

# Comparison of BK virus nephropathy risk between double-J-stent with anti-reflux mechanism and standart double-J-stent: single-center experience

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## ABSTRACT

**Aim:** Ureteral stent use is a risk factor for BK nephropathy (BKVN). In 2015, we compared the patients with anti-reflux mechanism DJS (ARD-DJS) and those used standard DJS (st-DJS) in terms of BKV and BKVN frequency in 90 kidney transplant patients in two centers. With the increase in the number of our patients over time and lengthening of the follow-up duration, we needed to re-evaluate the data in one center.

**Material and Method:** We retrospectively evaluated 211 patients who underwent kidney transplantation at Gazi Yaşargil Training and Research Hospital between September 2012 and September 2019. The following parameters were recorded, demographic data, immunosuppression protocols, presence of rejection, graft loss, plasma BKV levels, and presence of BKVN. Median and IQR follow-up time for ARD-DJS and St-DJS patients was 72 months (62,5-80,3 months) and 27,8 months (17,4-39,6 months) respectively.

**Results:** Thirteen patients (6,1%) had BKV viremia. BKVN was revealed by kidney biopsy in 3 of 13 patients. However, graft loss due to BKVN was observed in only one patient. ARD-DJS was used in 4 of these cases and standard DJS was used in 9 of these cases. Patients in whom BKV revealed in the first 3 months were compared in the aspect of DJS technique, BKV was significantly less observed in the ARD-DJS group (ARD-DJS: 2 patients; St-DJS:9 patients), ( $p=0,046$ ).

**Conclusion:** In our study, BKV was observed less in patients with ARD-DJS that were clinically significant but not statistically significant. Therefore, prospective randomized studies with high patient numbers are needed to determine the effectiveness of ARD-DJS.

**Keywords:** BKV, kidney transplantation, ureteral stent

## INTRODUCTION

BK virus (BKV) is a member of the polyomavirus family, which was first isolated in 1971 from the urine sample of a renal transplant patient, with clinical observations made over the years, it was understood that BKV is responsible for BKV nephropathy (BKVN) (1-3). The exact prevalence of BKVN is not known, however, it is estimated to be in the range of 1-15 %. BKVN is an important clinical problem causing graft loss in 15-50 % of transplant patients (4). Risk factors for BKV are aggressive immunosuppression, high human leukocyte antigen (HLA) mismatch, ureteral stent use, rejection therapy, prolonged ischemia duration, advanced age, male recipient, diabetes mellitus (DM), lymphocyte depleting induction therapies, tacrolimus, and mycophenolate-based regimens (5-10). It has been shown that the use

of double-J-Stent (DJS) in experimental animal models causes superficial epithelial destruction, ulceration, and inflammatory changes on the transitional epithelium in rat ureters, as well as increasing the incidence of BKVN by 4 times (2,11-13). Studies have shown that conditions that cause persistent hydronephroses, such as posttransplant ureter flexion and ureteral stenosis, may play a dynamic role in the pathogenesis of polyoma virus-associated nephropathy by causing ureteral reflux. Vesicoureteral reflux (VUR) may occur with normal bladder contraction while using DJS (14,15). In 2015, we compared the patients with anti-reflux mechanism DJS (ARD-DJS) and those used standard DJS (st-DJS) in terms of BKV and BKVN frequency in 90 kidney transplant patients in two centers (**Figure 1**). In this study, BKV was observed with significantly less frequency in

univariate analyzes in patients with ARD-DJS. However, no significant difference was observed in the multivariate analyzes. In this study, the small number of cases and the short follow-up duration were the factors limiting our study (13). With the increase in the number of our patients over time and lengthening of the follow-up duration, we needed to re-evaluate the data in one center.

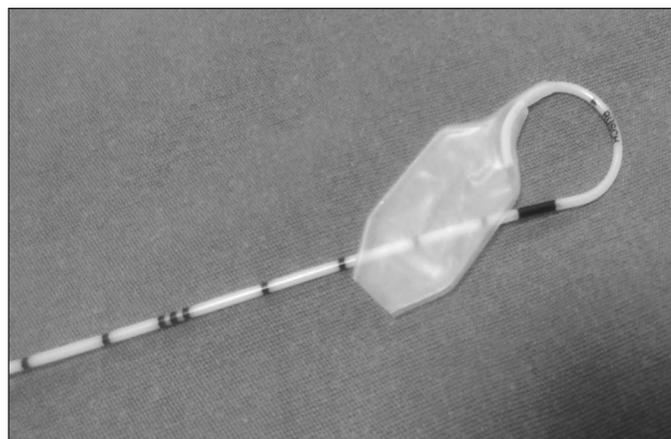


Figure. Anti-reflux mechanism double J stent

### MATERIAL AND METHOD

We retrospectively evaluated 211 patients who underwent kidney transplantation at Gazi Yaşargil Training and Research Hospital between September 2012 and September 2019. One hundred seventy of the patients had a living donor and 41 of them had deceased donor kidney transplantation. The following parameters were recorded, demographic data, immunosuppression protocols, presence of rejection, graft loss, plasma BKV levels, and presence of BKVN (Table 1,2).

The study was carried out with the permission of Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.03.2021, Decision No: 743). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

#### Immunosuppression and Prophylaxis

Basiliximab (20 mg at days 0 and 4 of operation) or anti-thymocyte globulin (ATG; for high-risk patients, 3 mg/kg during operation and 1,5 mg/kg at postoperative days 1 and 2) were used as induction therapy. Methylprednisolone 1000 mg was given intra-operatively. Methylprednisolone dose was decreased by half every day and 20 mg oral prednisolone was started on the 6th postoperative day for daily use. Oral prednisolone dosage was reduced gradually to reach 5 mg a day in the first year after transplantation. Calcineurin inhibitors (tacrolimus or cyclosporin) and mycophenolate mofetil (MMF; 2 g /day in two divided doses) or mycophenolate sodium (MMS; 1440 mg/day, in two divided doses) were used as maintenance immunosuppression therapy.

MMF was used as 600 mg/m<sup>2</sup> in two divided doses in children. We considered both mycophenolate mofetil and mycophenolate sodium in doses described above as the same drugs in our study. Everolimus was used in only one case (plasma level of the drug was targeted as 8-10 mg/dl). Trimethoprim/sulfamethoxazole and valganciclovir (450 mg a day) was prescribed for Pneumocystis jirovecii and cytomegalovirus (CMV) prophylaxis for 6 months after the transplantation. Acute rejection was diagnosed by kidney biopsy. The acute cellular rejection was treated with intravenous pulse methylprednisolone or ATG depending on the severity of the rejection. Plasmapheresis was added for acute humoral rejection. Delayed graft function (DGF) was described as a need for hemodialysis in the first week of kidney transplantation.

	St-DJS n=111	ARD-DJS n=100	P value
Sex F/M	46/65 (41.4%/58.6%)	42/58 (42%/58%)	0,935
Age (years)	30.99±13.4 (9-72)	35.06±12.8 (14-68)	0.018
Med / IQR follow up (m)	27.8 [17.4-39.6]	72 [62.5-80.3]	0.00
Living / deceased Donor	80/31 (72%/28%)	90/10 (90%/10%)	0.002
Relationship			
Parent to child	37 (33.3%)	32 (32%)	
Child to parent	0 (0%)	6 (6%)	
Sibling	11 (9.9%)	18 (18%)	
Between husband/wife	26 (23.4%)	29 (29%)	
3rd/4th degree relative	5 (4.5%)	6 (6%)	
donors			
Cadaveric	31 (28%)	10 (10%)	0.59
Preemptive	35 (31.2%)	35 (35%)	
Induction			
No	4 (3.6%)	11 (11%)	0.00
Basiliximab	9 (8.1%)	57 (57%)	0.00
ATG	98 (88.2%)	32 (32%)	0.00
Number of Rejection			
Cellular Rejection	7 (6,3%)	6 (6%)	1
Humoral Rejection	1 (0,9%)	2 (1.8%)	
CR + HR	2 (1.8%)	1 (0,9%)	
Graft loss	6 (5.4%)	6 (6%)	1
DGF	6 (5,4%)	3 (3%)	0.68
BKV	9 (8.1%)	4 (4%)	
500-5000	2 (1.8%)	2 (2%)	
5000-10000	1 (0.9%)	1 (1%)	
>10000	6 (5.4%)	1 (1%)	0.122
BKVAN	3	0	0.248
Last Cr level (mg/dl) med and IQR*	1.19 [0.96-1.47]	1.03 [0.86-1.25]	0,002

ARD-DJS: anti-reflux mechanism double J stenting; st-DJS: standart-DJS; ATG: anti thymocyte globülin DGF: delayed graft function; BKV: BK viremia; BKVAN: BKV-associated nephropathy; Cr: creatine.

Table 2. Comparison of BKV positive and negative cases			
	BKV + (>500)	BKV - (<500)	p
Donor			
Cadaveric	1 (0.05%)	40 (19%)	0.470
Alive	12 (5.6%)	158 (74.8%)	
Preemptive	6 (2.8%)	64 (30.3%)	0.365
Dialysis patient	7 (3.3%)	134 (63.5%)	
DGF (+)	0 (0%)	6 (2.8%)	1
DGF (-)	13(6.2%)	192 (90.2%)	
Mismatch			0,694
0 MM	0 (0%)	23 (10.9%)	
1MM	1 (0.005%)	6 (2.8%)	
2MM	2 (0.009%)	23 (10.9%)	
3 MM	5 (0.024%)	63 (29.9%)	
4 MM	1 (0.005%)	21 (9.9%)	
5 MM	1 (0.005%)	27 (12.8%)	
6 M	2 (0.009%)	15 (7.1%)	

DGF: delayed graft function; BKV: BK viremia

### Surgical Technique

An open or laparoscopic nephrectomy technique was applied for living donors. An extravesical technique (Lich-Gregoir) was applied to all transplanted patients for ureteroneocystostomy (UNS). Types of DJS used were dependent on the choice of surgeons. Cases were grouped later by whether their DJS had an anti-reflux mechanism or not (St-DJS vs ARD-DJS). Surgical drains were placed to all patients to the operation side. Urinary catheters were removed on the 5th postoperative day. Surgical drains were removed if there were no urinary leak and after urinary catheters were removed. All DJSs were removed by cystoscopy under local anesthesia at the 4th postoperative week. Urinary complication was described as the presence of urinary leak and stenosis at UNS.

### Follow-up

All patients were followed up closely for renal functions, BK viremia, and BKVN after kidney transplantation. First BKV tests were done during 1st postoperative month. All transplanted patients were tested for BKV from their serum by polymerase chain reaction (PCR) monthly in the first year after transplantation. All the patients were followed up at the posttransplant period for at least 12 months. Cases with >500 copies/ml by two or more consecutive measurements were accepted as having viremia. The immunosuppression dose was reduced when there was a higher viremia load (>5,000 copies/ml). Firstly MMF was discontinued and the prednisolone dose was reduced. If viremia continued, the calcineurin dose was reduced. Leflunomide was used for patients with BKVN. Kidney biopsy was performed to all cases with viremia for excluding BKVN.

### Statistical Analysis

Statistical analyses were performed using the SPSS software version 16. The variables were investigated using (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using medians and interquartile range (IQR) for the non-normally distributed and ordinal variables. The proportions of patients with ATG use, preemptive transplantation, and BKVN were grouped by types of DJS using cross-tabulations. The Chi-square test or Fisher's exact test, where appropriate, were used to compare these proportions in different groups. Blood creatinine measurements were not normally distributed; nonparametric tests were conducted to compare these parameters. The Mann-Whitney U test was used to compare the relationship between blood creatinine levels and the use of the ARD-DJS.

### RESULTS

In this study, the data of 211 patients who underwent kidney transplantation between September 2012 and September 2019 were retrospectively evaluated. The median and interquartile range (IQR) of age and time from kidney transplantation of patients was 32 years (22-42 years) and 48,9 months (26,2-71 months) respectively. Median and IQR follow-up time for ARD-DJS and St-DJS patients was 72 months (62,5-80,3 months) and 27,8 months (17,4-39,6 months) respectively.

Seventy patients (33,1%) underwent preemptive kidney transplantation. Basiliximab was used in 66 patients (31,3%) and ATG was used in 130 patients (61,6%) as induction therapy. Fifteen patients (7,1%) were not given induction therapy. Three cases used cyclosporin+MMF+ prednisolone, eight cases used everolimus+tacrolimus+prednisolone, and all other patients used tacrolimus+MMF+prednisolone for maintenance immunosuppression. Acute rejection was observed in 13 patients, humoral rejection in 3 patients, humoral, and cellular rejection in 3 patients. In 6 patients, graft loss due to rejection was observed (CR:3 HR:2 CR+HR: 1 patient). In postoperative duration DGF was observed in 9 patients (4,2%), graft loss was observed in 12 patients (5,7%). DJS was used in all patients, ARD-DJS was used in 100 patients (47,4). Thirteen patients (6,1%) had BKV viremia. BKV was revealed by kidney biopsy in 3 of 13 patients. However, graft loss due to BKVN was observed in only one patient. Except for 2 patients viremia was observed in the first 3 months in these patients, while in the other 2 patients, viremia was observed at 12 and 84 months after transplantation respectively. These 2 patients were in the group of ARD-DJS, in 4 of 13 patients with BKV, ARD-DJS, and in 9

patients st-DJS was used. Patients in whom BKV revealed in the first 3 months were compared in the aspect of DJS technique, BKV was significantly less observed in the ARD-DJS group (ARD-DJS: 2 patients; St-DJS: 9 patients), ( $p=0,046$ ). St-DJS was used in 6 of 7 patients with viremia level  $>10,000$ , however, this finding was not statistically significant. When the patients were compared according to their final blood creatinine levels, the creatinine levels in patients with st-DJS and ARD-DJS was 1,19 (range 0,96-1,47) and 1,03 (range 0,86-1,27) respectively which was statistically significant ( $p=0,002$ ). None of the patient groups had urinary leakage in the postoperative period. However, in one patient in each group, urinary stenosis was observed in the postoperative follow-up period and revision operation was performed.

## DISCUSSION

Ureteral stent use is considered as an independent risk factor for BKV viruria, BKV viremia, and BKVN. In a study conducted on 1147 patients, a ureteral stent was used in 443 (38,6%) of the patients, and BKV was observed in 17,2% of these patients, on the other hand, this ratio was 13,5% in patients without stent (16). Moreno et al. (17) detected BKV in 11 patients (6%) in their study conducted on 184 patients. In this study, they explained the low BKV rates by the different ureteral stent techniques. At the same time in this study, ureteral anastomosis was performed using the modified Taguchi extravesical reimplantation technique and, the stent was externalized from the skin with a 6 F radiopaque infant nasogastric tube, and the stent was removed on the 5th day (17). Gupta et al. (18) evaluated 402 transplant kidney biopsies between 2013 and 2016, BKVN was detected in 6 (1,49) patients. They attributed the lower rate of BKVN than the literature to the low immunosuppression dose and the high match in transplants from live relative donors. In our study, BKV was observed in 13 (6,1%) patients, which is lower than the rates of BKV in the literature. Another remarkable inference in our study is that BKV was observed in 9 (8,1%) of 111 patients in which st-DJS was used and in 4% of the patients used ARD-DJS, although these rates are not statistically significant among themselves, they show that ureteral stenting technique and stent type may also have a clinical meaning. BKVN was observed in 3 patients in our study, one of these patients resulted in graft loss, and also diffuse deep vein thrombosis occurred in the same patient. This patient died due to diffuse pulmonary embolism during follow-up. Considering that acute venous thrombosis was observed in a patient diagnosed with BKVN in a case report published in 2015, it is important to pay attention to the relationship between BKVN and DVT despite case-level studies (19).

In our study, we also reached some results that we could not interpret, when we compared the final blood creatinine levels in both groups we revealed that the creatinine level was lower in the patients with ARD-DJS, additionally, although the patients with ARD-DJS had a much longer follow-up period, the number of graft loss was similar to the patients with st-DJS.

The limitations of this study were its retrospective nature, the absence of a control group without DJS, and the need for much higher patient numbers, although the number of patients increased than our previous study. However, to the best of our knowledge, there are not enough studies in the literature evaluating the relationship between ARD-DJS and BKV.

## CONCLUSION

In our study, BKV was observed less in patients with ARD-DJS that were clinically significant but not statistically significant. Also, it was observed that the majority of patients with early developed BKV (first 3 months) were patients with st-DJS. Although close monitoring and reduction of immunosuppression prevent BKVN to a great extent, all arguments that can reduce the risk of BKV deserve to be investigated in detail. Therefore, prospective randomized studies with high patient numbers are needed to determine the effectiveness of ARD-DJS.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.03.2021, Decision No: 743).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The author has no conflicts of interest to declare.

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**Author Contributions:** The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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