

## Transplant Renal Artery Stenosis in Living Donor Kidney Transplant Recipients: A Single Center Experience from Nepal

Niraj Dhakal<sup>1</sup>, Mahesh R Sigdel<sup>1</sup>, Pawan R Chalise<sup>2</sup>, Nishan Bhurtyal<sup>1</sup>, Dibya S Shah<sup>1</sup>

### Author(s) affiliation

<sup>1</sup>Department of Nephrology, Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal

<sup>2</sup>Department of Urology and Renal Transplant Surgery, Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal

### Corresponding author

**Niraj Dhakal, MBBS, MD**  
dnirajdhakal@hotmail.com

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### ABSTRACT

#### Introduction

Transplant renal artery stenosis (TRAS) is the most common preventable vascular complication in kidney transplantation with significant rates of graft loss and mortality. We aimed to study the demographics, prevalence, clinical presentation, and outcome of TRAS.

#### Methods

We retrospectively reviewed medical records of all living donor kidney transplant recipients at Tribhuvan University Teaching Hospital from August 2008 to May 2021. Cases diagnosed with TRAS by ultrasound Doppler and/or renal CT angiogram were included. Data on demographics, clinical presentation, management, and outcomes were collected and analyzed. Among patients who underwent revascularization, pre and post-procedure creatinine, blood pressure (BP), and antihypertensive medicine burden were compared.

#### Results

Among 620 living donor kidney transplantation, TRAS was present in 17 recipients (Male:Female = 16:1) (2.6%); mean age was 35.47±12.71 years. The median duration at diagnosis was one-month post-transplant (range: 5 days-9 months). The most common clinical features of TRAS were graft dysfunction and uncontrolled hypertension. Diagnosis of TRAS was confirmed with CT angiography in 13 patients. Ten patients underwent revascularization. Pre and post-revascularization mean serum creatinine was 356±210.49 µmol/L and 122.8±30.48 µmol/L (p=0.007) respectively, mean systolic BP was 200±12.47 mmHg and 133±13.38 mmHg (p=0.005) respectively and mean diastolic BP was 105±15.09 mmHg and 80±9.43 mmHg (p=0.005) respectively. Significant reduction in anti-hypertensive pill burden was achieved.

#### Conclusion

Prevalence of TRAS was 2.6%. Most cases presented early with hypertension and graft dysfunction. Revascularization of significant stenosis had a favorable outcome in terms of BP control, antihypertensive pill burden, and preservation of renal function.

#### Keywords

Renal allograft outcome, revascularization, TRAS

## INTRODUCTION

Transplant renal artery stenosis (TRAS) is one of the most common vascular complication in kidney transplant recipients which constitutes more than 75% of all vascular complications and accounts for significant graft loss and mortality.<sup>1,2</sup> Its prevalence varies from 1-23%.<sup>3</sup> Though it can manifest at any time in the post-transplant period, the clinically significant stenotic lesion usually presents between the 3<sup>rd</sup> month to 2<sup>nd</sup> year after transplantation with uncontrolled hypertension (HTN), graft dysfunction, or occasionally with hypertensive crisis and flash pulmonary edema.<sup>4</sup>

A high index of clinical suspicion followed by Doppler ultrasound helps in the diagnosis of TRAS, renal CT angiography further supports the diagnosis, while conventional renal angiography is the gold standard technique and also aids in simultaneous intervention.<sup>5</sup> Allograft loss secondary to TRAS is largely preventable if timely diagnosis and intervention are done. Ten-year graft and patient survival following revascularization for TRAS were found to be the same as of patients who never had TRAS.<sup>6</sup> It has been more than a decade since the first successful living donor kidney transplantation was done in Nepal at Tribhuvan University Teaching Hospital (TUTH).<sup>7</sup>

Here, we reviewed and analyzed the demographics, prevalence, clinical presentation, and outcome of patients with TRAS in our cohort of kidney transplant recipients.

## METHODS

This was a retrospective single-center study done at TUTH, Kathmandu. Prior approval was obtained from the Institutional Review Committee (IRC) of the Institute of Medicine. We reviewed, medical records of all 620 living donor kidney transplant recipients in TUTH whose transplantation was done between August 2008 and May 2021.

All the cases of TRAS diagnosed based on peak systolic velocity (PSV) of >200 cm/sec in transplant renal artery with Doppler ultrasound and/or with or without significant stenosis (>50% of the lumen) of transplant renal artery in CT angiogram were included.<sup>8</sup> All our patients with TRAS received induction with rabbit Anti-thymocyte globulin and were on maintenance therapy with tacrolimus, mycophenolate mofetil, and low-dose steroid. Allograft renal artery and vein were patched to external iliac vessels in end to side anastomosis. After kidney transplantation and discharge, all patients were followed as an outpatient in the Transplant unit initially twice a week for two weeks, then weekly for four weeks then once in two weeks for two months, and monthly for six months after that patients were followed up monthly to

three months depending on their clinical status. Data on their demographics, clinical presentation, routine laboratory parameters, tacrolimus drug level, imaging findings, kidney biopsy findings, intervention and outcome in the form of BP control antihypertensive dose and number, graft function, and patient survival were collected. Patients follow-up data up to one year after the diagnosis of TRAS were recorded.

For descriptive statistics mean or median were used for continuous variables and percentage or proportion for categorical data. Among patients who underwent revascularization pre and post-procedure creatinine, systolic BP, diastolic BP, and antihypertensive medicine burden were recorded. Antihypertensive medicine burden was accessed as an antihypertensive score, where the maximum dose of antihypertensive medicine was scored as 1 and the dose was calculated as a fraction thereof if the patient was not taking the maximum dose of the given medications. Based on the published drug dose guideline, the maximum dosage of each antihypertensive drug was determined.<sup>9</sup> Delayed graft function (DGF) was defined as failure of the renal allograft to function immediately, with the need for dialysis in the first post-transplant week.<sup>10</sup>

Pre and post-revascularization data were compared with Wilcoxon Signed Ranks Test. A p-value <0.05 was considered statistically significant. Graft function was measured by estimated glomerular filtration rate (eGFR) as per The Modification of Diet in Renal Disease (MDRD) equation at 1 year after diagnosis of TRAS in all patients to determine the outcome of the patient.<sup>11</sup> All Statistical analyses were done with Statistical Package for Social Sciences (SPSS) software version 20.<sup>12</sup>

## RESULTS

Amongst the cohort of 620 patients who received living donor kidney transplantation in TUTH between 2008 and May 2021, 17(2.6%) recipients were identified to have TRAS. Their demographic and clinical characteristics are shown in Table 1.

The mean age of the patient with TRAS was 35.47±12.71 years and the mean age of their donor was 43.35±9.36 years. Except one all of the recipients with TRAS were male and 14 out of 17 donors were female. The native kidney disease was undetermined or presumed to be chronic glomerulonephritis in more than 50% of patients with TRAS. Among those whose native kidney disease was known, IgA nephropathy and diabetic kidney disease was the most common diagnosis. The median duration of dialysis before transplantation was 5 months (IQR: 3.5-12 months). All the patients had hypertension and 6 had diabetes, 3 had coronary artery disease (CAD), 1 had ischemic stroke and almost one-third had more

Table 1. Demographics and clinical characteristics of patient with TRAS

Characteristics	Values
Recipient Age (mean±SD years)	35.47±12.71
M:F	16:1
Donor Age (mean±SD years)	43.35±9.36
M:F	3:14
Native Kidney Disease: n (%)	
IgAN	3 (17.65)
Diabetic kidney disease	3 (17.65)
Hypertensive nephrosclerosis	1 (5.88)
Obstructive nephropathy	1 (5.88)
Undetermined	9 (52.94)
Duration of dialysis prior transplantation median in months, (IQR in months)	5, (IQR:3.5-12)
Comorbid conditions: n (%)	
Hypertension	17 (100)
Diabetes	6 (35.29)
CAD	3 (17.65)
Stroke	1 (5.88)
CMV IgG positive status: n (%)	17 (100)
Cold Ischemia time (mean±SD min)	34.59±18.37
Serum creatinine on Day 7 post-transplant (mean±SD µmol/L)	220.18±223.10
An episode of Rejection in biopsy: n (%)	5 (29.4)
Duration for TRAS diagnosis post-transplant (median months, (IQR months))	1, (IQR: 0.5-3)
PSV in Doppler study (mean±SD cm/s)	315±96.8

IgAN: IgA Nephropathy, CAD: coronary artery disease, CMV: cytomegalovirus, PSV: peak systolic velocity

than one comorbid condition. All the patients had positive IgG antibody status for cytomegalovirus (CMV).

Mean cold ischemia time was 34.59±18.37 min and mean 1st and 2nd warm ischemia time was 4.29±3.89 min and 38.94±9.13 min respectively. No major surgical complications were encountered during the surgery. A kidney biopsy was performed in all the patients and some form of rejection was present in 29.4%(n=5) of the cases with two patients having antibody-mediated rejection (ABMR), two patients with borderline acute cellular rejection (ACR), and one patient having features of both ABMR and ACR. Five patients had mild acute tubular injury only and one had IgA deposition in the biopsy. Normal kidney biopsy finding was present in the other six patients.

The median duration for the diagnosis of TRAS from the time of transplantation was 1 month (range: 5 days - 9 months). TRAS occurred in less than 3-months post-transplant in 10 cases (58.2%) and all other cases of TRAS occurred within a 1-year post-transplant period. The most common clinical

features that lead to suspicion of TRAS were graft dysfunction and uncontrolled HTN (Figure 1). The mean value of serum creatinine at diagnosis was 281.18±184.98 µmol/L (Range 95-800 µmol/L). All patients were evaluated by Doppler ultrasound and the mean PSV was 315±96.8 cm/s. Thirteen patients were further evaluated with angiography and the mean stenosis was 75.92±20.71% with 84.6% having significant stenosis of more than 50%.

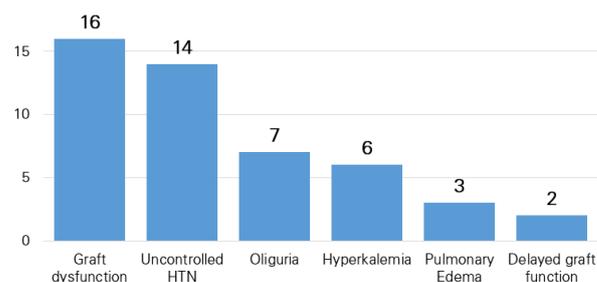


Figure 1. Clinical presentation of transplant renal artery stenosis

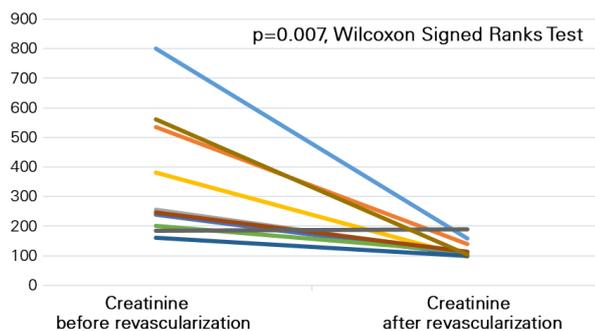


Figure 2. Creatinine before and after revascularization

Ten patients underwent revascularization, four with percutaneous transluminal renal angioplasty (PTRA), and six had transplant renal artery stenting. Among the patients who underwent revascularization pre and post-revascularization mean serum creatinine within seven days was  $356 \pm 210.49$   $\mu\text{mol/L}$  and  $122.8 \pm 30.48$   $\mu\text{mol/L}$  ( $p=0.007$ ) respectively (Figure 2) mean systolic BP was  $200 \pm 12.47$  mmHg and  $133 \pm 13.38$  mmHg ( $p=0.005$ ) respectively, mean diastolic BP was  $105 \pm 15.09$  mmHg and  $80 \pm 9.43$  mmHg ( $p=0.005$ ) respectively (Figure 3), and the anti-hypertensive score was  $2.26 \pm 1.43$  and  $0.64 \pm 0.61$  ( $p=0.008$ ) respectively.

Among seven patients who were treated conservatively, only 3 patients underwent CT angiography and had non-significant TRAS with less than 50% stenosis. Baseline systolic BP and serum creatinine were significantly less in patients who were treated conservatively as compared to the patients who underwent revascularization ( $174.29 \pm 21.49$  mmHg vs  $200 \pm 12.47$  mmHg;  $p=0.007$  and  $174.29 \pm 46.14$   $\mu\text{mol/L}$  vs  $356 \pm 210.49$   $\mu\text{mol/L}$ ;  $p=0.02$ , respectively). Five out of seven conservatively treated patients also had rejection in graft kidney biopsy.

At one-year follow-up after diagnosis of TRAS mean eGFR was  $55.14 \pm 25.77$  ml/min/1.73m<sup>2</sup>. Nine Patients (52.94%) had eGFR of  $\geq 60$  ml/min/1.73m<sup>2</sup> and three patients (17.64 %) had eGFR of  $<30$  ml/min/1.73m<sup>2</sup>. As compared with patients who were on conservative management eGFR was significantly higher in those who underwent revascularization,  $36.39 \pm 17.73$  vs  $68.26 \pm 22.50$  ml/min/1.73m<sup>2</sup> ( $p=0.015$ ) respectively.

## DISCUSSION

TRAS is the most common reversible vascular complication after kidney transplant surgery.<sup>1</sup> In our study, the prevalence of TRAS was 2.6%. Other studies have found the prevalence of TRAS from 1-23%.<sup>3</sup> Various risk factors for TRAS have been identified and reported which includes increasing age of donor or recipient with atherosclerosis of

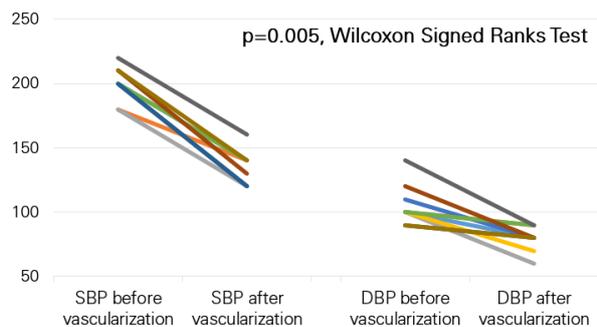


Figure 3. Systolic BP and diastolic BP before and after revascularization

renal artery or iliac vessels, retrieval damage to the renal artery, prolonged cold ischemia time, intimal damage during perfusion, faulty sutural technique, DGF, CMV infection, the immunological mechanism including rejection or calcineurin inhibitor vasculopathy.<sup>1,13,14</sup> All of our patients had positive CMV IgG status, two patients had DGF, five had rejection episode and all recipients had some form of comorbid illness either HTN, diabetes, CAD, or stroke, that is related to atherosclerosis and may have contributed to the development of TRAS (Table 1).

The median duration for the development of TRAS has been reported to be 3-12 months post-transplantation across various literature but it can present at any time.<sup>1,3,15-17</sup> The occurrence of TRAS can be classified as early, within 3 months post-transplant, and late, beyond 3 months.<sup>3</sup> The median time for the development of TRAS was 1 month in our cohort, ten cases (58.82 %) were diagnosed within 3 months and all the cases occurred within 1 year. This observation is in agreement with a similar study by Tauma et al, the median time for the presentation of TRAS was 40 days.<sup>18</sup> Nasserela et al, also in their study of 24 patients with TRAS reported 54.2% of the patient to have early stenosis and in 95.8%, stenosis occurred within 1-year.<sup>15</sup> Early detection in our cohort may be due to a high degree of suspicion, close follow up and routine Doppler scanning in the early post-transplant period. Though we didn't specifically identify surgical complications during transplantation, subtle surgical trauma to the vessels during retrieval, perfusion, or patching could have contributed to the early development of TRAS in our transplant patients.

The common presentations of TRAS are uncontrolled, accelerated, or refractory HTN, graft dysfunction, or oliguria, fluid retention, flash pulmonary edema, hyperkalemia, or rise in creatinine, or potassium with the use of angiotensin receptor blocker or angiotensin-converting enzyme inhibitor.<sup>3,4</sup> In our cohort graft dysfunction and uncontrolled HTN were the major clinical features that lead to suspicion for TRAS and more than one-

third of patients had oliguria and hyperkalemia and some had pulmonary edema (Figure 1). Similarly, graft dysfunction was the predominant presentation reported by Touma et al,<sup>18</sup> occurring in 82.3% in the study of 17 TRAS cases, and in the study of Patel et al,<sup>13</sup> hypertension and graft dysfunction were the predominant clinical feature. Kawaskar et al, found a decrease in urine output in 42% among TRAS cases and we found oliguria in 7 cases (41.2%) at presentation.<sup>16</sup>

Ten patients underwent revascularization, four with PTR, and in 6 patients graft renal artery stenting was done. There was a significant improvement in serum creatinine, systolic BP, diastolic BP, and antihypertensive score after revascularization (Figure 2 and 3). Only one patient had no improvement in serum creatinine and anti-hypertensive score in the immediate post-transplant period. After 1 year of follow up in patients who received revascularization, 8 patients (80%) had eGFR of  $\geq 60$  ml/min/1.73m<sup>2</sup>, only one patient had eGFR of  $<30$  ml/min/1.73m<sup>2</sup> and none required dialysis support. Kawaskar et al, had also reported that serum creatinine, systolic BP, and diastolic BP improved and antihypertensive pill burden decreased after revascularization of stenosed graft renal artery.<sup>16</sup> The graft survival rate following intervention was 86% in their study. In the study by Patil et al, among 24 patients who underwent PTR/stenting, there was a significant improvement in serum creatinine at 3 and 6 months post-intervention and the number of antihypertensive medications also decreased significantly. They also had a technical success rate of 100% and a clinical success rate of 79.2% at 6 months.<sup>19</sup> We observed that at one year of follow-up after diagnosis of TRAS, patients who underwent revascularization had better allograft function as compared to the patients who remained on conservative management strongly suggesting that early diagnosis and timely intervention of hemodynamically significant TRAS lesions have a good outcome.

The wider application of our finding is limited by a single-center study with a relatively small number of patients having TRAS and retrospective design. Moreover, not all of our patients with TRAS treated conservatively had undergone CT angiography. Thus, the possibility of missing significant stenotic lesions in those cases must be considered, which in addition to rejection may have accounted for poor allograft function at one year of follow up. However, our study highlights the fairly acceptable prevalence of TRAS in the first decade of starting kidney transplant and strong clinical suspicion leading to early diagnosis and intervention resulting in improved graft function; this could be a gratifying finding in transplant physicians and surgeons practicing in similar setups.

## CONCLUSION

Transplant renal artery stenosis had a prevalence of 2.6%. Graft dysfunction and uncontrolled hypertension were the two most common presentations. Close follow-up, strong clinical suspicion aided by renal Doppler study could clinch the diagnosis of TRAS. Percutaneous revascularization of the significant stenotic lesion had good clinical outcomes in terms of better BP control, reduction of antihypertensive pill burden, and preservation of graft function. Larger and elaborate studies could shed light on the risk factors for the development of TRAS.

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## CONFLICT OF INTEREST

The author(s) declare that they do not have any conflict of interest with respect to the research, authorship, and/or publication of this article.

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