risque de décès, et nous avons étudié cette valeur pronostique selon le statut diabétique des patients. Enfin, nous avons étudié l'association entre la variation de cet indice de résistance entre le 1er et le 3^{e} mois après transplantation et le risque de décès.

ARTICLE 1

Titre : L'association entre indice de résistance rénal et mortalité prématurée chez les transplantés rénaux est modifiée par le diabète du receveur : une étude de cohorte

Cet article a été publié :

de Freminville, Jean-Baptiste, Louis-Marie Vernier, Jérome Roumy, Frédéric Patat, Philippe Gatault, Bénédicte Sautenet, Elodie Bailly, Eloi Chevallier, Christelle Barbet, Hélène Longuet, Elodie Merieau, Christophe Baron, Matthias Büchler, and Jean-Michel Halimi. "The Association between Renal Resistive Index and Premature Mortality after Kidney Transplantation Is Modified by Pre-Transplant Diabetes Status: A Cohort Study." *Nephrology Dialysis Transplantation*, April 26, 2019.

Question posée :

Nous avions montré dans une précédente étude que l'indice de résistance rénal était associé chez les transplantés rénaux au diabète du receveur, mais pas au diabète du donneur (1). Ceci est cohérent avec l'idée que l'indice de résistance est plus caractéristique de l'environnement vasculaire systémique que des résistances vasculaires intra-rénales (7,10).

L'indice de résistance est un bon marqueur prédictif de mortalité chez les transplantés rénaux, mais nous ne savons pas si cela est vrai chez les patients diabétiques, chez qui l'indice de résistance est habituellement plus élevé.

Nous avons donc étudié l'association entre l'indice de résistance et la mortalité chez les patients transplantés rénaux diabétiques et non diabétiques.

Introduction

Kidney transplantation is unquestionably the best treatment of end-stage renal disease (ESRD), but kidney transplant recipients have a higher mortality rate than the general population(3). Doppler measurements, such as renal resistive index (RI) are a lot easier to measure than in native kidneys and are routinely measured in many renal-transplantation centers to evaluate renal allografts and recipients. Their clinical meaning is therefore a great subject of interest.

In a seminal study, Radermacher et al. found that high RI was associated with an increased risk of death, even after multiple adjustments(4). Other studies confirmed the its predictive value on the risk of death in renal transplantation and in atheromatous renovascular disease(5,15).

However, the clinical meaning of RI is not clearly understood. This parameter was originally interpreted as a reflection of renal vascular resistance, and studies indicated that it would increase as a result of decreasing cross sectional area of renal arterial bed(11). It was also reported that changes in renal interstitial pressure, nephrosclerosis, interstitial fibrosis/tubular atrophy, or loss of peritubular capillaries and arteriolosclerosis, result in RI changes(7,16–18). Finally, it occurred that the main determinants of RI were age and pulse pressure(7–10). Moreover, it was recently stated, based on theoretical concepts as well as experimental and clinical findings, that in recipients of renal transplants, RI primarily reflects recipient aortic stiffness rather than donor kidney characteristics(8,11–13).

High RI is usually observed in patients with diabetes mellitus and in the setting of diabetic nephropathy(7,15,19,20). Therefore, if kidney transplantation in a diabetic environment may modify RI, then it is important to assess whether it also alters its predictive value on the risk of death.

In this study, we analyzed RI early after transplantation, including the RI-age and RI-arterial pressure relationships, and we assessed its long-term predictive value for mortality in a large cohort of diabetic and non-diabetic renal transplant recipients followed 30 years.

Patients and Methods

Patients selection

We conducted a retrospective analysis of 2362 consecutive patients who received a renal

transplant from October 1985 to October 2017 at the Tours University Hospital, France. Among them, 113 died or returned to dialysis within the three first months following transplantation, 422 patients were excluded because renal doppler ultrasonography at 3 months was not available, and 27 were excluded because of a diagnosis of renal artery stenosis. Thus, 1800 patients were included in this study. Data were collected from the prospectively maintained institutional database of transplant patients of our hospital and the ASTRE database ("commission nationale informatique et liberté" (CNIL) agreement number: DR-2012-518). The study protocol was validated by the Ethics Committee in Human Research (Hôpital Bretonneau, CHU Tours, France) and is in accordance with the Helsinki declaration of 1975, as revised in 2013.

Visits in our hospital for the follow-up were organized as follows: three visits per week during the first two weeks; two visits per week during the first year; one visit every other month during the second year; three visits per year thereafter until death, or ESRD (i.e., dialysis or re-transplantation).

At the time of transplantation, the following variables were reviewed: donor age, gender, diabetes, double or single transplantation, machine perfusion; recipient age, gender, diabetes, graft rank, body mass index (BMI), hemodialysis time before transplantation. At the 3-month visit after transplantation, the following variables were reviewed: systolic, diastolic and pulse arterial pressure, serum creatinine level, eGFR (using MDRD equation), proteinuria (by a 24-h urine collection(21)) immunosuppressive induction and maintenance treatments, delayed graft function (DGF) after transplantation, and renal resistive index. For double transplantation, RI was the mean of both left and right graft RI value. Recipient diabetes was defined as diabetes diagnosed before transplantation; therefore, it did not include new onset diabetes after transplantation (NODAT). NODAT was defined according to the American Diabetes Association (ADA) : symptoms of diabetes plus casual plasma glucose concentration > 11.1 mmol/L, casual being defined as any time of day without regard to time since last meal ; or fasting glucose > 7 mmol/l, fasting being defined as no caloric intake for at least 8 h. Cardiovascular death for the donor was defined as death from cardiac or cerebrovascular cause.

Doppler ultrasonography studies

For the measurement of renal resistive index, three ultrasound systems were used: Toshiba Aplio XG with PVT-375BT probe, Esaote Technos MPX with probe and Siemens Antares Premium Edition with CH5-2 probe with vascular program for each exam(22). All the

observers were experimented as this parameter is studied in our hospital since the early seventies(23). Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured during Doppler ultrasonography spectral analysis in renal interlobar arteries at 3 different points of the kidney (upper, medium, lower). RI was calculated with PSV and EDV by the following equation:

$$RI = (PSV - EDV) \Big/ PSV$$

The mean of three consecutive measurements was used. Doppler ultrasonography studies were routinely performed at 3 months after transplantation. Renal artery stenosis was ruled out at the time of measurement(24,25). The results of other Doppler studies were not considered in this report.

Statistical analyses

All the variables had a normal distribution. Results are expressed as percentages or means ± standard deviations. Qualitative variables were compared using χ^2 test. Continuous variables between two groups were compared using Student t test, after verifying equal standard deviations in each group.

The patients were stratified in two groups: RI of 0.75 or higher, and RI of less than 0.75. Indeed, studies consider 0.70 as the upper threshold of normal RI(26,27), whereas others showed that a RI greater than 0.75 or 0.80 was associated with poor allograft survival and death(4,28,29). Sensitivity analyses were also performed with different thresholds.

In order to find potential confounding factors, characteristics of diabetic recipients and non-diabetic recipients were compared. To assess colinearity among the variables, we used Pearson correlation.

For survival analysis, the event of interest was death with a functioning graft. As graft loss (i.e. dialysis or re-transplantation) are events that hinder the observation of the event of interest, and are competing risks, we used the cumulative incidence competing risk (CICR) method. To assess the association between RI at 3 months and the risk of death with a functioning graft, we compared cumulative incidence functions, using the subdistribution hazard approach proposed by Fine and Gray(30) in univariate and multivariate analysis, after analyzing the effect of multiple variables on the risk of death with a functioning graft, in order to choose the confounding factors.

A p value < 0.05 was considered statistically significant. Analyses were performed using the statistical software RStudio (RStudio Team, 2015, v1.0.153).

Results

Baseline characteristics

Among these 1800 renal transplant recipients, 284 (15.7%) had diabetes mellitus before transplantation (diabetes status was missing in 30 renal transplant recipients). Among them, 111 (42.2%) had a RI of 0.75 or less (Table 1). Overall, 1327 patients (73.7%) had a RI of 0.75 or less (Table 2). It was the first transplantation for 1532 patients (85.1%). 1705 patients (94.7%) received a cadaveric graft and 990 (61.1%) received a kidney from a donor deceased from cardiovascular disease (Table 1). Regarding immunosuppression, induction was performed with anti-interleukin 2 receptor (45.5%) or thymoglobulin (53.3%), and methylprednisolone 250 mg before and after transplantation. Maintenance immunosuppressive treatment included prednisone with a gradual tapering and mycophenolate mofetyl (82.0%) or azathioprine (15.0%), associated with ciclosporin (39.6%), tacrolimus (56.0%) or mammalian target of rapamycin (m-TOR) inhibitors (6.4%) (Table 1).

RI and the risk of death

Univariate analysis

Median follow-up was 6.35 years (0.25 to 30.9 years; total observation period: 14,202 patient years). During follow-up, 61/284 (21.4%) of patients with pre-transplant diabetes and 172/1486 (11.5%) of non-diabetic patients died, while 354 patients returned to dialysis or had a new transplantation.

RI>0.75 was associated with a greater risk of death with a functioning graft (HR=3.18, [95% confidence interval (CI) = 2.46–4.10], p<0.001) (Figure 1a). This was also true in non-diabetic patients (hazard ratio (HR)=3.33, [2.45–4.54], p<0.001) (Figure 1b), but not in patients with pre-transplant diabetes (HR=1.32, [0.80–2.20], p=0.28) (Figure 1c).

Pre-transplant diabetes was associated with a greater risk of death with a functioning graft (HR=3.24 , [2.41–4.36], p<0.001).

Death with a functioning graft was also significantly associated in univariate analysis with donor cardiovascular death, donor age, use of machine perfusion, double transplantation, hemodialysis time, age, BMI, high systolic and pulse pressure, low diastolic blood pressure,

low eGFR and delayed graft function (Table 3).

These results remained unchanged when the variables were considered dichotomous rather than continuous (Table 3).

Multivariate analysis

A correlation of more than 0.7 was found between recipient age and donor age (r=0.803), and between systolic arterial pressure and pulse pressure at 3 months (r=0.779). Therefore donor age and systolic blood pressure were removed from the analysis.

In multivariate analyses, after multiple adjustments, the results remained unchanged: high RI was a strong predictor of death with a functioning graft in non-diabetic recipients (HR=2.18, [1.41–3.36], p<0.001), but not in patients with pre-transplant diabetes (HR=1.19, [0.53–2.68], p=0.670) (Table 4).

RI as a continuous variable was similarly a strong predictor of death with a functioning graft in non-diabetic recipients (HR per 0.1 increase = 1.71, [1.27–2.30], p<0.001), but not in patients with pre-transplant diabetes (HR per 0.1 increase=0.97, [0.57–1.64], p=0.910).

Sensitivity analysis

Results were similar when using different thresholds for RI (0.70 and 0.80) (supplementary table 1). We also performed the same analysis with patients transplanted after year 2000. Among our 1800 patients, 1485 were transplanted after year 2000, and 263 of them had pre-transplant diabetes (supplementary table 2).

RI>0.75 was also a strong predictor of death with a functioning graft in this population (supplementary table 3).

RI in diabetic and non-diabetics recipients and interaction with recipient age and pulse pressure

RI at 3 months was higher in diabetics than in non-diabetic subjects (0.76±0.07 vs. 0.68±0.08, p<0.001) (Table 1). RI>0.75 was found in 58.8% of diabetic recipients, and in 20.3% of non-diabetic recipients (p<0.001) (Table 1).

RI at 3 months increased with age (Figure 2a). Nevertheless, the slope between recipient age and RI value was not steeper in patients with pre-transplant diabetes, but the curve started at a higher level, indicating there was no interaction between diabetes and age (p=0.47).

There was also no interaction between diabetes and systolic blood pressure (p=0.25) (Figure 2b), and between diabetes and diastolic blood pressure (p=0.57) (Figure 2c).

However, we found an interaction between diabetes and pulse pressure (p=0.042). Indeed, the augmentation of RI with pulse pressure was less important in patients with pre-transplant diabetes than in non-diabetic patients (Figure 2d).

Discussion

The main result of our study is that high RI is a powerful predictor of death in non-diabetic patients receiving a renal transplant, but that there is no relationship between RI value and the risk of death in diabetic patients receiving a renal transplant. These results were confirmed after multiple adjustments.

Many studies suggest that RI is related to systemic vascular alterations, and poorly associated with renal vascular resistance (7,10,31). Some authors observed that it was increased in patients with atherosclerosis, and with diabetic nephropathy(19,20). Diabetic patients who undergo renal transplantation have suffered for years from chronic glucotoxicity, and therefore suffer from the vascular consequences of increased production of advanced glycation end products (32). These complications imply both systemic and renal vascularization; hence, the impact on RI, even though we do not know whether it is due to renal or systemic modifications. In this study, we observed that RI was higher in patients with pre-transplant diabetes than in non-diabetic patients, independently of other parameters. This seems consistent with the fact that RI is related to systemic vascular alterations. We also confirmed that pre-transplant diabetes was a strong predictor of death with a functioning graft, which seemed obvious given the vascular and renal complications linked to this disease.

Age and pulse pressure are known to be strong determinants of RI (7,9,10). Patients with pre-transplant diabetes were older at the time of graft. However, there was no interaction between recipient age and diabetes: the age-RI slope was not steeper in diabetic than in non-diabetic subjects. Patients with pre-transplant diabetes also had higher pulse pressure than non-diabetic patients. Moreover, we found an interaction between RI and pulse pressure: the augmentation of RI with pulse pressure was less important in patients with pre-transplant diabetes. The augmentation of RI in diabetic patients may be less important because RI is higher than in non-diabetic patients, due to increased aortic stiffness. Diabetic patients also have increased mortality due to cardiovascular damages. This could explain the absence of prognostic value of RI in patients with pre-transplant diabetes.

Our study confirmed the fact that RI was a predictor of death in renal transplant recipients in general, but it appears that it is not a predictor of death in patients with pre-transplant diabetes. It is important to note that similar findings were confirmed when RI was considered as a continuous variable or as a dichotomous variable, in univariate and in multivariate analyses, and with different thresholds. Moreover, because the profile of renal transplant recipients changed over the years, and that very few diabetic were transplanted before year 2000, we confirmed our results in patients who were transplanted after year 2000.

We confirmed that RI is higher in patients with pre-transplant diabetes, and that it should be linked to systemic vascular alterations due to diabetes. One could imagine that high RI is a good predictor of death because it is linked to systemic vascular alterations and atherosclerosis, and so that patients with a high RI have a high cardiovascular risk. Patients with pre-transplant diabetes also have a high cardiovascular risk, and hence have a higher risk of death than non-diabetic patients, regardless of the RI value. However, the reason why some diabetic patients have low RI is not known.

Our study has many strength. As far as we know, the respective prognostic value of RI in diabetic or non-diabetic patients has never been studied. It represents one of the largest cohorts of renal transplant recipients focused on the mechanism of increased RI in diabetic patients. The follow-up was long (up to 30 years). Regarding Doppler indices, they were measured by experienced physicians, as these parameters are studied in our hospital since the early seventies (23).

It also has limitations. It is a retrospective monocentric study, and therefore our findings would need to be replicated. The number of patients with pre-transplant diabetes was lower than non-diabetic patients. However, almost 300 diabetic patients were included in the present study; therefore lack of power seems unlikely. We did not differentiate cardiovascular and non-cardiovascular death: the difference in the prognostic value of RI between diabetic and non-diabetic renal transplant recipients may be less or more pronounced for cardiovascular death. This point could help explain the prognostic value of RI and would need further study. It was also not possible to provide the inter-observer variability of the RI measure. However, some studies showed a good reproducibility of this measure (33,34).

In conclusion, our study confirms high RI as a strong predictor of death in renal transplant patients, but it also clearly shows that RI constitutes a risk factor for death only in non-

diabetic renal transplant recipients. This discrepancy may be due to the fact that the relationship between pulse pressure and RI is different in diabetic and non-diabetic patients.

Tables and figures

Table 1. Baseline characteristics stratified with recipient characteristics

	Overall	Recipient Diabetes	Recipient Diabetes	p
Total patients	1800	1486	284	
Donor characteristics				
Cardiovascular death (%)	990 (61.1)	785 (59.1)	196 (70.3)	0.001
Deceased donor (%)	1705 (94.7)	1395 (93.9)	280 (98.6)	0.002
Donor age (years)	51.0 (17.6)	49.4 (17.5)	61.5 (13.9)	<0.001
Donor with diabetes (%)	101 (5.7)	73 (5.0)	28 (9.9)	0.002
Donor gender (% Male)	1076 (59.8)	899 (60.5)	153 (53.9)	0.044
Cold Ischemia (hours)	17.8 (7.8)	17.7 (8.0)	17.5 (6.3)	0.693
Recipient characteristics at time of transplantation				
Diabetes (%)	284 (16.0)	0 (0.0)	284 (100.0)	<0.001
NODAT (%)	221 (12.5)	221 (14.9)	0 (0.0)	<0.001
Hemodialysis time (years)	2.99 (3.41)	3.07 (3.61)	2.64 (2.19)	0.070
Age (years)	51.1 (14.9)	49.3 (14.9)	61.7 (9.5)	<0.001
Year of transplantation (%)				<0.001
1985-1989	45 (2.5)	22 (1.5)	0 (0.0)	
1990-1999	270 (15.0)	249 (16.8)	21 (7.4)	
2000-2009	647 (35.9)	568 (38.2)	73 (25.7)	
2010-2017	838 (46.6)	647 (43.5)	190 (66.9)	
Gender (% Male)	1145 (63.6)	932 (62.7)	193 (68.0)	0.107
BMI (kg/m2)	25.3 (4.9)	24.6 (4.6)	28.7 (5.3)	<0.001
Graft rank (%)				0.121
0	1532 (85.1)	1254 (84.4)	253 (89.1)	
1	227 (12.6)	194 (13.1)	29 (10.2)	
2	39 (2.2)	36 (2.4)	2 (0.7)	
3	2 (0.1)	2 (0.1)	0 (0.0)	
Perfusion machine (%)	266 (14.8)	174 (11.7)	92 (32.4)	<0.001
Double transplantation (%)	26 (1.4)	16 (1.1)	10 (3.5)	0.004
Recipients characteristics at 3 months				
SBP (mmHg)	138.4 (15.9)	137.2 (15.3)	145.1 (17.1)	<0.001
DBP (mmHg)	78.8 (10.6)	79.3 (10.4)	75.3 (11.2)	<0.001
PP (mmHg)	59.7 (15.2)	57.9 (14.1)	69.8 (17.1)	<0.001
DGF (%)	335 (18.6)	247 (16.6)	80 (28.2)	<0.001
eGFR MDRD (ml/min/1.73	51.7 (19.6)	52.1 (19.6)	47.8 (19.5)	0.002
Proteinuria (g/day)	0.78 (8.11)	0.82 (8.95)	0.59 (0.63)	0.724
Tacrolimus (%)	878 (56.0)	712 (54.3)	165 (71.7)	<0.001
Ciclosporine (%)	621 (39.6)	543 (41.4)	53 (23.0)	<0.001
Steroids (%)	1501 (95.8)	1261 (96.2)	221 (96.1)	1.000
MMF (%)	1286 (82.0)	1073 (81.8)	209 (90.9)	0.001
Azathioprine (%)	235 (15.0)	199 (15.2)	15 (6.5)	0.001
m-TOR inhibitors (%)	101 (6.4)	85 (6.5)	16 (7.0)	0.895
Thymoglobulin (%)	958 (53.3)	803 (54.1)	131 (46.1)	0.017
IL2-R antibodies (%)	815 (45.5)	660 (44.6)	153 (54.1)	0.004
Resistive index	0.69 (0.08)	0.68 (0.08)	0.76 (0.07)	<0.001
Resistive index > 0.75 (%)	473 (26.3)	302 (20.3)	167 (58.8)	<0.001

Values are mean (SD) or absolute (percentage) of patients

NODAT : New Onset Diabetes After transplantation; DGF : Delayed Graft Function ; BMI : Body Mass Index ; Filtration Rate

SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular;

m-TOR : Mammalian target of rapamycin ; IL2-R : interleukin 2 receptor ; MMF : mycophenolate mofetil

Table 2. Baseline characteristics stratified with resistive index as a binary variable

	RI < 0.75	RI > 0.75	p
Total patients	1327	473	
Donor characteristics			
Cardiovascular death (%)	667 (57.3)	323 (71.1)	<0.001
Deceased donor (%)	1242 (93.6)	463 (97.9)	0.001
Donor age (years)	47.0 (16.6)	62.3 (15.4)	<0.001
Donor with diabetes (%)	50 (3.8)	51 (10.8)	<0.001
Donor gender (% Male)	801 (60.4)	275 (58.1)	0.429
Cold ischemia (hours)	17.7 (8.1)	18.0 (7.1)	0.458
Recipient characteristics at time of transplantation			
Diabetes (%)	117 (9.0)	167 (35.6)	<0.001
NODAT (%)	157 (12.1)	64 (13.6)	0.424
Hemodialysis time (years)	3.03 (3.58)	2.87 (2.92)	0.380
Age (years)	46.79 (14.01)	63.36 (9.47)	<0.001
Year of transplantation (%)			<0.001
1985-1989	40 (3.0)	5 (1.1)	
1990-1999	219 (16.5)	51 (10.8)	
2000-2009	513 (38.7)	134 (28.3)	
2010-2017	555 (41.8)	283 (59.8)	
Gender (% Male)	858 (64.7)	287 (60.7)	0.136
BMI (kg/m2)	24.71 (4.70)	26.84 (5.14)	<0.001
Graft rank (%)			0.542
0	1126 (84.9)	406 (85.8)	
1	167 (12.6)	60 (12.7)	
2	32 (2.4)	7 (1.5)	
3	2 (0.2)	0 (0.0)	
Perfusion machine (%)	123 (9.3)	143 (30.2)	<0.001
Double transplantation (%)	13 (1.0)	13 (2.7)	0.011
Recipients characteristics at 3 months			
SBP (mmHg)	136.9 (14.9)	143.1 (17.7)	<0.001
DBP (mmHg)	80.4 (10.1)	73.9 (10.8)	<0.001
PP (mmHg)	56.4 (13.1)	69.2 (16.8)	<0.001
DGF (%)	212 (16.0)	123 (26.0)	<0.001
eGFR MDRD (ml/min/1.73 m2)	54.0 (20.1)	44.8 (16.1)	<0.001
Proteinuria (g/day)	0.87 (9.53)	0.55 (0.56)	0.566
Tacrolimus (%)	629 (53.7)	249 (62.7)	0.002
Ciclosporine (%)	503 (43.0)	118 (29.7)	<0.001
Steroids (%)	1121 (95.8)	380 (95.7)	1.000
MMF (%)	947 (80.9)	339 (85.4)	0.051
Azathioprine (%)	193 (16.5)	42 (10.6)	0.006
m-TOR inhibitors (%)	59 (5.0)	42 (10.6)	<0.001
Thymoglobulin (%)	723 (54.6)	235 (49.7)	0.076
IL2-R antibodies (%)	581 (43.9)	234 (49.7)	0.036
Resistive index	0.66 (0.06)	0.79 (0.04)	<0.001

Values are mean (SD) or absolute (percentage) of patients
NODAT : New Onset Diabetes After transplantation; DGF : Delayed Graft Function ; BMI : Body Mass Index ; Filtration Rate
SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular;
m-TOR : Mammalian target of rapamycin ; IL2-R : interleukin 2 receptor ; MMF : mycophenolate mofetil

Table 3. Determinants of death with a functioning graft in univariate analysis

	HR	p
Donor characteristics		
Cardiovascular death	1.50 [1.12-2.00]	0.006
Donor with diabetes	1.18 [0.63-2.19]	0.610
Donor gender (Male)	0.97 [0.75-1.27]	0.850
Donor Age (per 10 year increase)	1.31 [1.21-1.43]	<0.001
Donor Age > 60	1.85 [1.45-2.36]	<0.001
Cold ischemia (per 1 hour increase)	1.00 [0.99-1.02]	0.57
Recipents characteristics at time of transplantation		
Diabetes	3.24 [2.41-4.36]	<0.001
NODAT	0.84 [0.59-1.2]	0.34
Hemodialysis time > 1 year	1.42 [1.03-1.96]	0.033
Hemodialysis time (per 1 year increase)	1.03 [1.01-1.06]	0.018
Age (per 10 year increase)	1.92 [1.72-2.15]	<0.001
Age > 60 years	3.68 [2.87-4.72]	<0.001
Male gender	1.27 [0.98-1.66]	0.076
BMI > 25	1.59 [1.23-2.06]	<0.001
BMI (per 5 pt increase)	1.3 [1.15-1.48]	<0.001
Year of transplantation (ref = 1985-1989)		
1990-1999	0.99 [0.60-1.66]	0.980
2000-2009	1.07 [0.67-1.72]	0.770
2010-2017	1.48 [0.88-2.47]	0.130
double transplantation	2.75 [1.08-7.03]	0.035
Perfusion machine	2.72 [1.73-4.30]	<0.001
Recipients characteristics at 3 months		
SBP > 140 mmHg	1.62 [1.25-2.10]	<0.001
SBP (per 10 mmHg increase)	1.14 [1.06-1.22]	<0.001
DBP > 90 mmHg	0.52 [0.28-0.95]	0.033
DPB (per 10 mmHg increase)	0.88 [0.78-0.98]	0.022
PP > 50 mmHg	1.98 [1.46-2.68]	<0.001
PP (per 10 mmHg increase)	1.24 [1.15-1.33]	<0.001
eGFR < 45 ml/min	1.36 [1.05-1.76]	0.019
eGFR MDRD (per 10ml/min/1.73 m2 increase)	0.90 [0.84-0.98]	0.016
Tacrolimus	1.30 [0.99-1.70]	0.052
IL2-R antibodies	1.23 [0.45-1.63]	0.130
DGF	1.38 [1.02-1.86]	0.035
RI > 0.75	3.18 [2.46-4.10]	<0.001
RI > 0.70	2.88 [2.21-3.75]	<0.001
RI > 0.80	2.70 [1.92-3.81]	<0.001
RI (per 0.1 increase)	2.25 [1.91-2.65]	<0.001

Values are absolute [IC95%]
NODAT : New Onset Diabetes After transplantation; DGF : Delayed Graft Function ; BMI : Body Mass Index ; Filtration Rate
SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular;
m-TOR : Mammalian target of rapamycin ; IL2-R : interleukin 2 receptor ; MMF : mycophenolate mofetil; RI : Resistive index

Table 4. Determinants of death with a functioning graft in multivariate analysis with resistive index as a binary variable and as a continuous variable

Resistive index as a binary variable

	all patients		patients with pre-transplant diabetes		nondiabetic patients	
	HR	p	HR	p	HR	p
Resistive index > 0.75	1.90	0.001	1.19	0.670	2.18	<0.001
Donor cardiovascular death	1.19	0.290	2.14	0.068	1.02	0.940
Hemodialysis time > 1 year	1.54	0.036	1.20	0.680	1.62	0.041
Age > 60 years	2.17	<0.001	1.71	0.160	2.39	<0.001
BMI > 25	0.94	0.730	0.78	0.480	0.98	0.900
DFG < 45 ml/min	0.93	0.660	0.83	0.500	0.96	0.840
DGF	1.19	0.340	1.35	0.360	1.16	0.510
PP > 50 mmHg	1.21	0.340	0.56	0.810	1.20	0.390
DBP > 90 MMhG	0.78	0.490	0.69	0.710	0.65	0.320
double transplantation	1.35	0.620	1.24	0.770	1.09	0.900
Perfusion machine	1.58	0.099	2.27	0.045	1.44	0.350
Diabetes	1.51	0.043				

Resistive index as a continous variable

	all patients		patients with pre-transplant diabetes		nondiabetic patients	
	HR	p	HR	p	HR	p
Resistive index (per 0.1 increase)	1.51	0.003	0.97	0.910	1.71	<0.001
Donor cardiovascular death	1.16	0.37	2.14	0.071	0.97	0.870
Hemodialysis time > 1 year	1.48	0.059	1.20	0.670	1.52	0.076
Age > 60 years	2.21	<0.001	1.88	0.061	2.36	<0.001
BMI > 25	0.92	0.62	0.77	0.460	0.93	0.700
DFG < 45 ml/min	0.91	0.56	0.81	0.460	0.96	0.840
DGF	1.20	0.32	1.35	0.370	1.18	0.450
PP > 50 mmHg	1.15	0.49	0.92	0.870	1.12	0.600
DBP > 90 MMhG	0.81	0.55	1.23	0.760	0.71	0.420
double transplantation	1.40	0.57	1.27	0.840	1.23	0.760
Perfusion machine	1.58	0.098	2.33	0.040	1.45	0.330
Diabetes	1.52	0.040				

A correlation of more than 0.5 was found between recipient age and donor age,
and between systolic arterial pressure and pulse pressure at 3 months. .
Therefore donor age and systolic blood pressure were removed from the analysis

Supplementary Table 1. Determinants of death with a functioning graft in multivariate analysis with resistive index as a binary variable using different thresholds

Resistive index > 0.80

	patients with pre-transplant diabetes		nondiabetic patients	
	HR	**p**	**HR**	**p**
Resistive index > 0.80	1.02	0.950	1.75	0.039
Donor cardiovascular death	2.15	0.070	1.02	0.92
Hemodialysis time > 1 year	1.20	0.680	1.64	0.037
Age > 60 years	1.85	0.064	2.96	<0.001
BMI > 25	0.77	0.480	0.99	0.950
DFG < 45 ml/min	0.81	0.460	1.01	0.950
DGF	1.35	0.360	1.18	0.470
PP > 50 mmHg	0.90	0.850	1.22	0.360
DBP > 90 MMhG	1.24	0.750	0.58	0.200
double transplantation	1.30	0.820	1.51	0.550
Perfusion machine	2.30	0.038	1.53	0.270

Resistive index > 0.70

	patients with pre-transplant diabetes		nondiabetic patients	
	HR	**p**	**HR**	**p**
Resistive index > 0.80	0.96	0.910	1.57	0.040
Donor cardiovascular death	2.14	0.071	0.97	0.89
Hemodialysis time > 1 year	1.20	0.680	1.57	0.058
Age > 60 years	1.88	0.065	2.82	<0.001
BMI > 25	0.77	0.460	0.97	0.880
DFG < 45 ml/min	0.81	0.460	0.99	0.950
DGF	1.34	0.370	1.20	0.410
PP > 50 mmHg	0.92	0.880	1.18	0.440
DBP > 90 MMhG	1.24	0.750	0.65	0.320
double transplantation	1.26	0.850	1.22	0.770
Perfusion machine	2.33	0.041	1.56	0.250

Supplementary Table 2. Baseline characteristics for patients transplanted after 2000

		Overall	Recipient Diabetes -	Recipient Diabetes +	p
Total patients		1485	1215	263	
Donor characteristics					
Cardiovascular death		845 (60.7)	660 (58.7)	181 (69.9)	0.001
Deceased donor (%)		1392 (93.7)	1126 (92.7)	259 (98.5)	0.001
Donor age (years)		53.92 (16.90)	52.11 (17.03)	62.70 (13.24)	<0.001
Donor with diabetes (%)		101 (6.9)	73 (6.1)	28 (10.7)	0.011
Donor gender (% Male)		867 (58.4)	720 (59.3)	143 (54.4)	0.165
Cold Ischemia (hours)		16.67 (6.97)	16.57 (7.18)	17.06 (5.93)	0.300
Recipient characteristics at time of					
Diabetes (%)		263 (17.8)	0 (0.0)	263 (100.0)	<0.001
NODAT (%)		173 (11.7)	173 (14.3)	0 (0.0)	<0.001
Hemodialysis time (years)		2.94 (3.29)	3.01 (3.48)	2.68 (2.26)	0.157
Age (years)		52.64 (14.63)	50.56 (14.75)	62.33 (9.34)	<0.001
Year of transplantation > 2010 (%)		838 (56.4)	647 (53.3)	190 (72.2)	<0.001
Gender (% Male)		948 (63.8)	765 (63.0)	178 (67.7)	0.170
BMI (kg/m2)		25.36 (5.01)	24.64 (4.63)	28.78 (5.34)	<0.001
Graft rank (%)					0.125
	0	1260 (84.8)	1021 (84.0)	233 (88.6)	
	1	186 (12.5)	157 (12.9)	28 (10.6)	
	2	37 (2.5)	35 (2.9)	2 (0.8)	
	3	2 (0.1)	2 (0.2)	0 (0.0)	
Perfusion machine (%)		266 (17.9)	174 (14.3)	92 (35.0)	<0.001
Double transplantation (%)		26 (1.8)	16 (1.3)	10 (3.8)	0.012
Recipients characteristics at 3 months					
SBP (mmHg)		137.71	136.49 (14.94)	144.03 (16.86)	<0.001
DBP (mmHg)		77.63 (10.46)	78.24 (10.22)	74.46 (11.03)	<0.001
PP (mmHg)		60.08 (15.23)	58.25 (14.08)	69.57 (17.25)	<0.001
DGF (%)		258 (17.4)	185 (15.2)	72 (27.4)	<0.001
eGFR MDRD (ml/min/1.73 m2)		50.51 (19.02)	51.11 (18.84)	47.37 (19.74)	0.009
Proteinuria (g/day)		0.80 (8.46)	0.85 (9.38)	0.58 (0.61)	0.703
Tacrolimus (%)		857 (68.0)	696 (66.5)	160 (76.6)	0.006
Ciclosporine (%)		335 (26.6)	295 (28.2)	37 (17.7)	0.002
Steroids (%)		1214 (96.3)	1010 (96.5)	200 (95.7)	0.733
MMF (%)		1222 (97.0)	1015 (96.9)	203 (97.1)	1.000
Azathioprine (%)		6 (0.5)	4 (0.4)	2 (1.0)	0.582
m-TOR inhibitors (%)		101 (8.0)	85 (8.1)	16 (7.7)	0.938
Thymoglobulin (%)		648 (43.6)	534 (44.0)	112 (42.6)	0.737
IL2-R antibodies (%)		814 (55.0)	659 (54.5)	153 (58.4)	0.275
Resistive index		0.70 (0.08)	0.68 (0.08)	0.76 (0.07)	<0.001
RI > 0.75		417 (28.1)	260 (21.4)	156 (59.3)	<0.001

Supplementary Table 3. Determinants of death with a functioning graft in multivariate analysis with RI as a binary variable in patients transplanted after 2000

	all patients		patients with pre-transplant diabetes		nondiabetic patients	
			HR	p	HR	p
Resistive index > 0.80	2.23	<0.001	1.18	0.720	2.51	<0.001
Donor cardiovascular death	1.12	0.570	1.92	0.160	0.89	0.600
Hemodialysis time > 1 year	1.57	0.075	1.12	0.800	1.84	0.054
Age > 60 years	2.24	<0.001	1.59	0.280	2.38	0.002
BMI > 25	0.76	0.130	0.90	0.800	0.62	0.033
DFG < 45 ml/min	0.91	0.590	0.67	0.200	1.08	0.750
DGF	1.47	0.070	1.59	0.180	1.32	0.320
PP > 50 mmHg	1.35	0.210	1.14	0.860	1.30	0.330
DBP > 90 MMhG	1.42	0.360	2.08	0.370	1.18	0.730
double transplantation	1.32	0.640	1.59	0.700	1.07	0.930
Perfusion machine	1.70	0.056	2.22	0.054	1.49	0.290

Figure 1: cumulative incidence curve for death with a functioning graft according to RI at 3 months in all patients (1A), in patients with pre-transplant diabetes(1B), and in non-diabetic patients (1C)

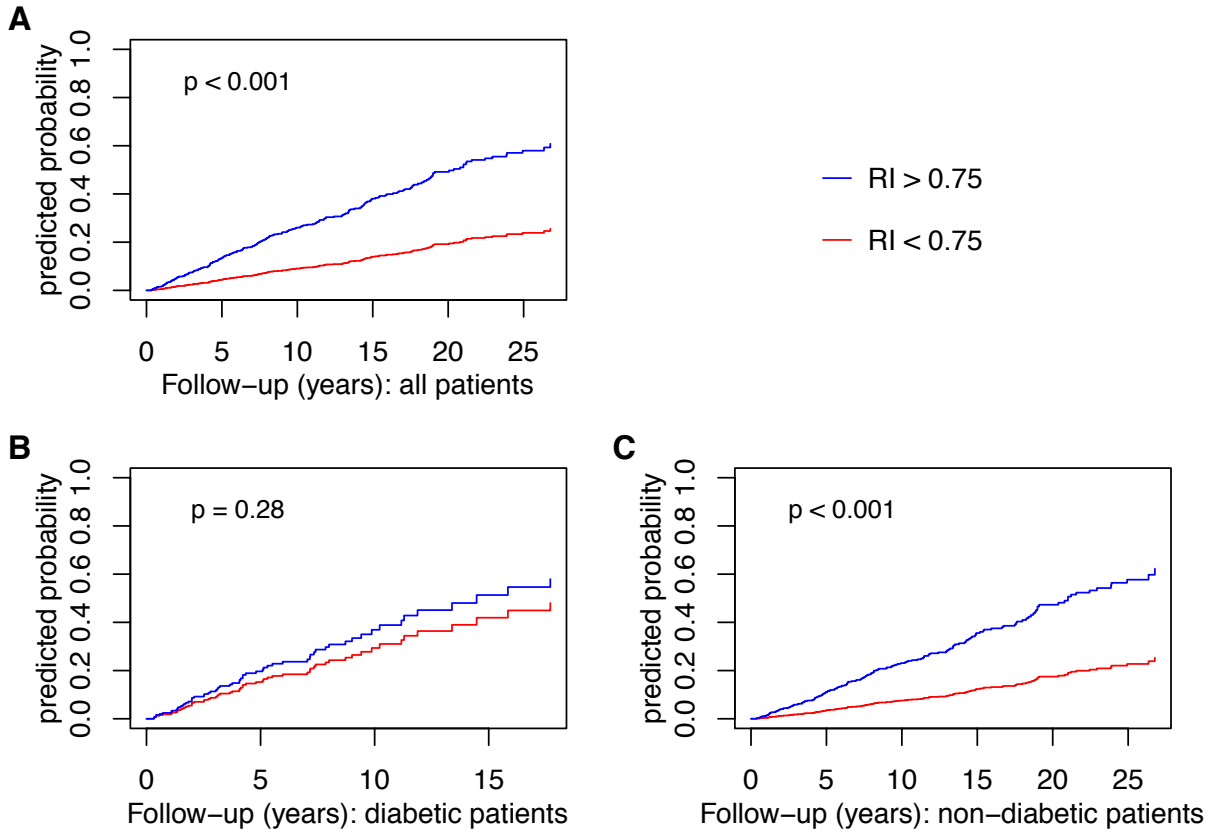
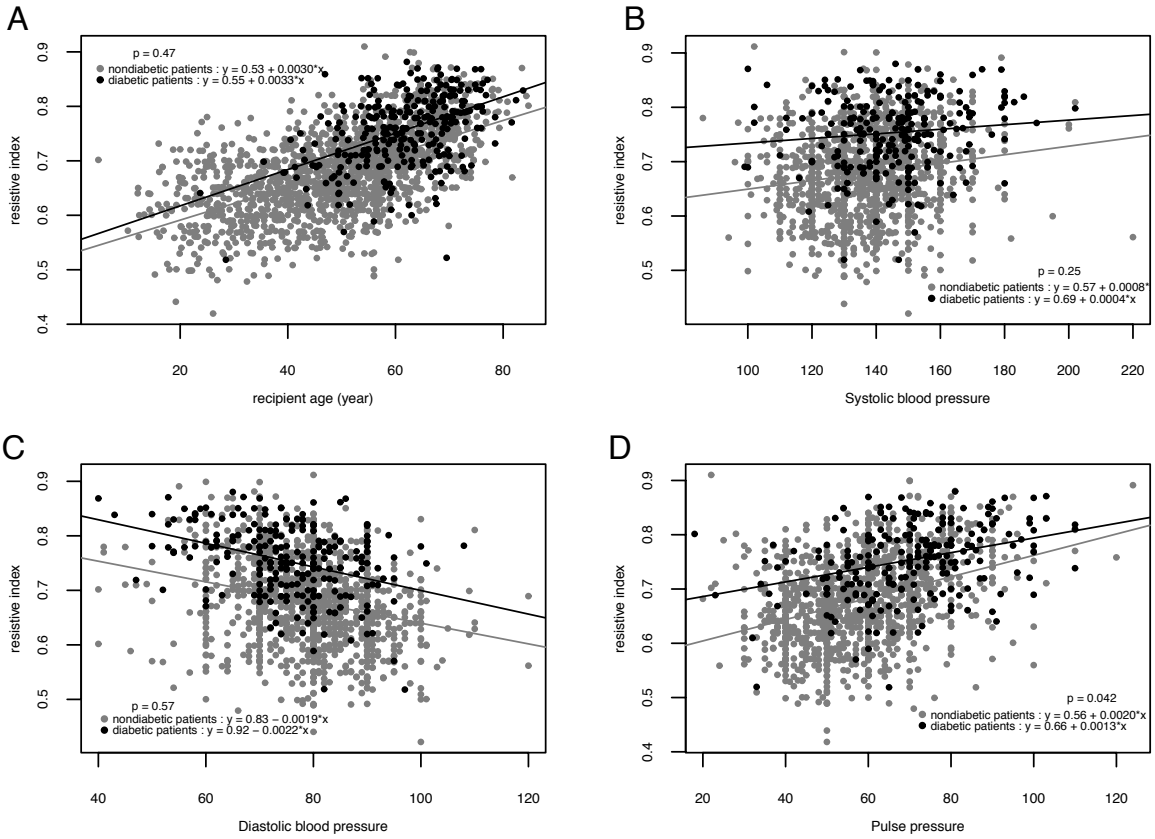


Figure 2: RI in diabetic and non-diabetic recipients and interaction with recipient age (2A), systolic blood pressure (2B), diastolic blood pressure (2C) and pulse pressure (2D)



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Nephrology Dialysis Transplantation

The association between renal resistive index and premature mortality after kidney transplantation is modified by pre-transplant diabetes status: a cohort study

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ABSTRACT

Background. Renal resistive index (RI) predicts mortality in renal transplant recipients, but we do not know whether this is true in diabetic patients. The objective of this study was to analyse the long-term predictive value of RI for death with a functioning graft (DWFG) in renal transplant recipients with or without pre-transplant diabetes.

Methods. We conducted a retrospective study in 1800 renal transplant recipients between 1985 and 2017 who were followed for up to 30 years (total observation period: 14 202 patient years). Donor and recipient characteristics at time of transplantation and at 3 months were reviewed. The long-term predictive value of RI for DWFG and the age–RI and arterial pressure–RI relationships were assessed.

Results. A total of 284/1800 (15.7%) patients had diabetes mellitus before transplantation. RI was <0.75 in 1327/1800 patients (73.7%). High RI was associated with a higher risk of DWFG in non-diabetic patients [hazard ratio (HR) = 3.39, 95% confidence interval 2.50–4.61; $P < 0.001$], but not in patients with pre-transplant diabetes (HR = 1.25, 0.70–2.19; $P = 0.39$), even after multiple adjustments. There was no interaction between diabetes and age. In contrast, there was an interaction between RI and pulse pressure.

Conclusion. Our study indicates that RI is not a predictor of DWFG in diabetic renal transplant recipients, in contrast to non-diabetic recipients. These findings could be due to a different age–RI or pulse pressure–RI relationship.

Keywords: diabetes mellitus, kidney transplantation, renal resistive index, ultrasonography, vascular resistance

INTRODUCTION

Kidney transplantation is unquestionably the best treatment of end-stage renal disease (ESRD), but kidney transplant recipients have a higher mortality rate than the general population [1]. Doppler measurements, such as renal resistive index (RI), are a lot easier to measure than in native kidneys and are routinely measured in many renal transplantation centres to evaluate renal allografts and recipients. Their clinical meaning is therefore a subject of great interest.

In a seminal study, Radermacher *et al.* [2] found that high RI was associated with an increased risk of death, even after multiple adjustments. Other studies confirmed that it has predictive value for the risk of death in renal transplantation and in atheromatous renovascular disease [3, 4].

However, the clinical meaning of RI is not clearly understood. This parameter was originally interpreted as a reflection of renal vascular resistance, and studies indicated that it would increase as a result of decreasing cross-sectional area of renal arterial bed [5]. It was also reported that changes in renal interstitial pressure, nephrosclerosis, interstitial fibrosis/tubular atrophy or loss of peritubular capillaries and arteriolosclerosis result in RI changes [6–9]. Finally, it was determined that the main determinants of RI were age and pulse pressure (PP) [7, 10–12]. Moreover, it was recently stated, based on theoretical concepts as well as experimental and clinical findings, that in recipients of renal transplants, RI primarily reflects recipient aortic stiffness rather than donor kidney characteristics [5, 10, 13, 14].

High RI is usually observed in patients with diabetes mellitus and in the setting of diabetic nephropathy [4, 7, 15, 16].

Table 1. Baseline characteristics stratified with recipient characteristics

	Overall	Recipient diabetes −	Recipient diabetes +	P-value
Total patients	1800	1486	284	
Donor characteristics				
Cardiovascular death (%)	990 (61.1)	785 (59.1)	196 (70.3)	0.001
Deceased donor (%)	1705 (94.7)	1395 (93.9)	280 (98.6)	0.002
Donor age (years)	51.0 (17.6)	49.4 (17.5)	61.5 (13.9)	<0.001
Donor with diabetes (%)	101 (5.7)	73 (5.0)	28 (9.9)	0.002
Donor gender (% male)	1076 (59.8)	899 (60.5)	153 (53.9)	0.044
Cold ischaemia (h)	17.8 (7.8)	17.7 (8.0)	17.5 (6.3)	0.693
Recipient characteristics at time of transplantation				
Diabetes (%)	284 (16.0)	0 (0.0)	284 (100.0)	<0.001
NODAT (%)	221 (12.5)	221 (14.9)	0 (0.0)	<0.001
Haemodialysis time (years)	2.99 (3.41)	3.07 (3.61)	2.64 (2.19)	0.070
Age (years)	51.1 (14.9)	49.3 (14.9)	61.7 (9.5)	<0.001
Year of transplantation (%)				<0.001
1985–89	45 (2.5)	22 (1.5)	0 (0.0)	
1990–99	270 (15.0)	249 (16.8)	21 (7.4)	
2000–09	647 (35.9)	568 (38.2)	73 (25.7)	
2010–17	838 (46.6)	647 (43.5)	190 (66.9)	
Gender (% male)	1145 (63.6)	932 (62.7)	193 (68.0)	0.107
BMI (kg/m^2)	25.3 (4.9)	24.6 (4.6)	28.7 (5.3)	<0.001
Graft rank (%)				0.121
0	1532 (85.1)	1254 (84.4)	253 (89.1)	
1	227 (12.6)	194 (13.1)	29 (10.2)	
2	39 (2.2)	36 (2.4)	2 (0.7)	
3	2 (0.1)	2 (0.1)	0 (0.0)	
Perfusion machine (%)	266 (14.8)	174 (11.7)	92 (32.4)	<0.001
Double transplantation (%)	26 (1.4)	16 (1.1)	10 (3.5)	0.004
Recipients characteristics at 3 months				
SBP (mmHg)	138.4 (15.9)	137.2 (15.3)	145.1 (17.1)	<0.001
DBP (mmHg)	78.8 (10.6)	79.3 (10.4)	75.3 (11.2)	<0.001
PP (mmHg)	59.7 (15.2)	57.9 (14.1)	69.8 (17.1)	<0.001
DGF (%)	335 (18.6)	247 (16.6)	80 (28.2)	<0.001
eGFR MDRD (mL/min/1.73 m^2)	51.7 (19.6)	52.1 (19.6)	47.8 (19.5)	0.002
Proteinuria (g/day)	0.78 (8.11)	0.82 (8.95)	0.59 (0.63)	0.724
Tacrolimus (%)	878 (56.0)	712 (54.3)	165 (71.7)	<0.001
Cyclosporine (%)	621 (39.6)	543 (41.4)	53 (23.0)	<0.001
Steroids (%)	1501 (95.8)	1261 (96.2)	221 (96.1)	1.000
MMF (%)	1286 (82.0)	1073 (81.8)	209 (90.9)	0.001
Azathioprine (%)	235 (15.0)	199 (15.2)	15 (6.5)	0.001
m-TOR inhibitors (%)	101 (6.4)	85 (6.5)	16 (7.0)	0.895
Thymoglobulin (%)	958 (53.3)	803 (54.1)	131 (46.1)	0.017
IL2-R antibodies (%)	815 (45.5)	660 (44.6)	153 (54.1)	0.004
RI	0.69 (0.08)	0.68 (0.08)	0.76 (0.07)	<0.001
RI ≥0.75 (%)	473 (26.3)	302 (20.3)	167 (58.8)	<0.001

Values are mean (SD) or absolute number (percentage) of patients.
m-TOR, Mammalian target of rapamycin; MMF, mycophenolate mofetil.

Therefore, if kidney transplantation in a diabetic environment may modify RI, then it is important to assess whether it also alters its predictive value on the risk of death.

In this study, we analysed RI early after transplantation, including the RI–age and RI–arterial pressure relationships, and we assessed its long-term predictive value for death with a functioning graft (DWFG) in a large cohort of diabetic and non-diabetic renal transplant recipients followed for up to 30 years.

MATERIALS AND METHODS

Patient selection

We conducted a retrospective analysis of 2362 consecutive patients who received a renal transplant from October 1985 to October 2017 at the Tours University Hospital, France. Some patients were transplanted more than once and were followed-up for each transplantation. Among them, 113 died or returned to dialysis within the first 3 months following transplantation, 422 patients were excluded because renal Doppler ultrasonography at 3 months was not available and 27 were excluded because of a diagnosis of renal artery stenosis. Thus, 1800 patients were included in this study. Data were collected from the prospectively maintained institutional database of transplant patients of our hospital and the ASTRE database ['commission nationale informatique et liberté' (CNIL) agreement number: DR-2012-518]. The study protocol was validated by the Ethics Committee in Human Research (Hôpital Bretonneau, CHU Tours, France) and is in accordance with the Helsinki declaration of 1975, as revised in 2013.

Table 2. Baseline characteristics stratified with RI as a binary variable

	RI <0.75	RI ≥ 0.75	P-value
Total patients	1327	473	
Donor characteristics			
Cardiovascular death (%)	667 (57.3)	323 (71.1)	<0.001
Deceased donor (%)	1242 (93.6)	463 (97.9)	0.001
Donor age (years)	47.0 (16.6)	62.3 (15.4)	<0.001
Donor with diabetes (%)	50 (3.8)	51 (10.8)	<0.001
Donor gender (% male)	801 (60.4)	275 (58.1)	0.429
Cold ischaemia (h)	17.7 (8.1)	18.0 (7.1)	0.458
Recipient characteristics at time of transplantation			
Diabetes (%)	117 (9.0)	167 (35.6)	<0.001
NODAT (%)	157 (12.1)	64 (13.6)	0.424
Haemodialysis time (years)	3.03 (3.58)	2.87 (2.92)	0.380
Age (years)	46.79 (14.01)	63.36 (9.47)	<0.001
Year of transplantation (%)			<0.001
1985–89	40 (3.0)	5 (1.1)	
1990–99	219 (16.5)	51 (10.8)	
2000–09	513 (38.7)	134 (28.3)	
2010–17	555 (41.8)	283 (59.8)	
Gender (% male)	858 (64.7)	287 (60.7)	0.136
BMI (kg/m^2)	24.71 (4.70)	26.84 (5.14)	<0.001
Graft rank (%)			0.542
0	1126 (84.9)	406 (85.8)	
1	167 (12.6)	60 (12.7)	
2	32 (2.4)	7 (1.5)	
3	2 (0.2)	0 (0.0)	
Perfusion machine (%)	123 (9.3)	143 (30.2)	<0.001
Double transplantation (%)	13 (1.0)	13 (2.7)	0.011
Recipients characteristics at 3 months			
SBP (mmHg)	136.9 (14.9)	143.1 (17.7)	<0.001
DBP (mmHg)	80.4 (10.1)	73.9 (10.8)	<0.001
PP (mmHg)	56.4 (13.1)	69.2 (16.8)	<0.001
DGF (%)	212 (16.0)	123 (26.0)	<0.001
eGFR MDRD (mL/min/1.73 m^2)	54.0 (20.1)	44.8 (16.1)	<0.001
Proteinuria (g/day)	0.87 (9.53)	0.55 (0.56)	0.566
Tacrolimus (%)	629 (53.7)	249 (62.7)	0.002
Cyclosporine (%)	503 (43.0)	118 (29.7)	<0.001
Steroids (%)	1121 (95.8)	380 (95.7)	1.000
MMF (%)	947 (80.9)	339 (85.4)	0.051
Azathioprine (%)	193 (16.5)	42 (10.6)	0.006
m-TOR inhibitors (%)	59 (5.0)	42 (10.6)	<0.001
Thymoglobulin (%)	723 (54.6)	235 (49.7)	0.076
IL2-R antibodies (%)	581 (43.9)	234 (49.7)	0.036
RI	0.66 (0.06)	0.79 (0.04)	<0.001

Values are mean (SD) or absolute (percentage) of patients. MMF, mycophenolate mofetil; m-TOR, Mammalian target of rapamycin.

Visits to our hospital for the follow-up were organized as follows: three visits per week during the first 2 weeks; two visits per week during the first year; one visit every other month during the second year; and three visits per year thereafter until death or ESRD (i.e. dialysis or re-transplantation).

At the time of transplantation, the following variables were reviewed: donor age, gender, diabetes, double or single transplantation, machine perfusion, recipient age, gender, diabetes, graft rank, body mass index (BMI) and haemodialysis time before transplantation. At the 3-month visit after transplantation, the following variables were reviewed: systolic, diastolic and pulse arterial pressure, serum creatinine level, estimated glomerular filtration rate (eGFR) (using modification of diet in renal disease (MDRD) equation), proteinuria (by a 24-h urine collection [17]) immunosuppressive induction and maintenance treatments, delayed graft function (DGF) after transplantation and renal RI. Regarding immunosuppressive induction, patients received T-cell depletion therapy or basiliximab according to the protocol of our service [systematic T-cell therapy in case of donor-specific antigen (DSA), donor cardiac arrest type Maastricht 2, according to immunological risk in other situations]. For double transplantation, RI was the mean of both left and right graft RI value. Recipient diabetes was defined as diabetes diagnosed before transplantation; therefore, it did not include new-onset diabetes after transplantation (NODAT). NODAT was defined according to the American Diabetes Association: symptoms of diabetes plus casual plasma glucose concentration >11.1 mmol/L, casual being defined as any time of day without regard to time since last meal; or fasting glucose >7 mmol/L, fasting being defined as no caloric intake for at least 8 h (oral glucose tolerance tests were not usually performed in our centre, because they are not recommended in routine practice). These criteria were confirmed by repeat testing on a different day. Cardiovascular death for the donor was defined as death from cardiac or cerebrovascular cause.

Doppler ultrasonography studies

For the measurement of renal RI, three ultrasound systems were used: Toshiba Aplio XG with PVT-375BT probe, Esaote Technos MPX with probe and Siemens Antares Premium Edition with CH5-2 probe with vascular programme for each exam [18]. All the observers were experienced as this parameter has been studied in our hospital since the early 1970s [19]. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured during Doppler ultrasonography spectral analysis in renal interlobar arteries at three different points of the kidney (upper, medium and lower). RI was calculated with PSV and EDV by the following equation:

$$RI = (PSV - EDV)/PSV$$

The mean of three consecutive measurements was used. Doppler ultrasonography studies were routinely performed at 3 months after transplantation. Renal artery stenosis was ruled out at the time of measurement [20, 21]. The results of other Doppler studies were not considered in this report.

Statistical analyses

All the variables had a normal distribution. Results are expressed as percentages or means ± standard deviations. Qualitative variables were compared using Chi-square test. Continuous variables between two groups were compared using Student *t*-test, after verifying equal standard deviations in each group.

The patients were stratified in two groups: RI of 0.75 or higher and RI of <0.75. Indeed, studies consider 0.70 as the upper threshold of normal RI [22, 23], whereas others showed that a RI ≥0.75 or 0.80 was associated with poor allograft survival and death [2, 24, 25]. Sensitivity analyses were also performed with different thresholds.

In order to find potential confounding factors, characteristics of diabetic recipients and non-diabetic recipients were compared. To assess colinearity among the variables, we used Pearson correlation.

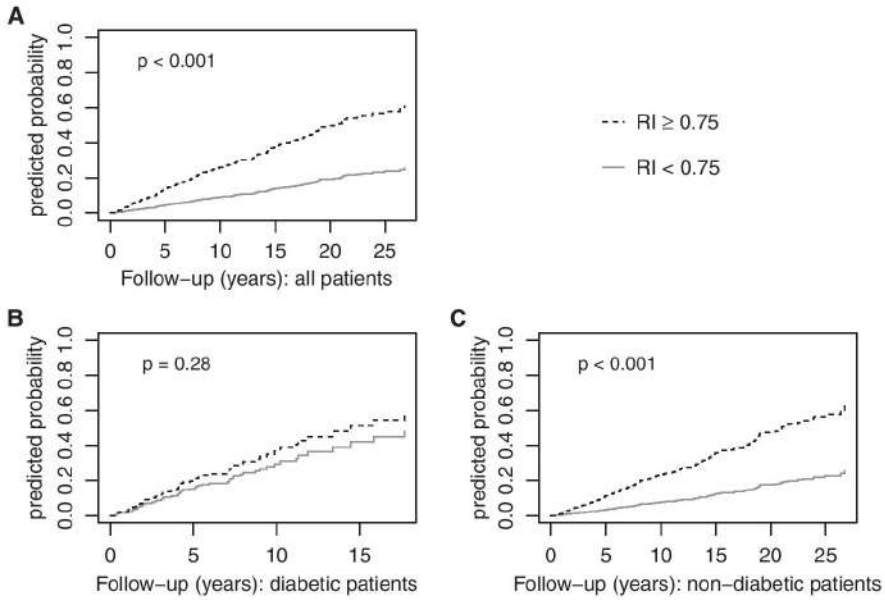

FIGURE 1: Cumulative incidence curve for DWFG according to RI at 3 months in all patients (**A**), in patients with pre-transplant diabetes (**B**) and in non-diabetic patients (**C**).

For survival analysis, the event of interest was DWFG. As graft losses (i.e. dialysis or re-transplantation) are events that hinder the observation of the event of interest, and are competing risks, we used the cumulative incidence competing risk method. To assess the association between RI at 3 months and the risk of DWFG, we compared cumulative incidence functions, using the subdistribution hazard approach proposed by Fine and Gray [26] in univariate and multivariate analysis, after analysing the effect of multiple variables on the risk of DWFG to choose the confounding factors.

A $P < 0.05$ was considered statistically significant. Analyses were performed using the statistical software RStudio (RStudio Team, 2015, v1.0.153).

RESULTS

Baseline characteristics

Among these 1800 renal transplant recipients, 284 (15.7%) had diabetes mellitus before transplantation (diabetes status was missing in 30 renal transplant recipients). Among them, 111 (42.2%) had an RI of ≤0.75 (Table 1). Overall, 1327 patients (73.7%) had an RI of ≤0.75 (Table 2). It was the first transplantation for 1532 patients (85.1%). A total of 1705 patients (94.7%) received a cadaveric graft and 990 (61.1%) received a kidney from a donor deceased from cardiovascular disease (Table 1). Regarding immunosuppression, induction was performed with anti-interleukin 2 receptor (IL2-R) (45.5%) or thymoglobulin (53.3%), and methylprednisolone 250 mg before and after transplantation. Maintenance immunosuppressive treatment included prednisone with a gradual tapering and mycophenolate mofetil (82.0%) or azathioprine (15.0%), associated with ciclosporin (39.6%), tacrolimus (56.0%) or mammalian-target of rapamycin inhibitors (6.4%) (Table 1).

RI and the risk of DWFG

Univariate analysis. Median follow-up was 6.35 years (range 0.25–30.9 years; total observation period: 14 202 patient years). During follow-up, 61/284 (21.4%) of patients with pre-transplant diabetes and 172/1486 (11.5%) of non-diabetic patients died, whereas 354 patients returned to dialysis or had a new transplantation.

RI ≥0.75 was associated with a greater risk of DWFG [hazard ratio (HR) = 3.18, 95% confidence interval (CI) 2.46–4.10; $P < 0.001$] (Figure 1A). This was also true in non-diabetic patients (HR = 3.33, 95% CI 2.45–4.54; $P < 0.001$) (Figure 1B), but not in patients with pre-transplant diabetes (HR = 1.32, 95% CI 0.80–2.20; P = 0.28) (Figure 1C).

Pre-transplant diabetes was associated with a greater risk of DWFG (HR = 3.24, 95% CI 2.41–4.36; $P < 0.001$).

DWFG was also significantly associated in univariate analysis with donor cardiovascular death, donor age, use of machine perfusion, double transplantation, haemodialysis time, age, BMI, high systolic and PP, low diastolic blood pressure (DBP), low eGFR and DGF (Table 3).

These results remained unchanged when the variables were considered dichotomous rather than continuous (Table 3).

Multivariate analysis. A correlation of more than 0.7 was found between recipient age and donor age ($r = 0.803$), and between systolic arterial pressure and PP at 3 months ($r = 0.779$). Therefore, donor age and systolic blood pressure (SBP) were removed from the analysis.

In multivariate analyses, after multiple adjustments, the results remained unchanged: high RI was a strong predictor of DWFG in non-diabetic recipients (HR = 2.18, 95% CI 1.41–3.36; $P < 0.001$), but not in patients with pre-transplant diabetes (HR = 1.19, 95% CI 0.53–2.68; P = 0.670) (Table 4).

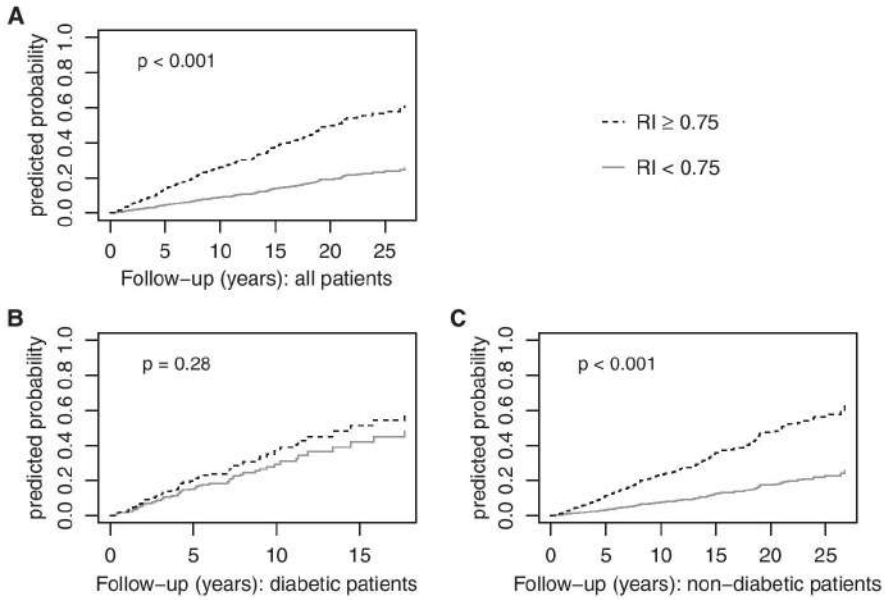

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Table 3. Determinants of DWFG in univariate analysis

	HR (95% CI)	P-value
Donor characteristics		
Cardiovascular death	1.50 (1.12–2.00)	0.006
Donor with diabetes	1.18 (0.63–2.19)	0.610
Donor gender (male)	0.97 (0.75–1.27)	0.850
Donor age (per 10 year increase)	1.31 (1.21–1.43)	<0.001
Donor age >60 years	1.85 (1.45–2.36)	<0.001
Cold ischaemia (per 1 h increase)	1.00 (0.99–1.02)	0.57
Recipients characteristics at time of transplantation		
Diabetes	3.24 (2.41–4.36)	<0.001
NODAT	0.84 (0.59–1.2)	0.34
Haemodialysis time >1 year	1.42 (1.03–1.96)	0.033
Haemodialysis time (per 1 year increase)	1.03 (1.01–1.06)	0.018
Age (per 10 year increase)	1.92 (1.72–2.15)	<0.001
Age >60 years	3.68 (2.87–4.72)	<0.001
Male gender	1.27 (0.98–1.66)	0.076
BMI >25	1.59 (1.23–2.06)	<0.001
BMI (per 5 point increase)	1.3 (1.15–1.48)	<0.001
Year of transplantation (ref = 1985–89)		
1990–99	0.99 (0.60–1.66)	0.980
2000–09	1.07 (0.67–1.72)	0.770
2010–17	1.48 (0.88–2.47)	0.130
Double transplantation	2.75 (1.08–7.03)	0.035
Perfusion machine	2.72 (1.73–4.30)	<0.001
Recipients characteristics at 3 months		
SBP >140 mmHg	1.62 (1.25–2.10)	<0.001
SBP (per 10 mmHg increase)	1.14 (1.06–1.22)	<0.001
DBP >90 mmHg	0.52 (0.28–0.95)	0.033
DPB (per 10 mmHg increase)	0.88 (0.78–0.98)	0.022
PP >50 mmHg	1.98 (1.46–2.68)	<0.001
PP (per 10 mmHg increase)	1.24 (1.15–1.33)	<0.001
eGFR <45 mL/min	1.36 (1.05–1.76)	0.019
eGFR MDRD (per 10 mL/min/1.73 m^2 increase)	0.90 (0.84–0.98)	0.016
Tacrolimus	1.30 (0.99–1.70)	0.052
IL2-R antibodies	1.23 (0.45–1.63)	0.130
DGF	1.38 (1.02–1.86)	0.035
RI ≥0.75	3.18 (2.46–4.10)	<0.001
RI >0.70	2.88 (2.21–3.75)	<0.001
RI >0.80	2.70 (1.92–3.81)	<0.001
RI (per 0.1 increase)	2.25 (1.91–2.65)	<0.001

RI as a continuous variable was similarly a strong predictor of DWFG in non-diabetic recipients (HR per 0.1 increase = 1.71, 95% CI 1.27–2.30; P < 0.001), but not in patients with pre-transplant diabetes (HR per 0.1 increase = 0.97, 95% CI 0.57–1.64; P = 0.910).

Sensitivity analysis

Results were similar when using different thresholds for RI (0.70 and 0.80) (Supplementary data, Table S1). We also performed the same analysis with patients transplanted after Year 2000. Among our 1800 patients, 1485 were transplanted after Year 2000 and 263 of them had pre-transplant diabetes (Supplementary data, Table S2).

RI ≥0.75 was also a strong predictor of DWFG in this population (Supplementary data, Table S3).

Finally, as 14.9% of patients had previously been transplanted, we performed the same analysis only with first transplantations, and the results remained unchanged (Supplementary data, Tables S4 and S5).

RI and all mortality

We also analysed all-cause death in diabetic and non-diabetic transplant recipients. Therefore, we performed a Kaplan–Meier analysis with death in all patients whether they lost their graft or not. RI ≥0.75 was associated with a greater risk of death in non-diabetic patients (HR = 3.87, 95% CI 2.91–5.13; P < 0.001) (Supplementary data, Figure S1A) but not in patients with pre-transplant diabetes (HR = 1.46, 95% CI 0.90–2.37; P = 0.128) (Supplementary data, Figure S1B).

RI in diabetic and non-diabetics recipients and interaction with recipient age and PP

RI at 3 months was higher in diabetics than in non-diabetic subjects (0.76 ± 0.07 versus 0.68 ± 0.08, P < 0.001) (Table 1). RI ≥0.75 was found in 58.8% of diabetic recipients, and in 20.3% of non-diabetic recipients (P < 0.001) (Table 1).

RI at 3 months increased with age (Figure 2A). Nevertheless, the slope between recipient age and RI value was not steeper in patients with pre-transplant diabetes, but the curve started at a higher level, indicating there was no interaction between diabetes and age (P = 0.47).

There was also no interaction between diabetes and SBP (P = 0.25) (Figure 2B), or between diabetes and DBP (P = 0.57) (Figure 2C).

However, we found an interaction between diabetes and PP (P = 0.042). Indeed, the augmentation of RI with PP was less important in patients with pre-transplant diabetes than in non-diabetic patients (Figure 2D).

DISCUSSION

The main result of our study is that high RI is a powerful predictor of DWFG in non-diabetic patients receiving a renal transplant, but that there is no relationship between RI value and the risk of DWFG in diabetic patients receiving a renal transplant. These results were confirmed after multiple adjustments.

Many studies have suggested that RI is related to systemic vascular alterations, and poorly associated with renal vascular resistance [7, 12, 27]. Some authors observed that it was increased in patients with atherosclerosis, and with diabetic nephropathy [15, 16]. Diabetic patients who undergo renal transplantation have suffered for years from chronic glucotoxicity, and therefore suffer from the vascular consequences of increased production of advanced glycation end products [28]. These complications imply both systemic and renal vascularization; hence, the impact on RI, even though we do not know whether it is due to renal or systemic modifications. In this study, we observed that RI was higher in patients with pre-transplant diabetes than in non-diabetic patients, independently of other parameters. This seems consistent with the fact that RI is related to systemic vascular alterations. We also confirmed that pre-transplant diabetes was a strong predictor of DWFG, which seemed obvious given the vascular and renal complications linked to this disease.

Age and PP are known to be strong determinants of RI [7, 11, 12]. Patients with pre-transplant diabetes were older at the time of graft. However, there was no interaction between

Table 4. Determinants of DWFG in multivariate analysis with RI as a binary variable and as a continuous variable

	All patients		Patients with pre-transplant diabetes		Non-diabetic patients	
	HR	P-value	HR	P-value	HR	P-value
RI as a binary variable						
RI ≥0.75	1.90	0.001	1.19	0.670	2.18	<0.001
Donor cardiovascular death	1.19	0.290	2.14	0.068	1.02	0.940
Haemodialysis time >1 year	1.54	0.036	1.20	0.680	1.62	0.041
Age >60 years	2.17	<0.001	1.71	0.160	2.39	<0.001
BMI >25	0.94	0.730	0.78	0.480	0.98	0.900
DFG <45 mL/min	0.93	0.660	0.83	0.500	0.96	0.840
DGF	1.19	0.340	1.35	0.360	1.16	0.510
PP >50 mmHg	1.21	0.340	0.56	0.810	1.20	0.390
DBP >90 mmHg	0.78	0.490	0.69	0.710	0.65	0.320
Double transplantation	1.35	0.620	1.24	0.770	1.09	0.900
Perfusion machine	1.58	0.099	2.27	0.045	1.44	0.350
Diabetes	1.51	0.043				
RI as a continuous variable						
RI (per 0.1 increase)	1.51	0.003	0.97	0.910	1.71	<0.001
Donor cardiovascular death	1.16	0.37	2.14	0.071	0.97	0.870
Haemodialysis time >1 year	1.48	0.059	1.20	0.670	1.52	0.076
Age >60 years	2.21	<0.001	1.88	0.061	2.36	<0.001
BMI >25	0.92	0.62	0.77	0.460	0.93	0.700
DFG <45 mL/min	0.91	0.56	0.81	0.460	0.96	0.840
DGF	1.20	0.32	1.35	0.370	1.18	0.450
PP >50 mmHg	1.15	0.49	0.92	0.870	1.12	0.600
DBP >90 mmHg	0.81	0.55	1.23	0.760	0.71	0.420
Double transplantation	1.40	0.57	1.27	0.840	1.23	0.760
Perfusion machine	1.58	0.098	2.33	0.040	1.45	0.330
Diabetes	1.52	0.040				

A correlation of >0.5 was found between recipient age and donor age, and between systolic arterial pressure and PP at 3. Therefore, donor age and SBP were removed from the analysis months.

recipient age and diabetes: the age–RI slope was not steeper in diabetic than in non-diabetic subjects. Patients with pre-transplant diabetes also had higher PP than non-diabetic patients. Moreover, we found an interaction between RI and PP: the augmentation of RI with PP was less important in patients with pre-transplant diabetes. The augmentation of RI in diabetic patients may be less important because RI is higher than in non-diabetic patients, due to increased aortic stiffness. Diabetic patients also have increased mortality due to cardiovascular damages. This could explain the absence of prognostic value of RI in patients with pre-transplant diabetes.

Our study confirmed the fact that RI was a predictor of DWFG in renal transplant recipients in general, but it appears that it is not a predictor of DWFG in patients with pre-transplant diabetes. We also found the same results when analysing death in all patients even those who had returned to dialysis after allograft failure. It is important to note that similar findings were confirmed when RI was considered as a continuous variable or as a dichotomous variable, in univariate and in multivariate analyses, and with different thresholds. Moreover, because the profile of renal transplant recipients changed over the years, and that very few diabetic were transplanted before Year 2000, we confirmed our results in patients who were transplanted after Year 2000.

We confirmed that RI is higher in patients with pre-transplant diabetes, and that it should be linked to systemic vascular alterations due to diabetes. One could imagine that high RI is a good predictor of death because it is linked to systemic vascular alterations and atherosclerosis, and so that patients with a high RI have a high cardiovascular risk. Patients with pre-transplant diabetes also have a high cardiovascular risk, and hence have a higher risk of death than non-diabetic patients, regardless of the RI value. However, the reason why some diabetic patients have low RI is not known.

Our study has many strength. As far as we know, the respective prognostic value of RI in diabetic or non-diabetic patients has never been studied. It represents one of the largest cohorts of renal transplant recipients focused on the mechanism of increased RI in diabetic patients. The follow-up was long (up to 30 years). Regarding Doppler indices, these parameters are measured in routine practice and have been studied in our hospital since the early 1970s [19].

This study also has limitations. It is a retrospective monocentric study, and therefore our findings would need to be replicated. The number of patients with pre-transplant diabetes was lower than non-diabetic patients, and the number of events in this group is limited. Regarding the number of events, we forced variables in the diabetes multivariate model to match the non-diabetic group, knowing that it could over-stretch the model, but we verified that the results remained the same when doing a stepwise analysis. We did not differentiate cardiovascular and non-cardiovascular death: the difference in the prognostic value of RI between diabetic and non-diabetic renal transplant recipients may be less or more pronounced for cardiovascular death. This point could help explain the prognostic value of RI and would need further study. Then, we had missing data

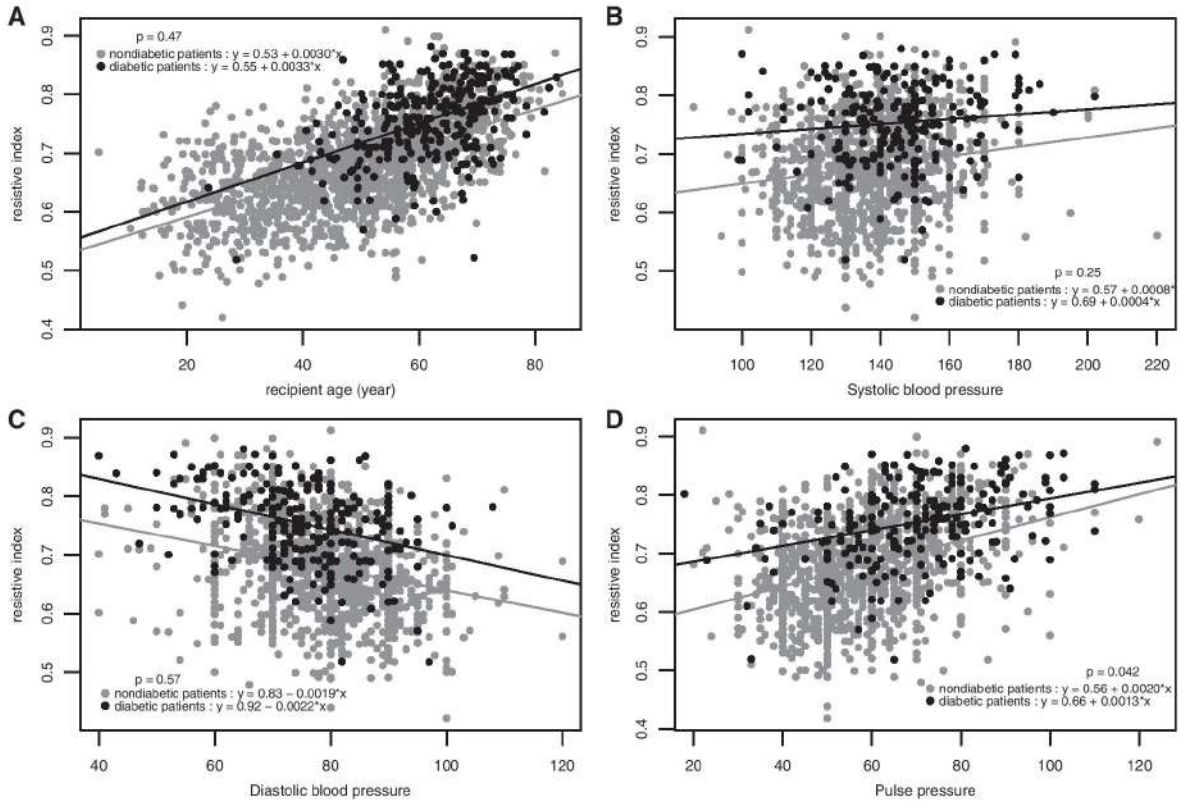

FIGURE 2: RI in diabetic and non-diabetic recipients and interaction with recipient age (**A**), SBP (**B**), DBP (**C**) and PP (**D**).

concerning cardiovascular and peripheral vascular history of patients in 92% of patients, which are potential confounders for RI [29]. As these data were only available in our cohort from 2016, and therefore in patients who were older, with a higher frequency of diabetes, and more extended criteria donors, the related biases were too important. We also lacked data regarding diabetes severity. Another limit is that we did not handle NODAT as a time-varying covariate, whereas it could have been legitimate because including time-dependent covariate in regression model for competing risks data may lead to biased results [30]. We discussed evaluating NODAT as a third group but we assumed that patients with NODAT did not suffer from vascular consequences of chronic glucotoxicity at the time of RI measurement and so belonged to the non-diabetic group. It was also not possible to provide the inter-observer variability of the RI measure, and given the long follow-up, RI was not always measured by the same person. However, some studies have shown a good reproducibility of this measure [31, 32].

In conclusion, our study confirms high RI as a strong predictor of DWFG in renal transplant patients, but it also clearly shows that RI constitutes a risk factor only in non-diabetic renal transplant recipients. These findings could be interesting for the management of transplanted patients with higher risk of death. Non-diabetic patients with high RI may benefit from intensive cardiovascular monitoring and optimization. Further studies are needed to evaluate this benefit.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

J.-B.deF. contributed to the conception of the work, analysis and interpretation of the data, drafting and revising of the article, and final approval of the version to be published. L.-M.V. contributed to the conception of the work, critical revision of the article and final approval of the version to be published. J.R., F.P., P.G., B.S., E.B., E.C., C.Barbet, H.L., E.M., C.Baron and M.B. contributed to the data collection, critical revision of the article and final approval of the version to be published. J.-M.H. contributed to the conception of the work, analysis and interpretation of the data, critical revision of the article and final approval of the version to be published.

CONFLICT OF INTEREST STATEMENT

The authors of this manuscript have no conflicts of interest to disclose as described by *Nephrology Dialysis Transplantation*.

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ARTICLE 2

Titre : Changements précoces de l'indice de résistance, diabète et mortalité en transplantation rénale: une étude de cohorte

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de Freminville, Jean-Baptiste, Louis-Marie Vernier, Jérome Roumy, Frédéric Patat, Philippe Gatault, Bénédicte Sautenet, Claire Geneste, Eloi Chevallier, Christelle Barbet, Hélène Longuet, Elodie Merieau, Christophe Baron, Matthias Büchler, and Jean-Michel Halimi. "Early changes in renal resistive index and mortality in diabetic and nondiabetic kidney transplant recipients: a cohort study." *Nephrology Dialysis Transplantation*, 2019 (manuscript number : NDT-01336-2019)

Question posée :

Nous avons donc montré dans l'article précédent que l'indice de résistance était associé à la mortalité chez les patients non diabétiques, mais pas chez les patients diabétiques. Cette absence de valeur pronostique chez les patients diabétiques pourrait s'expliquer par une relation différente entre l'âge et le RI ou entre la pression pulsée et le RI selon le statut diabétique ou non des patients.

Le moment de la mesure du RI dans les différentes études étudiant son impact pronostique est très variable. Certaines études ont par ailleurs montré que sa variation pourrait avoir un impact pronostique intéressant.

Nous avons donc étudié l'association entre la variation de l'indice de résistance entre 1 et 3 mois et la mortalité chez les patients transplantés rénaux diabétiques et non diabétiques.

Introduction

Kidney transplantation is unquestionably the best treatment of end-stage renal disease (ESRD), but kidney transplant recipients have a higher mortality rate than the general population (3). In a seminal study, Radermacher et al. found that high renal Resistive Index (RI) measured at least 3 months after renal transplantation was associated with an increased risk of death (4). However, the timing of RI measurements in this study was very variable, with a median of 40 months. Naesens et al. confirmed its predictive value on the risk of death in renal transplantation at different time-points (3, 12 and 24 months) (5).

However, some caution may be applied regarding the use of RI to assess the risk of death. First, we reported that high RI at 3 months was not associated with an increased risk of death in a large cohort of diabetic renal transplant recipients (RTR), so the prognostic value of RI may be different in diabetic as compared to nondiabetic RTR (2). Second, the timing of RI measurement may impact its prognostic value: it was demonstrated that RI measured on the early post-transplant period (between the second and fourth day after transplantation) (6), and RI measured before 12 months after transplantation, were not associated with the risk of death in some studies (14). These findings may suggest that the RI value can change overtime in some patients, and that one single measurement may be insufficient to accurately evaluate the risk of death.

In the present study, we analysed RI changes between 1 month and 3 months after transplantation, and we assessed its long-term predictive value for death with a functioning graft (DWFG) in a large cohort of diabetic and non-diabetic renal transplant recipients followed up to 30 years.

Materials and Methods

Patient selection

We conducted a retrospective analysis of 2362 consecutive patients who received a renal transplant from October 1985 to October 2017 at the Tours University Hospital, France. Among them, 113 died or returned to dialysis within the three first months following transplantation, 537 patients were excluded because renal Doppler ultrasonography at 1 month or at 3 months after transplantation was not available, and 27 were excluded because of a diagnosis of renal artery stenosis. Thus, 1685 patients were included in this study. Data were collected from the prospectively maintained institutional database of transplant patients of our hospital and the ASTRE database [“commission nationale informatique et liberté” (CNIL)

agreement number: DR-2012-518]. The study protocol was validated by the Ethics Committee in Human Research (Hôpital Bretonneau, CHU Tours, France) and is in accordance with the Helsinki declaration of 1975, as revised in 2013.

Visits in our hospital for the follow-up were organized as follows: three visits per week during the first 2 weeks; two visits per week during the first month; one visit per week during the three first months; one visit per month during the first year; one visit every other month during the second year; three visits per year thereafter until death, or ESRD (i.e., dialysis or re-transplantation).

At the time of transplantation, the following variables were reviewed: donor age, gender, diabetes, double or single transplantation, machine perfusion; recipient age, gender, diabetes, graft rank, body mass index (BMI), hemodialysis time before transplantation. At the 3-month visit after transplantation, the following variables were reviewed: systolic, diastolic and pulse arterial pressure, serum creatinine level, estimated glomerular filtration rate (eGFR) (using MDRD equation), proteinuria (by a 24-h urine collection(21)) immunosuppressive induction and maintenance treatments, delayed graft function (DGF) after transplantation, and RI. Regarding immunosuppressive induction treatment, patients received T-cell depletion therapy or basiliximab according to the protocol of our service (systematic T-cell therapy in case of Donor Specific Antigen (DSA), donor cardiac arrest type Maastricht 2, according to immunological risk in other situations). For double transplantation, RI was the mean of both left and right graft RI value. Recipient diabetes was defined as diabetes diagnosed before transplantation; therefore, it did not include new-onset diabetes after transplantation (NODAT). NODAT was defined according to the American Diabetes Association (ADA): symptoms of diabetes plus casual plasma glucose concentration > 11.1 mmol/L, casual being defined as any time of day without regard to time since last meal or fasting glucose > 7 mmol/l, fasting being defined as no caloric intake for at least 8 h (oral glucose tolerance tests were not usually performed in our centre, because they are not recommended in routine practice). These criteria were confirmed by repeat testing on a different day. Cardiovascular death for the donor was defined as death from cardiac or cerebrovascular cause.

Doppler ultrasonography studies

For the measurement of renal RI, three ultrasound systems were used: Toshiba Aplio XG with PVT-375BT probe, Esaote Technos MPX with probe and Siemens Antares Premium Edition with CH5-2 probe with vascular programme for each exam(22). All the observers were experimented as this parameter is studied in our hospital since the early seventies(23).

Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured during Doppler ultrasonography spectral analysis in renal interlobar arteries at three different points of the kidney (upper, medium and lower). RI was calculated with PSV and EDV by the following equation:

$$RI = (PSV - EDV) / PSV$$

The mean of three consecutive measurements was used. Doppler ultrasonography studies were routinely performed at 3 months after transplantation. Renal artery stenosis was ruled out at the time of measurement (24,25). The results of other Doppler studies were not considered in this report.

Statistical analyses

All the variables had a normal distribution. Results are expressed as percentages or means ± standard deviations. Qualitative variables were compared using Chi-square test. Continuous variables were compared between two groups using Student t test and between multiple groups using analysis of variance (ANOVA), after verifying equal standard deviations in each group.

The patients were stratified in four groups depending on the value of RI at 1 month and at 3 months after transplantation. We used 0.70 as cut-off because it was the closest value from the mean and the median of RI in our cohort. Moreover, studies consider 0.70 as the upper threshold of normal RI (26,27), whereas others showed that a RI greater than 0.75 or 0.80 was associated with death (4,28,29). We used 0.75 as cut-off in sensitivity analyses. We did not use 0.80 as a cut-off because too few patients had a RI of more than 0.80.

To assess colinearity among the variables, we used Pearson correlation.

For survival analysis, the event of interest was death with a functioning graft (DWFG). As graft loss (i.e. dialysis or re-transplantation) are events that hinder the observation of the event of interest, and are competing risks, we used the cumulative incidence competing risk (CICR) method. To assess the association between RI at 1 month and 3 months and the risk of DWFG, we compared cumulative incidence functions, using the subdistribution hazard approach proposed by Fine and Gray (30) in univariate and multivariate analysis, after analyzing the effect of multiple variables on the risk of DWFG, in order to choose the confounding factors. We also assessed RI at 1 month and RI at 3 months after transplantation

as continuous variables in splines-based hazard ratio curves (35).

A p value < 0.05 was considered statistically significant. Analyses were performed using the statistical software RStudio (RStudio Team, 2015, v1.0.153).

Results

Baseline characteristics

Median follow-up was 6.36 years (0.25 to 30.9 years; total observation period: 13,427 patient years).

Among these 1685 renal transplant recipients, 821 patients (48.7%) at 1 month, and 877 patients (52.0%) at 3 months had a RI of less than 0.70 (Table 1). 263 patients had pre-transplant diabetes. It was the first transplantation for 1433 patients (85.0%). 1590 patients (94.4%) received a cadaveric graft and 924 (61.4%) received a kidney from a donor deceased from cardiovascular disease (Table 1). Regarding immunosuppression, induction was performed with anti-interleukin 2 receptor (44.3%) or thymoglobulin (54.4%), and methylprednisolone 250 mg before and after transplantation. Maintenance immunosuppressive treatment included prednisone with a gradual tapering and mycophenolate mofetyl (81.0%) or azathioprine (15.9%), associated with ciclosporin (39.8%), tacrolimus (55.9%) or mammalian target of rapamycin (m-TOR) inhibitors (6.6%) (Table 1).

RI at 1 and 3 months and the risk of death with functioning graft in the whole population and in patients with diabetes mellitus

In the whole population, RI (used as categorical parameter) at 1 month (hazard ratio (HR)=1.93, [95% confidence interval (95%CI)=1.65–2.24], p<0.001) and at 3 months (HR=2.27, [1.91–2.69], p<0.001) were both associated with an increased risk of DWFG (Table 2). When RI was used as a continuous parameter, we observed that the risk of death increased with increasing RI value both at 1 month (Figure 1a) and 3 months (Figure 1b) in the whole population.

Pre-transplant diabetes was associated with an increased risk of DWFG (HR = 3.44, [2.52-4.70], p<0.001) (Table 2). RI (used as a continuous variable) measured at 1 (Figure 2a) and 3 months (Figure 2b) was not associated with the risk of DFWG in patients with pretransplant diabetes.

Changes in RI value from 1 to 3 months and risk of death with a functioning graft in the whole population and in patients with pretransplant diabetes

Whole population

Individual changes in RI occurred between 1 and 3 months despite the fact that the mean RI value was almost identical at 1 month and 3 months after transplantation: among patients with RI<0.70 at 1 month, 160 (19.5%) had a RI≥0.70 at 3 months, and among patients with RI≥0.70 at 1 month, 216 (25%) had a RI<0.70 at 3 months (Table 1).

Overall, the best survival was observed in the group of patients with RI<0.70 both at 1 month and 3 months, and the worst survival was found in patients with RI≥0.70, both at 1 and 3 months (HR = 3.77, [2.71–5.24], p<0.001). The risk of DWFG was intermediate for patients with RI<0.70 at 1 month and RI≥0.70 at 3 months (HR = 2.15, [1.29-3.60], p=0.003) and in those with RI≥0.70 at 1 month and RI<0.70 at 3 months (HR = 1.90, [1.20-3.03], p=0.006) (Table 2) (Figure 3).

Consequently, based on the RI value at 1 month, 864/1685 (51.3%) patients would have been considered as “high risk” patients for the risk of DWFG (i.e. RI≥0.70); however, 216 (25.0%) of these 864 “high risk” patients were reclassified as “intermediate risk” patients using RI value both at 1 month and 3 months. Similarly, based on the RI value at 1 month, 821/1685 (48.7%) patients would have been considered as “low risk” patients (i.e. RI<0.70); however, 160 (19.5%) of these 821 “low risk” patients were reclassified as “intermediate risk” patients using both 1 month and 3 months RI values.

We also used multivariate analysis. A correlation of more than 0.7 was found between recipient age and donor age (r=0.807), and between systolic blood pressure and pulse pressure at 3 months (r=0.776). Therefore, donor age and systolic blood pressure were removed from the analysis.In multivariate analyses, after multiple adjustments: RI>0.70 at 1 months and 3 months (HR = 1.72, [1.07-2.79], p=0.026), as well as RI<0.70 at 1 month and ≥0.70 at 3 months (HR = 1.77, [1.02-3.07], p=0.044), but not RI≥0.70 at 1 months and <0.70 at 3 months (HR = 1.34, [0.76-2.37], p=0.310) remained a predictor of DWFG (Table 3).

Impact of pretransplant diabetes

The RI value changed between 1 and 3 months, but this change was different in diabetic and nondiabetic patients: among patients with RI<0.70 at 1 month, more diabetic than nondiabetic RTR had a RI value ≥0.70 at 3 months (48.6% vs 18.1%, p<0.001); in contrast, among patients with RI≥0.70 at 1 month, RI was <0.70 at 3 months in less diabetic than nondiabetic

patients (13.7% vs 28.5%, p<0.001).

Among diabetic RTR, RI≥0.70 at 1 month and 3 months, RI<0.70 at 1 month and ≥0.70 at 3 months and RI≥0.70 at 1 month and <0.70 at 3 months were not associated with an increased risk of DWFG in univariate analysis (Table 4a). In multivariate analysis, only the group of patients with RI<0.70 at 1 month and ≥0.70 at 3 months had an increased risk of DWFG (vs the group of patients with RI<0.70 both at 1 month and 3 months) (HR = 4.69, [1.07-20.52], p=0.040) (Table 4b).

Sensitivity analysis

Changes in RI value from 1 to 3 months and risk of DWFG graft using a threshold of 0.75

1217 patients (72.2%) at 1 month, and 468 patients (27.7%) at 3 months had a RI<0.75 (Table 1). Among patients with RI<0.75 at 1 month, 140 (11.5%) had a RI≥0.75 at 3 months, and among patients with RI≥0.75 at 1 month, 164 (35.0%) had a RI<0.75 at 3 months (Supplementary Table 1).

Best survival was also observed in patients with RI<0.75 at 1 month and 3 months after transplantation. RI>0.75 at 1 months and 3 months remained a predictor of DWFG (HR = 3.77, [2.73-5.21], p<0.001), as well as RI<0.75 at 1 month and ≥0.75 at 3 months (HR = 3.48, [2.33-5.18], p<0.001), and RI≥0.75 at 1 month and <0.75 at 3 months (HR = 2.53, [1.73-3.68], p<0.001).

In multivariate analyses: the risk of DWFG was associated with RI≥0.75 at 1 months and 3 months (HR = 1.72, [1.06-2.78], p=0.027) and increasing RI from 1 month to 3 months (HR = 2.30, [1.41-2.74], p<0.001) but not decreasing RI from 1 month to 3 months (HR = 1.45, [0.88-2.40], p=0.140) (Supplementary Table 2).

Based on the RI value at 1 month, 468/1685 (27.8%) patients would have been considered as “high risk” patients for the risk of death with functioning graft (i.e.RI≥0.75); however, 164 (35%) of these 468 “high risk” patients were reclassified as “intermediate risk” patients using RI values at 1 and 3 months. Similarly, based on the RI value at 1 month, 1217/1685 (72.2%) patients would have been considered as “low risk” patients (i.e. RI<0.75); however, 140 (11.5%) of these 1217 “low risk” patients were reclassified as “intermediate risk” patients using RI values at 1 and 3 months.

Discussion

In a recent study, we showed that RI measured at 3 months after kidney transplantation was a good predictor of death with functioning graft in nondiabetic patients but not in patients with pre-transplant diabetes. In the present study, we confirmed that RI as a continuous variable was correlated to DWFG, whether it is measured at 1 or 3 months after kidney transplantation. Then we showed that the short-term change in RI between 1 month and 3 months after transplantation was also associated with death with functioning graft. In diabetic patients the results were quite different. First, the relationship between RI at 1 month or at 3 months and the risk of DWFG was not the same in diabetic and in nondiabetic patients. Second, significantly more diabetic than nondiabetic patients with RI>0.70 at 1 month remained with RI>0.70 at 3 months whereas significantly less diabetic than nondiabetic patients with RI<0.70 at 1 month remained with a RI<0.70 at 3 months. Then, among diabetic patients, an increased risk of DWFG was observed only in those with low RI à 1 month and high RI at 3 months, indicating that the relationship between RI and DWFG was not similar in diabetic patients than in nondiabetic patients.

High RI is observed in patients with DGF, in acute rejection, and also in all causes of acute tubular necrosis (36). On the other hand, many studies suggest that RI is related to systemic vascular alterations, and poorly associated with renal vascular resistance (1,7,10,31). Some authors observed that it was increased in patients with atherosclerosis, and with diabetic nephropathy (19,20). Diabetic patients who undergo renal transplantation have suffered for years from chronic glucotoxicity, and therefore suffer from the vascular consequences of increased production of advanced glycation end products(32). These complications imply both systemic and renal vascularisation; hence, the impact on RI. In a previous study, we showed that RI does not have the same prognostic value in diabetic patients receiving a kidney transplant (2). Indeed, in the present study, we found a very different association between RI as a continuous variable and the risk of DWFG, which confirms that RI is more difficult to interpret in patients with pre-transplant diabetes.

In our previous studies, we only analysed RI measured at 3 months after kidney transplantation. The prognostic value of resistance index after kidney transplantation is well-known, but authors diverge on the best timing of the RI measurement (6,14,37). Some authors also found that the variation of RI would be of interest (38). In the present study, we analysed the variation of RI between 1 and 3 months after kidney transplantation. We found that the variation of RI could refine its prognostic value. Indeed, in all patients, compared to low RI at 1 month and 3 months, high RI at 1 month and 3 months was always associated with a higher

risk of DWFG. Increasing RI (meaning low RI at 1 month and high RI at 3 months) was also always associated with a higher risk of DWFG. On the other hand, depending on the cut-off, decreasing RI (meaning high RI at 1 month and low RI at 3 months) could be of better prognosis, as it was not always associated with a higher risk of DWFG.

Moreover, in patients with pre-transplant diabetes, only increasing RI was associated with a higher risk of DWFG in multivariate analyses. In our previous study (2), we found that RI at 3 months was not a good predictor of DWFG in patients with pre-transplant diabetes. We hypothesized that the increase of RI was less important in diabetic patients because RI was higher in diabetic patients than in non-diabetic patients, due to aortic stiffness, and that it could explain the absence of prognostic value of RI in patients with pre-transplant diabetes. However, in the present study, in patients with pre-transplant diabetes, increasing RI was associated with DWFG, which means that patients with a low RI at 1 month and high RI at 3 months had a worst prognosis than others. In this way, the evolution of RI between 1 month and 3 months refines its prognostic value.

Our study has many strengths. It represents one of the largest cohorts of renal transplant recipients focused on RI variations early after transplantation. The follow-up was long (up to 30 years). Regarding Doppler indices, there is a good expertise on measuring and studying this parameter, as these parameters are studied in our hospital since the early seventies (23).

It also has limitations. It is a retrospective monocentric study, and therefore our findings would need to be replicated. The number of patients with pre-transplant diabetes was lower than non-diabetic patients, and the number of events in this group is limited. However, more than 250 diabetic patients were included in the present study. We did not differentiate cardiovascular and non-cardiovascular death: the difference in the prognostic value of RI between diabetic and non-diabetic renal transplant recipients may be less or more pronounced for cardiovascular death. Then, we missed data concerning cardiovascular and peripheral vascular history of patients, which are potential confounders for RI (39). As these data were only available in our cohort from 2016, and therefore in patients older, with a higher frequency of diabetes, and more extended criteria donors, the related bias were too important. We also lacked data regarding diabetes severity. It was also not possible to provide the inter-observer variability of the RI measure, and given the long follow-up, RI was not always measured by the same person. However, some studies showed a good reproducibility of this measure (33,34).

In conclusion, our study indicates that high RI at different time early after transplantation is a

strong predictor of DWFG graft in renal transplant patients, but has a different interpretation in diabetic patients. It also refines its prognostic value by analysing its variation between 1 month and 3 months. These findings could be interesting in the management of patients early after transplantation. Non-diabetic patients with high RI at 1 month, 3 months, or both, as well as diabetic patients with increasing RI between 1 month and 3 months could benefit from intensive cardiovascular monitoring.

Tables et figures

Table 1. Baseline characteristics stratified with RI at 1 month and 3 months after transplantation

	Overall	RI<0.70 1 month RI<0.70 3 months	RI<0.70 1 month RI≥0.70 3 months	RI≥0.70 1 month RI<0.70 3 months	RI≥0.70 1 month RI≥0.70 3 months	p
Total patients	1685	661	160	216	648	
Donor characteristics						
Cardiovascular death (%)	924 (61.4)	296 (52.4)	103 (70.5)	110 (58.8)	415 (68.4)	<0.001
Deceased donor (%)	1590 (94.4)	606 (91.7)	150 (93.8)	203 (94.0)	631 (97.4)	<0.001
Donor age (years)	50.95 (17.54)	42.12 (15.65)	51.86 (16.09)	50.99 (15.36)	59.72 (15.87)	<0.001
Donor with diabetes (%)	95 (5.7)	14 (2.1)	3 (1.9)	13 (6.1)	65 (10.1)	<0.001
Donor gender (% Male)	1002 (59.5)	407 (61.6)	90 (56.2)	129 (59.7)	376 (58.0)	0.481
Cold Ischemia (hours)	17.81 (7.95)	17.36 (8.22)	17.41 (7.49)	17.59 (8.23)	18.43 (7.66)	0.085
Recipient characteristics at time of transplantation						
Diabetes (%)	263 (15.9)	19 (2.9)	18 (11.2)	31 (14.9)	195 (30.5)	<0.001
NODAT (%)	214 (12.9)	76 (11.7)	24 (15.1)	23 (11.1)	91 (14.2)	0.379
Hemodialysis time (years)	2.95 (3.34)	3.00 (3.83)	2.79 (2.95)	2.99 (3.33)	2.91 (2.90)	0.902
Age (years)	51.15 (14.78)	41.33 (12.69)	51.00 (12.45)	50.95 (12.88)	61.28 (10.47)	<0.001
Year of transplantation (%)						<0.001
1985-1989	44 (2.6)	23 (3.5)	3 (1.9)	6 (2.8)	12 (1.9)	
1990-1999	270 (16.0)	120 (18.2)	28 (17.5)	39 (18.1)	83 (12.8)	
2000-2009	584 (34.7)	257 (38.9)	69 (43.1)	70 (32.4)	188 (29.0)	
2010-2017	787 (46.7)	261 (39.5)	60 (37.5)	101 (46.8)	365 (56.3)	
Gender (% Male)	1074 (63.7)	440 (66.6)	99 (61.9)	149 (69.0)	386 (59.6)	0.019
BMI (kg/m2)	25.31 (4.88)	24.14 (4.59)	24.86 (4.95)	25.18 (4.67)	26.67 (4.91)	<0.001
Graft rank (%)						0.772
1	1433 (85.0)	551 (83.4)	139 (86.9)	187 (86.6)	556 (85.8)	
2	213 (12.6)	95 (14.4)	19 (11.9)	22 (10.2)	77 (11.9)	
3	37 (2.2)	14 (2.1)	2 (1.2)	7 (3.2)	14 (2.2)	
4	2 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	
Perfusion machine (%)	242 (14.4)	38 (5.7)	12 (7.5)	23 (10.6)	169 (26.1)	<0.001
Double transplantation (%)	26 (1.5)	2 (0.3)	3 (1.9)	3 (1.4)	18 (2.8)	0.004
DGF (%)	320 (19.0)	88 (13.3)	26 (16.2)	45 (20.8)	161 (24.8)	<0.001
Thymoglobulin (%)	915 (54.4)	373 (56.6)	89 (55.6)	115 (53.2)	338 (52.2)	0.422
IL2-R antibodies (%)	744 (44.3)	271 (41.2)	68 (42.8)	99 (45.8)	306 (47.4)	0.144
Recipients characteristics at 3 months						
SBP (mmHg)	138.54 (15.90)	135.58 (14.86)	135.69 (15.79)	136.80 (14.52)	143.10 (16.45)	<0.001
DBP (mmHg)	78.79 (10.57)	81.61 (10.03)	78.81 (9.24)	79.96 (9.35)	75.31 (10.88)	<0.001
PP (mmHg)	59.75 (15.19)	53.96 (12.32)	56.88 (13.79)	56.84 (11.93)	67.80 (15.90)	<0.001
eGFR (ml/min/1.73 m2)	51.39 (19.09)	56.89 (21.13)	49.71 (16.66)	51.10 (16.56)	45.94 (16.36)	<0.001
Proteinuria (g/day)	0.80 (8.39)	1.23 (13.41)	0.43 (0.41)	0.55 (0.87)	0.55 (0.70)	0.648
Tacrolimus (%)	823 (55.9)	315 (53.0)	68 (47.6)	109 (57.1)	331 (60.7)	0.010
Ciclosporine (%)	586 (39.8)	267 (44.9)	66 (46.2)	74 (38.7)	179 (32.8)	<0.001
Steroids (%)	1408 (95.7)	571 (96.1)	135 (95.1)	180 (94.2)	522 (95.8)	0.711
MMF (%)	1193 (81.0)	480 (80.8)	116 (81.1)	149 (78.0)	448 (82.2)	0.651
Azathioprine (%)	234 (15.9)	99 (16.7)	23 (16.1)	34 (17.9)	78 (14.3)	0.602
m-TOR inhibitors (%)	97 (6.6)	19 (3.2)	13 (9.1)	12 (6.2)	53 (9.7)	<0.001
Resistive index M1	0.70 (0.08)	0.63 (0.05)	0.65 (0.04)	0.73 (0.03)	0.77 (0.06)	<0.001
Resistive index M3	0.69 (0.08)	0.62 (0.05)	0.73 (0.03)	0.65 (0.04)	0.77 (0.05)	<0.001
Resistive index M1 > 0.70	864 (51.3)	0 (0.0)	0 (0.0)	216 (100.0)	648 (100.0)	<0.001
Resistive index M3 > 0.70	808 (48.0)	0 (0.0)	160 (100.0)	0 (0.0)	648 (100.0)	<0.001

Values are mean (SD) or absolute (percentage) of patients

NODAT : New Onset Diabetes After transplantation; DGF : Delayed Graft Function ; BMI : Body Mass Index ; SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular filtration Rate using MDRD formula; m-TOR : Mammalian target of rapamycin ; IL2-R : interleukin 2 receptor ; MMF : mycophenolate mofetil

Table 2. Determinants of death with functioning graft in univariate analyses

	HR	p
Donor characteristics		
Catégories RI (ref = RI < 0.70 both at 1 month & 3 months)	1	
RI < 0.70 at 1 month & RI ≥ 0.70 at 3 months	2.15 [1.29-3.60]	0.003
RI ≥ 0.70 at 1 month & RI < 0.70 at 3 months	1.90 [1.20-3.03]	0.006
RI ≥ 0.70 at 1 month & RI ≥ 0.70 at 3 months	3.77 [2.71-5.24]	<0.001
Cardiovascular death	1.59 [1.16-2.16]	0.003
Donor with diabetes	1.07 [0.54-2.11]	0.850
Donor gender (Male)	1.01 [0.77-1.33]	0.950
Donor Age (per 10 year increase)	1.30 [1.20-1.42]	<0.001
Donor Age > 60	1.85 [1.44-2.39]	<0.001
Cold ischemia (per 1 hour increase)	1.01 [0.99-1.02]	0.47
Recipents characteristics at time of transplantation		
Diabetes	3.44 [2.52-4.70]	<0.001
NODAT	0.75 [0.66-1.35]	0.75
Hemodialysis time > 1 year	1.38 [0.98-1.92]	0.059
Hemodialysis time (per 1 year increase)	1.02 [0.99-1.06]	0.099
Age (per 10 year increase)	1.92 [1.71-2.16]	<0.001
Age > 60 years	3.70 [2.85-4.80]	<0.001
Male gender	1.25 [0.95-1.65]	0.110
BMI > 25	1.68 [1.28-2.20]	<0.001
BMI (per 5 pt increase)	1.35 [1.18-1.54]	<0.001
Year of transplantation (ref = 1985-1989)		
1990-1999	0.98 [0.59-1.64]	0.940
2000-2009	1.03 [0.64-1.66]	0.900
2010-2017	1.42 [0.85-2.40]	0.180
Double transplantation	2.86 [1.11-7.40]	0.030
Perfusion machine	2.49 [1.50-4.15]	<0.001
DGF	1.38 [1.01-1.89]	0.041
Recipients characteristics at 3 months		
SBP > 140 mmHg	1.67 [1.27-2.18]	<0.001
SBP (per 10 mmHg increase)	1.15 [1.07-1.23]	<0.001
DBP > 90 mmHg	0.47 [0.24-0.91]	0.026
DPB (per 10 mmHg increase)	0.87 [0.77-0.98]	0.024
PP > 50 mmHg	2.12 [1.54-2.91]	<0.001
PP (per 10 mmHg increase)	1.25 [1.25-1.35]	<0.001
eGFR < 45 ml/min	1.39 [1.06-1.82]	0.016
eGFR MDRD (per 10ml/min/1.73 m2 increase)	0.89 [0.82-0.96]	0.024
Tacrolimus	1.18 [0.89-1.57]	0.26
IL2-R antibodies	1.18 [0.89-1.57]	0.250
RIM1 (per 0.1 increase)	1.93 [1.65- 2.24]	<0.001
RIM3 (per 0.1 increase)	2.27 [1.91-2.69]	<0.001

Values are mean (SD) or absolute (percentage) of patients

NODAT : New Onset Diabetes After transplantation; DGF : Delayed Graft Function ; BMI : Body Mass Index ; SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular filtration Rate using MDRD formula

Table 3. Determinants of the risk of death with functioning graft in multivariate analysis

	HR	p
Categories RI (ref = RI < 0.70 both at 1 month & 3 months)	1	
RI < 0.70 at 1 month & RI ≥0.70 at 3 months	1.77 [1.02-3.07]	0.044
RI ≥ 0.70 at 1 month & RI < 0.70 at 3 months	1.34 [0.76-2.37]	0.310
RI ≥ 0.70 at 1 month & RI ≥0.70 at 3 months	1.72 [1.07-2.79]	0.026
Recipient Diabetes	1.82 [1.23-2.70]	0.003
Age > 60 years	2.73 [1.86-4.01]	<0.001
Donor cardiovascular death	1.27 [0.90-1.79]	0.180
BMI > 25	0.96 [0.69-1.33]	0.800
Perfusion machine	1.29 [0.73-2.30]	0.380
double transplantation	1.43 [0.52-3.89]	0.490
PP > 50 mmHg	1.00 [0.99-1.01]	0.600
DBP > 90 mmHg	1.00 [0.99-1.02]	0.760
DGF	1.25 [0.87-1.80]	0.230
eGFR < 45 ml/min/1.73m^2	0.71 [0.41-1.22]	0.210

Values are mean (SD) or absolute (percentage) of patients

DGF : Delayed Graft Function ; BMI : Body Mass Index ; SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular filtration Rate using MDRD formula

Table 4. Determinants of death with functioning graft in patients with pre-transplant diabetes

	Univariate		Multivariate*	
	HR	p	HR	p
Catégories RI (ref = RI < 0.70 both at 1 month & 3 months)	1		1	
RI < 0.70 at 1 month & RI ≥ 0.70 at 3 months	3.67 [0.94-14.32]	0.061	4.69 [1.07-20.52]	0.040
RI ≥ 0.70 at 1 month & RI < 0.70 at 3 months	2.16 [0.63-7.41]	0.220	1.63 [0.42-6.30]	0.480
RI ≥ 0.70 at 1 month & RI ≥ 0.70 at 3 months	2.15 [0.74-6.25]	0.160	1.34 [0.43-4.20]	0.610

Values are mean (SD) or absolute (percentage) of patients

*Multivariate analysis adjusted on age, donor cardiovascular death, body mass index, perfusion machine, double transplantation, pulse pressure, diastolic blood pressure, delayed graft function, and estimated glomerular filtration rate

Supplementary table 1. Baseline characteristics stratified with RI at 1 month and 3 months after transplantation using a threshold of 0.75

	Overall	RI<0.75 1 month RI<0.75 3 months	RI<0.75 1 month RI≥0.75 3 months	RI≥0.75 1 month RI<0.75 3 months	RI≥0.75 1 month RI≥0.75 3 months	p
Total patients	1685	1077	140	164	304	
Donor characteristics						
Cardiovascular death (%)	924 (61.4)	535 (57.5)	88 (66.7)	89 (59.7)	212 (72.4)	<0.001
Deceased donor (%)	1590 (94.4)	995 (92.4)	135 (96.4)	161 (98.2)	299 (98.4)	<0.001
Donor age (years)	50.95 (17.54)	45.97 (16.27)	58.29 (15.50)	53.87 (16.76)	63.63 (15.12)	<0.001
Donor with diabetes (%)	95 (5.7)	32 (3.0)	11 (7.9)	14 (8.6)	38 (12.5)	<0.001
Donor gender (% Male)	1002 (59.5)	649 (60.3)	83 (59.3)	94 (57.3)	176 (57.9)	0.823
Cold Ischemia (hours)	17.81 (7.95)	17.51 (8.28)	19.09 (8.01)	19.01 (7.67)	17.64 (6.70)	0.030
Recipient characteristics at time of transplantation						
Diabetes (%)	263 (15.9)	64 (6.0)	33 (23.9)	41 (26.3)	125 (41.4)	<0.001
NODAT (%)	214 (12.9)	127 (12.0)	24 (17.4)	21 (13.3)	42 (13.9)	0.321
Hemodialysis time (years)	2.95 (3.34)	2.90 (3.43)	2.79 (3.12)	3.49 (3.89)	2.90 (2.75)	0.211
Age (years)	51.15 (14.78)	45.36 (13.45)	59.71 (11.12)	56.37 (12.89)	64.92 (8.19)	<0.001
Year of transplantation (%)						<0.001
1985-1989	44 (2.6)	31 (2.9)	3 (2.1)	8 (4.9)	2 (0.7)	
1990-1999	270 (16.0)	196 (18.2)	12 (8.6)	23 (14.0)	39 (12.8)	
2000-2009	584 (34.7)	410 (38.1)	58 (41.4)	52 (31.7)	64 (21.1)	
2010-2017	787 (46.7)	440 (40.9)	67 (47.9)	81 (49.4)	199 (65.5)	
Gender (% Male)	1074 (63.7)	706 (65.6)	80 (57.1)	100 (61.0)	188 (61.8)	0.159
BMI (kg/m2)	25.31 (4.88)	24.54 (4.59)	26.24 (5.87)	26.17 (4.82)	27.15 (4.82)	<0.001
Graft rank (%)						0.863
1	1433 (85.0)	913 (84.8)	117 (83.6)	140 (85.4)	263 (86.5)	
2	213 (12.6)	135 (12.5)	22 (15.7)	21 (12.8)	35 (11.5)	
3	37 (2.2)	27 (2.5)	1 (0.7)	3 (1.8)	6 (2.0)	
4	2 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	
Perfusion machine (%)	242 (14.4)	86 (8.0)	31 (22.1)	24 (14.6)	101 (33.2)	<0.001
Double transplantation (%)	26 (1.5)	9 (0.8)	2 (1.4)	4 (2.5)	11 (3.6)	0.005
DGF (%)	320 (19.0)	136.23 (14.92)	138.07 (18.06)	141.64 (13.59)	145.91 (17.08)	<0.001
Thymoglobulin (%)	915 (54.4)	80.85 (9.85)	76.74 (11.00)	77.19 (10.23)	72.76 (10.60)	<0.001
IL2-R antibodies (%)	744 (44.3)	55.38 (12.60)	61.33 (16.16)	64.45 (13.99)	73.15 (15.73)	<0.001
Recipients characteristics at 3 months						
SBP (mmHg)	138.54 (15.90)	157 (14.6)	30 (21.4)	44 (26.8)	89 (29.3)	<0.001
DBP (mmHg)	78.79 (10.57)	54.47 (19.68)	46.67 (17.74)	47.72 (17.17)	43.91 (15.25)	<0.001
PP (mmHg)	59.75 (15.19)	0.94 (10.58)	0.53 (0.58)	0.64 (1.21)	0.57 (0.56)	0.930
eGFR (ml/min/1.73 m2)	51.39 (19.09)	509 (53.1)	72 (57.6)	80 (58.0)	162 (64.5)	0.011
Proteinuria (g/day)	0.80 (8.39)	423 (44.1)	41 (32.8)	49 (35.5)	73 (29.1)	<0.001
Tacrolimus (%)	823 (55.9)	917 (95.7)	117 (93.6)	132 (95.7)	242 (96.4)	0.653
Ciclosporine (%)	586 (39.8)	768 (80.1)	112 (89.6)	107 (77.5)	206 (82.1)	0.051
Steroids (%)	1408 (95.7)	165 (17.2)	10 (8.0)	27 (19.6)	32 (12.7)	0.016
MMF (%)	1193 (81.0)	45 (4.7)	14 (11.2)	12 (8.7)	26 (10.4)	0.001
Azathioprine (%)	234 (15.9)	601 (55.9)	73 (52.1)	89 (54.3)	152 (50.0)	0.303
m-TOR inhibitors (%)	97 (6.6)	455 (42.4)	66 (47.5)	74 (45.4)	149 (49.0)	0.176
Resistive index M1	0.70 (0.08)	0.65 (0.06)	0.71 (0.03)	0.78 (0.04)	0.81 (0.05)	<0.001
Resistive index M3	0.69 (0.08)	0.65 (0.06)	0.78 (0.03)	0.70 (0.04)	0.80 (0.04)	<0.001
Resistive index M1 > 0.75	864 (51.3)	0 (0.0)	140 (100.0)	0 (0.0)	304 (100.0)	<0.001
Resistive index M3 > 0.75	808 (48.0)	0 (0.0)	0 (0.0)	164 (100.0)	304 (100.0)	<0.001

Values are mean (SD) or absolute (percentage) of patients

NODAT : New Onset Diabetes After transplantation; DGF : Delayed Graft Function ; BMI : Body Mass Index ; SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular filtration Rate using MDRD formula; m-TOR : Mammalian target of rapamycin ; IL2-R : interleukin 2 receptor ; MMF : mycophenolate mofetil

Supplementary table 2. Determinants of death with a functioning graft in multivariate analysis using a threshold of 0.75

	HR	p
Catégories RI (ref = RI < 0.75 both at 1 month & 3 months)	1	
RI < 0.75 at 1 month & RI ≥ 0.75 at 3 months	2.30 [1.41-3.74]	<0.001
RI ≥ 0.75 at 1 month & RI < 0.75 at 3 months	1.45 [0.88-2.40]	0.140
RI ≥ 0.75 at 1 month & RI ≥ 0.75 at 3 months	1.72 [1.06-2.78]	0.027
Diabetes	1.73 [1.15-2.59]	0.009
Age > 60 years	2.51 [1.70-3.72]	<0.001
Donor cardiovascular death	1.32 [0.94-1.85]	0.110
BMI > 25	0.96 [0.70-1.33]	0.810
Perfusion machine	1.25 [0.70-2.22]	0.460
double transplantation	1.52 [0.56-4.12]	0.420
PP > 50 mmHg	1.00 [0.99-1.01]	0.530
DBP > 90 mmHg	1.00 [0.99-1.02]	0.690
DGF	1.21 [0.84-1.73]	0.310
eGFR < 45 ml/min/1.73m2	0.71 [0.41-1.22]	0.210

Values are mean (SD) or absolute (percentage) of patients

DGF : Delayed Graft Function ; BMI : Body Mass Index ;; SBP : Systolic Blood Pressure ; DBP : Diastolic Blood Pressure ; PP : Pulse Pressure ; eGFR : estimated Glomerular filtration Rate using MDRD formula

Figure 1: Risk of death with functioning graft according to RI at 1 month (1A), and according to RI at 3 months (1B), after kidney transplantation

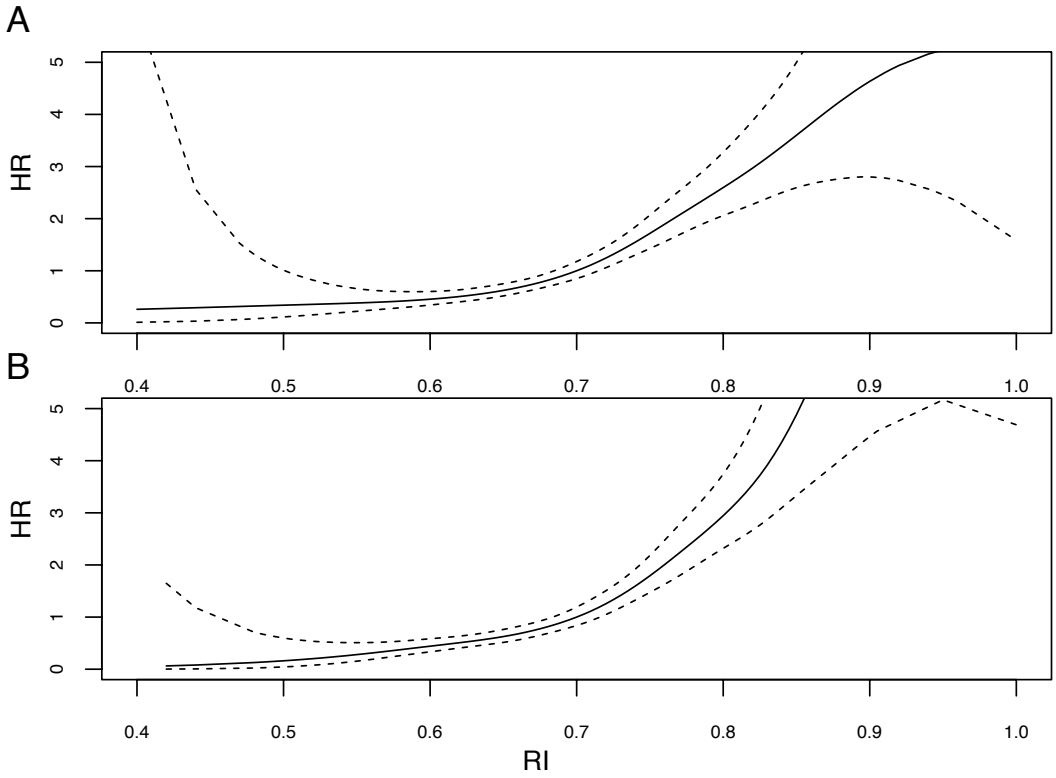


Figure 2: Risk of death with functioning graft in patients with pre-transplant diabetes according to RI at 1 month (2A), and RI at 3 months (2B), after kidney transplantation

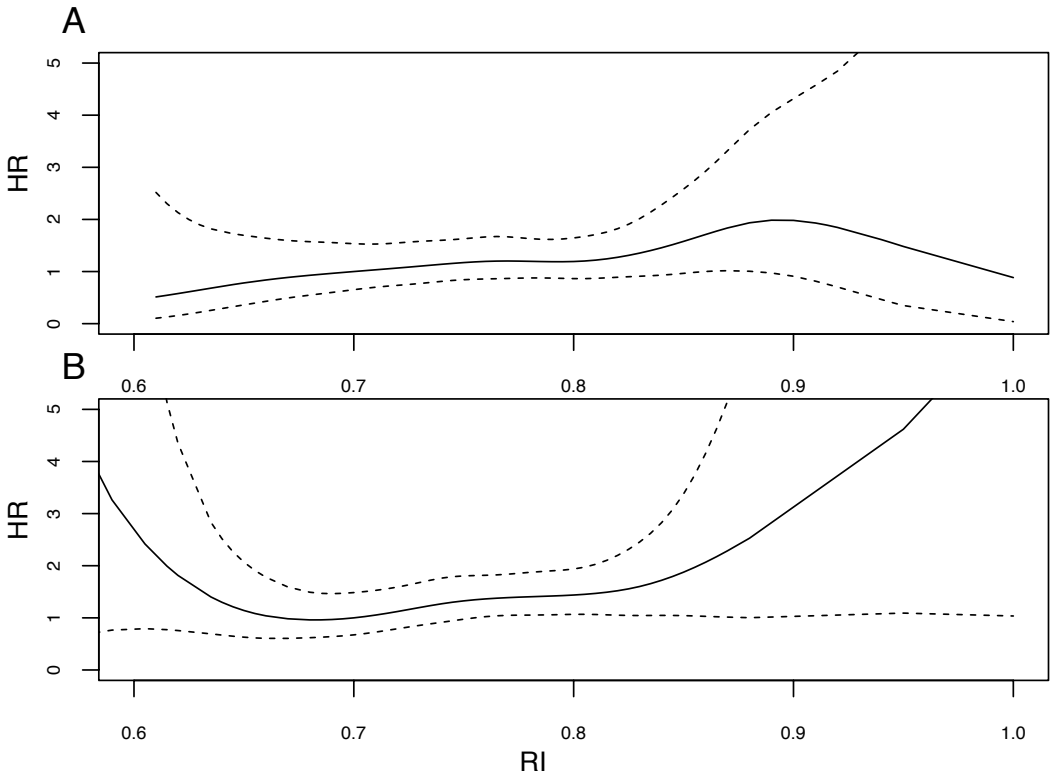
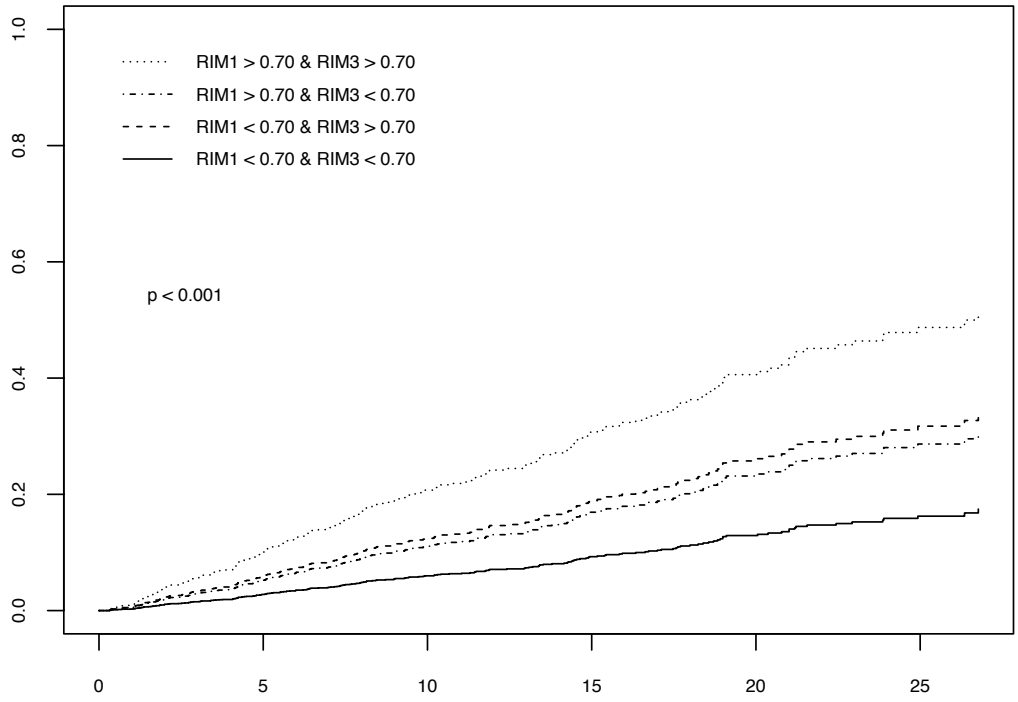


Figure 3: Cumulative incidence of death with functioning graft according to RI variations between 1 month and 3 months after transplantation

Légende ?



Discussion globale et perspectives

Dans cette travail, nous avons confirmé la fait que l'indice de résistance était un bon prédicteur de la mortalité greffon fonctionnel chez les transplantés rénaux chez les patients non diabétiques, mais pas chez les patients diabétiques. Nous avons ensuite confirmé qu'en l'analysant comme variable continue, une valeur plus élevée du RI était corrélée à un risque plus important de décès, qu'il soit mesuré à 1 mois ou à 3 mois après la transplantation. Enfin, nous avons montré que la variation du RI entre 1 mois et 3 mois après la transplantation était aussi associée avec le décès.

Chez les patients diabétiques, les résultats étaient très différents. En premier lieu, la relation entre le RI à 1 mois ou à 3 mois et le décès n'était pas la même chez les patients diabétiques ou non diabétiques. Ensuite, parmi les patients avec RI $\geq$ 0.70 à 1 mois, proportionnellement plus de diabétiques que de non diabétiques gardaient un indice de résistance $\geq$ 0.70 à 3 mois, alors que parmi les patients avec RI < 0.70 à 1 mois, proportionnellement moins de patients diabétiques que de non diabétiques gardaient un RI < 0.70. Enfin, parmi les patients diabétiques, un risque plus élevé de décès était observé uniquement dans le groupe des patients avec RI < 0.70 à 1 mois et $\geq$ 0.70 à 3 mois.

Un indice de résistance élevé est notamment observé après transplantation rénale chez les patients avec reprise retardée de fonction du greffon, rejet aigu, et aussi en cas de nécrose tubulaire aigüe (36). Par ailleurs, un certain nombre d'études suggèrent que le RI est lié à la vascularisation systémique, et peu associé aux résistances vasculaires rénales (1,7,10,31). Il a aussi été décrit une augmentation du RI avec l'athérosclérose et la néphropathie diabétique (19,20). Les patients diabétiques transplantés rénaux ont souffert des conséquences vasculaires chroniques de la glucotoxicité, avec des conséquences à la fois systémiques et rénales, d'où l'impact sur l'indice de résistance. Dans cette étude, nous avons montré que le RI n'avait pas la même valeur pronostique chez les patients diabétiques ayant été transplantés. Nous avons trouvé une relation très différente entre l'indice de résistance en tant que variable continue et le risque de décès entre les patients diabétiques ou non diabétiques, ce qui confirme que sa valeur pronostique est plus difficile à interpréter chez les patients diabétiques.

Nous avons initialement analysé l'indice de résistance à 3 mois après la transplantation (2). La valeur pronostique de l'indice de résistance après la transplantation rénale est bien connue, mais le point de vue des auteurs diverge concernant le meilleur moment pour la mesure (6,14,37). Certains auteurs ont par ailleurs suggéré que la variation du RI pourrait avoir un

intérêt (38). Nous avons donc aussi analysé la variation du RI entre 1 et 3 mois après la transplantation. Nous avons trouvé que la variation du RI pourrait permettre d'affiner sa valeur pronostique. En effet, en analysant tous les patients, en comparaison du groupe de patients avec RI bas à 1 mois et à 3 mois après la transplantation, un RI élevé à 1 mois et à 3 mois après la transplantation était toujours associé à un risque de décès plus important. Un RI bas à 1 mois et élevé à 3 mois était aussi toujours associé à un risque plus élevé de décès. Cependant, selon le seuil choisi, un RI élevé à 1 mois et bas à 3 mois n'était pas toujours associé à un plus fort risque de décès.

De plus, chez les patients diabétiques, seul le RI bas à 1 mois et élevé à 3 mois était associé à un risque plus élevé de décès en analyse multivariée. Nous avons précédemment montré que le RI à 3 mois n'était pas un bon prédicteur du risque de décès chez les patients diabétiques. Nous avons fait l'hypothèse que l'augmentation du RI était moins importante chez les patients diabétiques que chez les patients non diabétiques, et que cela pourrait expliquer l'absence de valeur pronostique du RI chez les patients diabétiques. Cependant, chez les patients diabétiques, les patients avec RI < 0.70 à 1 mois et ≥ 0.70 à 3 mois avaient un moins bon pronostic que les autres. En ce sens, l'évolution du RI entre 1 et 3 mois affine sa valeur pronostique.

Les points forts de notre étude sont notamment la taille de la cohorte (à notre connaissance, il s'agit d'une des plus grandes cohortes de patients transplantés rénaux focalisée sur les variations d'indice de résistance et le diabète), la durée du suivi, et l'expertise de notre centre dans la mesure et l'étude de l'indice de résistance (cet indice est étudié dans notre centre depuis les années 70) (23).

Notre étude a cependant des limites. La principale est le caractère rétrospectif et monocentrique de l'étude. De ce fait, nos conclusions nécessiteraient d'être répliquées de manière prospective. Le nombre de patients diabétiques avant la transplantation était largement inférieur au nombre de patients non diabétiques, et le nombre d'évènements était limité. Cependant, plus de 250 patients diabétiques ont été inclus. Nous n'avons par ailleurs pas différencié les décès cardiovasculaires ou non cardiovasculaires : la différence de valeur pronostique du RI entre diabétiques et non diabétiques pourrait être plus ou moins prononcées pour les décès cardiovasculaires. Ensuite, certaines données concernant les antécédents cardiovasculaires des patients, qui pourraient être des facteurs confondants, étaient manquantes (39). Nous avions aussi des données manquantes concernant la sévérité du diabète. Il n'était pas non plus possible de fournir la variabilité inter-observateur du RI alors

que du fait du suivi prolongé, le RI n'a pas toujours mesuré par la même personne. Cependant, certaines études ont montré une bonne reproductibilité de cette mesure (33,34).

En conclusion, notre étude montre que l'indice de résistance rénal mesuré précocement à différents moments après la transplantation est un fort prédicteur du risque de décès avec greffon fonctionnel chez les transplantés rénaux, mais qu'il a une interprétation différente chez les patients diabétiques. L'étude de la variation de l'indice de résistance entre 1 et 3 mois après la transplantation affine par ailleurs le pronostic, notamment chez les patients diabétiques. Ces résultats pourraient être intéressants pour la gestion des patients précocement après la transplantation rénale. Les patients non diabétiques avec indice de résistance élevé à 1 mois, 3 mois, ou les deux, ainsi que les patients diabétiques avec indice de résistance < 0.70 à 1 mois et ≥ 0.70 à 3 mois, pourraient bénéficier d'un suivi plus rapproché notamment en ce qui concerne la prévention du risque cardiovasculaire. Ceci pourrait de plus s'appliquer aux patients diabétiques avec RI élevé à 1 mois.

Dans les suites de ce travail, nous souhaitons étudier les paramètres constituants l'indice de résistance afin de mieux comprendre sa signification. Nous ne savons connaissons pas actuellement le lien entre la valeur pronostique du RI et la vitesse de pic systolique d'un part, que l'on peut intuitivement associer à la rigidité artérielle et à la vascularisation systémique, et à d'autre part à la vitesse télé-diastolique, plus vraisemblablement associée aux résistances intra-rénale en tant que telles. Cela fera l'objet d'une étude ultérieure.

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Résumé :
Introduction L'indice de résistance rénal (RI) prédit la mortalité chez les receveurs de transplantation rénale. Cependant sa valeur varie avec le temps et selon le statut diabétique du receveur. L'objectif de cette étude était d'analyser les variations de l'indice de résistance entre 1 mois et 3 mois après la transplantation rénale chez les patients diabétiques et non diabétiques, et sa valeur prédictive pour le décès avec greffon fonctionnel (DCGF).
Méthodes Nous avons réalisé une étude rétrospective chez les patients transplantés rénaux à Tours (France) entre 1985 et 2017. Les caractéristiques du donneur et du receveur ont été recueillies au moment de la transplantation et à 3 mois.
Résultats 1800 patients à 3 mois, et 1685 patients à 1 mois et 3 mois avaient une mesure de RI disponible. RI ≥ 0.75 était associé au décès chez les patients non diabétiques (hazard ratio (HR) = 3.33, [intervalle de confiance à 95% 2.46–4.36], p < 0.001), mais pas chez les patients diabétiques (HR = 1.32, [0.80–2.20], p = 0.28). Le risque de décès augmentait de manière continue avec l'indice de résistance à 1 mois et 3 mois, mais pas chez les patients diabétiques. La meilleure survie était observée chez les patients avec RI < 0.70 à 1 mois et 3 mois, et la moins bonne survie chez les patients avec RI ≥ 0.70 à 1 mois et 3 mois (HR = 3.77, [2.71–5.24], p < 0.001). Le risque était intermédiaire chez les autres patients. Chez les patients diabétiques, seul le RI < 0.70 à 1 mois et ≥ 0.70 à 3 mois était associés à une augmentation du risque de décès (HR = 4.69, [1.07-20.52], p=0.040).
Conclusion Le RI mesuré précocement et son évolution à court terme après la transplantation prédit le risque de décès à long terme chez les receveurs non diabétiques, mais son interprétation est différente chez les receveurs diabétiques, chez qui seule l'élévation du RI entre 1 mois et 3 mois semble associée à un mauvais pronostic.

Mots clés : Indice de résistance rénal, transplantation rénale, diabète, échographie- doppler, résistances vasculaires

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