Clinical Risk Factors and Protective Factors for Transplant Renal Artery Stenosis: A Postprint

Authors: Liu Yanna, Yu Lixin, Deng Wenfeng, Li Kaiqun, Liu Rumin, Ye Guirong, Fu Fangxiang, Li Jiangtao, Miao Yun

Date: 2018-06-15T00:00:00+00:00

Abstract

Objective: To analyze the factors associated with transplant renal artery stenosis. Methods: A retrospective analysis was performed on the clinical data of 26 patients with transplant renal artery stenosis (TRAS) (TRAS group), compared with 40 concurrent renal transplant patients without TRAS (non-TRAS concurrent group). Among the TRAS group, 14 patients (TRAS same-donor group) whose other recipient of the same donor kidney (without TRAS) formed a nested control (non-TRAS same-donor group). Results: Compared with the non-TRAS concurrent group, the TRAS group had a higher incidence of acute rejection (P=0.004), longer donor kidney warm ischemia time (P=0.015), and lower high-density lipoprotein cholesterol (HDL-C) levels in recipients at 5 months post-transplantation (P=0.009). Logistic regression results indicated that AR (P=0.007) and prolonged warm ischemia time (P=0.046) were risk factors for TRAS, while high HDL-C levels (P=0.022) were a protective factor. In recent years, an increasing number of TRAS patients have been able to receive early diagnosis, the time from transplantation to TRAS diagnosis has shortened year by year, and eGFR at the time of TRAS diagnosis has shown an upward trend. Conclusion: In addition to surgical factors, acute rejection and prolonged warm ischemia time are risk factors for TRAS occurrence, while high HDL-C levels are a protective factor. The improvement in ultrasound technology for TRAS diagnosis is the main reason for the early diagnosis of TRAS in recent years.

Full Text

Preamble

LIU Yanna, YU Lixin, DENG Wenfeng, LI Kaiqun, LIU Rumin, YE Guirong, FU Fangxiang, LI Jiangtao, MIAO Yun

Department of Organ Transplantation, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China

Abstract

Objective To investigate the factors associated with the occurrence of transplant renal artery stenosis (TRAS).
Methods A retrospective analysis was conducted in 26 recipients who developed TRAS and 40 concurrent renal recipients without TRAS. We also conducted a nested case-control study in 14 patients with TRAS (TRAS-SD group) and another 14 non-TRAS recipients who received the allograft from the same donor (non-TRAS-SD group).
Results Compared with those in the concurrent recipients without TRAS, acute rejection (AR) occurred at a significantly higher incidence (P=0.004), the warm ischemia time (WIT) was significantly longer (P=0.015), and the level of high-density lipoprotein cholesterol (HDL-C) was significantly lower (P=0.009) in the recipients with TRAS. Logistic regression analysis suggested that AR (P=0.007) and prolonged WIT (P=0.046) were risk factors of TRAS while HDL-C (P=0.022) was the protective factor against TRAS. In recent years early diagnosis of TRAS had been made in increasing cases, the interval from transplantation to TRAS diagnosis became shortened steadily, and the recipients tended to have higher estimated glomerular filtration rate at the time of TRAS diagnosis.
Conclusion Apart from the surgical technique, AR and prolonged WIT are also risk factors of TRAS while a high HDL-C level is the protective factor against TRAS. The improvement of the diagnostic accuracy by ultrasound is the primary factor contributing to the increased rate of early TRAS diagnosis in recent years.

Keywords: Transplant renal artery stenosis; acute rejection; warm ischemia time; high-density lipoprotein cholesterol

Introduction

Transplant renal artery stenosis (TRAS) is the most common vascular complication after kidney transplantation, accounting for 75% of post-transplant vascular complications and representing a significant cause of graft loss and transplant failure. TRAS typically occurs between 3 months and 2 years after transplantation, with reported incidence rates ranging from 1% to 23% across different centers. This wide variation may be attributed to differences in diagnostic criteria and examination capabilities among institutions. Previous studies have identified risk factors including delayed graft function (DGF), rejection reactions, atherosclerosis, and cytomegalovirus (CMV) infection. In its early stages, TRAS often presents without specific manifestations of stenosis, leading to missed opportunities for early diagnosis. As the condition progresses, it can result in refractory hypertension, compromised transplant kidney function, and

even graft loss.

Investigating the factors associated with TRAS enables proactive prevention and enhanced surveillance for at-risk patients, thereby improving early diagnostic rates. Additionally, early intervention in TRAS patients helps preserve graft function and reduces the incidence of other complications. While numerous international studies have reported risk factors for TRAS, protective factors remain unreported in the literature. Domestic research on TRAS risk and protective factors is scarce, limited by small sample sizes, and lacks recent updates. Therefore, exploring these factors is crucial for early diagnosis, treatment, and preservation of transplant kidney function. This study retrospectively analyzed 26 TRAS patients who underwent kidney transplantation at Nanfang Hospital, Southern Medical University between November 2003 and December 2014.

Methods

Study Design

We conducted a retrospective analysis of 26 TRAS patients (TRAS group) and compared them with 40 age-matched (within 5 years) concurrent kidney transplant recipients without TRAS (non-TRAS-SP group). Additionally, we performed a nested case-control study using 14 TRAS patients (TRAS-SD group) whose kidney donors also provided allografts to another recipient who did not develop TRAS (non-TRAS-SD group, n=14) [Figure 1: see original paper]. We collected demographic, clinical, and follow-up data from all 80 recipients. DGF was defined as the need for hemodialysis within one week post-transplantation, and CMV infection was diagnosed when serum CMV-DNA quantification exceeded 500 copies/mL.

TRAS Diagnosis

Recipients experiencing unexplained progressive or recurrent creatinine elevation (>20%), with or without refractory hypertension or decreased urine output, underwent ultrasound examination. Suspicious TRAS was preliminarily diagnosed when ultrasound images suggested transplant renal artery stenosis, with peak systolic velocity >200 cm/s providing further support. Digital subtraction angiography (DSA) was subsequently performed to confirm the diagnosis [Figure 2: see original paper].

Estimated Glomerular Filtration Rate

The estimated glomerular filtration rate (eGFR) was calculated using the modified MDRD formula for Chinese patients: eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) = $186 \times Scr^{-1.1}$ (mg/dL) $\times$ age $^{-.2}$ ^{3} $\times$ 0.742 (if female) $\times$ 1.233.

Statistical Analysis

SPSS 19.0 software was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± standard deviation, while categorical data were presented as percentages. Comparisons between normally distributed independent samples used the two-sample t-test, non-normally distributed data used the Mann-Whitney U test, and comparisons of proportions used ^{2} test or Fisher' s exact test. Binary logistic regression analysis was employed to identify TRAS risk and protective factors, with variables included if $P<0.2$ in univariate analysis. All statistical tests were two-tailed, with $P<0.05$ considered statistically significant.

Results

2.1 Recipient Characteristics

The 80 recipients had a mean age of 40.61 years, all receiving deceased-donor kidney transplants for the first time, with no concurrent vascular diseases. The median pre-transplant dialysis duration was 9.75 months (range 0-92.00), and the median post-transplant follow-up was 33.09 months (range 0.30-193.43). Primary diseases, pre-transplant dialysis modalities, and long-term immunosuppressive regimens are summarized in .

Comparisons of demographic data among groups are shown in and . No significant differences were observed between the TRAS and non-TRAS-SP groups in age, gender, body mass index (BMI), pre-transplant dialysis duration, or cold ischemia time (all $P>0.05$), but warm ischemia time differed significantly ($P=0.015$). The TRAS group had a higher post-transplant AR incidence than the non-TRAS-SP group ($P=0.004$). In the nested comparison between TRAS-SD and non-TRAS-SD groups, no significant differences were found in any parameters except a higher AR incidence in the TRAS-SD group ($P=0.077$).

2.2 Correlation Between Lipid Levels and Stenosis Occurrence

The time from transplantation to TRAS diagnosis is shown in [Figure 3: see original paper]. Most TRAS cases occurred approximately 5 months post-transplantation; therefore, lipid levels at 5 months post-transplant were recorded for non-TRAS patients. HDL-C levels were significantly lower in the TRAS group compared with the non-TRAS-SP group ($P=0.009$), with no significant differences in other lipid parameters [Figure 4: see original paper]. In the nested comparison, VLDL-C levels were lower in the non-TRAS-SD group ($P=0.022$), but both groups' values remained within normal ranges, limiting clinical significance. No other significant differences were observed [Figure 5: see original paper].

2.3 TRAS Risk and Protective Factors

Binary logistic regression analysis between the TRAS and non-TRAS-SP groups included variables with P<0.2 in univariate analysis. The results identified AR (OR=31.384, P=0.007) and prolonged warm ischemia time (OR=2.136, P=0.046) as TRAS risk factors, while HDL-C was a protective factor (OR=0.090, P=0.022).

2.4 Trends in Time to TRAS Diagnosis and eGFR at Diagnosis

Scatter plots with linear fitting for the 26 TRAS patients showed that the interval from transplantation to TRAS diagnosis shortened over the years, while mean eGFR at diagnosis increased [Figure 6: see original paper].

Discussion

3.1 Analysis of TRAS Risk and Protective Factors

Surgical factors such as vascular traction during kidney preparation or cannulation for perfusion may damage the intima and lead to TRAS. However, due to the lack of quantifiable standards, these were not included in our risk factor analysis.

Both comparisons—with concurrent transplant recipients and with same-donor recipients—showed higher post-transplant AR incidence in TRAS patients. The difference was statistically significant between the TRAS and non-TRAS-SP groups (P=0.004) but not between the TRAS-SD and non-TRAS-SD groups (P=0.077), likely due to the smaller sample size (n=14) in the latter comparison. Logistic regression confirmed AR as a TRAS risk factor (OR=31.384, P=0.007), consistent with previous reports. During AR, expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelium increases, enhancing leukocyte migration and adhesion to endothelial cells. This inflammatory response causes vascular wall thickening, leading to microvascular and macrovascular injury that results in TRAS.

Prolonged warm ischemia time was also identified as a TRAS risk factor. The TRAS group had significantly longer warm ischemia times than the non-TRAS-SP group (P=0.021), and multivariate regression confirmed this as a risk factor (OR=2.136, P=0.046). Prolonged warm ischemia exacerbates ischemia-reperfusion injury, which is associated with oxygen free radical production. Reactive oxygen species directly and indirectly regulate renal hemodynamics by mediating vasoconstriction and inducing inflammatory responses. Inflammation causes endothelial injury, repair, and scarring, potentially leading to TRAS. The role of oxidative stress in renal vascular disease pathogenesis is increasingly recognized. Therefore, minimizing warm ischemia time during transplantation may reduce TRAS risk.

Logistic regression also revealed that elevated HDL-C level was a protective fac-

tor against TRAS (OR=0.090, P=0.022). In univariate analysis, TRAS patients had significantly lower HDL-C levels than non-TRAS-SP patients (P=0.009). Recent data demonstrate that low HDL-C levels correlate significantly with reduced eGFR. Becker et al. proposed that HDL-C reduces TRAS or pseudo-TRAS risk. Animal studies show HDL inhibits aortic wall fatty streak formation and cholesterol deposition and can regress established atherosclerotic lesions. ApoA-I Milano, a variant of apoA-I (the main protein component of HDL), has been shown in animal and clinical studies to prevent atherosclerosis or reduce plaque volume. HDL' s anti-atherosclerotic mechanisms include: (1) promoting cholesterol efflux from lipid-laden macrophage-derived foam cells in atherosclerotic plaques for hepatic clearance; (2) directly stimulating nitric oxide production in vascular endothelial cells, which exerts anti-inflammatory, anticoagulant, and anti-thrombotic effects; and (3) serving as the primary transporter of lipid oxidation products while containing antioxidant enzymes that reduce lipid oxidation. Since low HDL-C is a major atherosclerosis risk factor and late-onset TRAS (years post-transplant) typically involves atherosclerotic disease in the transplant renal artery or adjacent iliac artery, elevated HDL-C reduces TRAS risk. In our nested comparison, HDL-C levels were higher in the TRAS-SD group than in the non-TRAS-SD group, but the difference was not significant (P=0.167), possibly due to the small sample size (n=14) or dominance of other factors such as donor kidney characteristics and ischemia times. Since lipid levels are modifiable, early prevention efforts should aim to maintain transplant recipients' lipid profiles within normal ranges to potentially delay stenosis events.

3.2 Trends in Transplant-TRAS Diagnosis Time and eGFR at Diagnosis

Our study found that TRAS diagnosis has become increasingly early over the years, with the interval from transplantation to diagnosis shortening annually and mean eGFR at diagnosis rising. This reflects two emerging characteristics of TRAS: earlier diagnosis and better-preserved renal function at diagnosis. Several factors explain this trend: (1) Improved ultrasound diagnostic capabilities, with color Doppler and power Doppler ultrasound providing direct visualization of TRAS, enhancing early detection rates; (2) Increased clinician awareness, with ultrasound performed promptly upon unexplained progressive or recurrent creatinine elevation and incorporated as a routine examination, enabling diagnosis of asymptomatic TRAS cases; and (3) Ultrasound' s non-invasive nature and lack of nephrotoxicity, making it more acceptable to patients and increasing examination rates. Due to improved diagnostic rates and earlier detection, most patients are diagnosed before severe graft function impairment occurs, as evidenced by the overall increasing trend in eGFR at diagnosis [Figure 6: see original paper].

In conclusion, AR and prolonged warm ischemia time are TRAS risk factors, while high HDL-C level is protective. Improved diagnostic rates and earlier detection represent new TRAS characteristics. Although substantial literature

exists on TRAS etiology and pathogenesis, conclusions vary across centers, and the mechanisms underlying TRAS require further investigation.

References

[1] Bruno S. Transplant renal artery stenosis[J]. J Am Soc Nephrol, 2004, 15: 134-41.
[2] Tafur-Soto JD, White CJ. Renal artery stenosis[J]. Cardiol Clin, 2015, 33(1): 59-73.
[3] Braga AF, Catto RC, Dalio MB, et al. Endovascular approach to transplant renal artery stenosis[J]. Ann Transplant, 2015, 24(20):
[4] Biederman DM, Fischman AM, Titano JJ, et al. Tailoring the endovascular management of transplant renal artery stenosis[J]. Am J Transplant, 2015, 15(4): 1039-49.
[5] Wang L, Liu B, Yan J, et al. Interventional Therapy for transplant renal artery stenosis is safe and effective in preserving allograft function and improving hypertension[J]. Vasc Endovascular Surg, 2017, 51(1): 4-11.
[6] Ghirardo G, De Franceschi M, Vidal E, et al. Transplant renal artery stenosis in children: risk factors and outcome after endovascular treatment[J]. Pediatr Nephrol, 2014, 29(3): 461-7.
[7] Hedegard W, Saad WE, Davies MG. Management of vascular and nonvascular complications after renal transplantation[J]. Tech Vasc Interv Radiol, 2009, 12(4): 240-62.
[8] Humar A, Uknis M, Papaluis V, Gillingham K, Matas A. Is there an association between cytomegalovirus and renal artery stenosis in kidney transplant recipients[J]? Transplantation, 2000, 69(suppl):
[9] Da Silva RG, Lima VC, Amorim JE et al: Angioplasty with stent is the preferred therapy for posttransplant renal artery stenosis[J]. Transplant Proc, 2002, 34(2): 514-5.
[10] Mueller-Peltzer K, Rübenthaler J, Fischereder M, et al. The diagnostic value of contrast-enhanced ultrasound (CEUS) as a new technique imaging of vascular complications in renal transplants compared to standard imaging modalities[J]. Clin Hemorheol Microcirc, 2017, 67(3-4), 407-13.
[11] Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease[J]. J Am Soc Nephrol, 2006, 17: 2937-44.
[12] Fernández-Nájera JE, Beltrán S, Aparicio M, et al. Transplant renal artery stenosis: association with acute vascular rejection[J]. Transpl Proc, 2006, 38: 2404-5.
[13] Audard V, Matignon M, Hemery F, et al. Risk factors and long-term outcome of transplant artery stenosis in adult recipients after treatment by percutaneous transluminal angioplasty[J]. Am J Transplant, 2006, 6: 95-9.
[14] Kłoda K, Domanski L, Pawlik A, et al. Effect of the ICAM1 and VCAM1 gene polymorphisms on delayed graft function and acute kidney allograft rejection[J]. Ann Transplant, 2010, 15(4): 15-20.
[15] Mengal V, Silva PH, Tiradentes RV, et al. Aliskiren and l-arginine

treatments restore depressed baroreflex sensitivity and decrease oxidative stress in renovascular hypertension rats[J]. Hypertens Res, 2016, 39(11): 769-76.
[16] Bowe B, Xie Y, Xian H, et al. Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression[J]. Kidney Int, 2016, 89(4): 886-96.
[17] Becker BN, Odorico JS, Becker YT, et al. Peripheral vascular disease and renal transplant artery stenosis: a reappraisal of transplant renovascular disease[J]. Clin Transpalnt, 1999, 13: 349-55.
[18] Badimon JJ, Badimon L, Fuster V. Regression of atherosclerotic lesions by high density lipoprotein plasma fraction in the cholesterol-fed rabbit[J]. J Clin Invest, 1990, 85: 1234-41.
[19] Badimon JJ, Badimon L, Galvez A, et al. High density lipoprotein plasma fractions inhibit aortic fatty streaks in cholesterol-fed rabbits[J]. Lab Invest, 1989, 60: 455-61.
[20] Ibanez B, Vilahur G, Cimmino G, et al. Rapid change in plaque size, composition, and molecular footprint after recombinant apolipoprotein A-I Milano (ETC-216) administration: magnetic resonance imaging study experimental model atherosclerosis[J]. J Am Coll Cardiol, 2008, 51(11): 1104-9.
[21] Ibanez B, Giannarelli C, Cimmino G, et al. Recombinant HDL (Milano) exerts greater anti-inflammatory and plaque stabilizing properties than HDL(wild-type)[J]. Atherosclerosis, 2012, 220(1):
[22] Rader DJ. Molecular regulation of HDL metabolism and function: implications for novel therapies[J]. J Clin Invest, 2006, 116: 3090-
[23] Besler C, Luscher TF, Landmesser U. Molecular mechanisms of vascular effects high-density lipoprotein: alterations cardiovascular disease[J]. Embo Mol Med, 2012, 4: 251-68.
[24] Proudfoot JM, Barden AE, Loke WM, et al. HDL is the major lipoprotein carrier of plasma F2-isoprostanes[J]. J Lip Res, 2009, 50: 716-22.
[25] Safian RD. Transplant renal artery stenosis: what lessons should we learn[J]? Catheter Cardio Interv, 2011, 77: 294-5.
[26] Granata A, Clementi S, Londrino F, et al. Renal transplant vascular complications: the role of Doppler ultrasound[J]. J Ultrasound, 2014, 18(2): 101-7.
[27] Fananapazir G, McGahan JP, Corwin MT, et al. Screening for transplant renal artery stenosis: ultrasound-based stenosis probability stratification[J]. AJR Am J Roentgenol, 2017, 209(5):

Note: Figure translations are in progress. See original paper for figures.