Utility of Rejection Biomarker Tutivia in Managing Kidney Transplant Recipients at Risk of BK Nephropathy

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Abstract #3864

Poster
P1.07.253

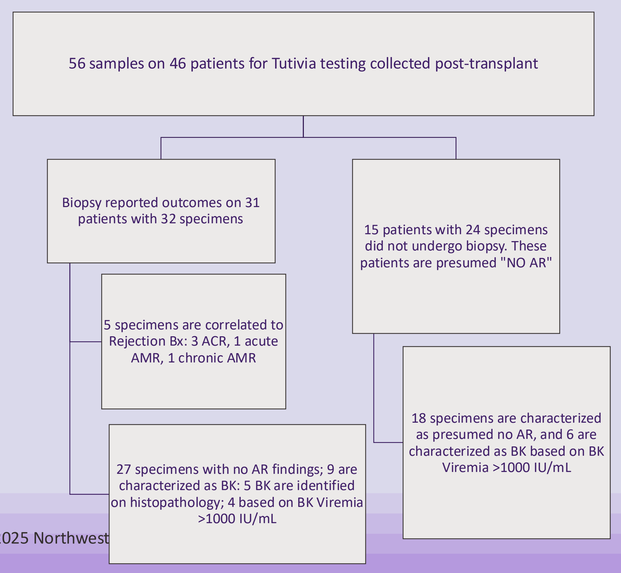
Background

Purpose: BK Polyoma Virus infection in Kidney Transplant Recipients (KTR) is a significant problem. It can manifest initially as development of BK viruria progressing to viremia, high levels of which correlate with BK nephropathy (BKVAN). BKVAN is associated with increased risk of rejection and graft failure. Currently, the only established treatment is reduction of immunosuppression, which in turn increases the risk of rejection. Indeed, in many cases of BKVAN, rejection due to reduction of immunosuppression contributes to eventual graft failure. We aimed to study the utility of Tutivia – a novel gene expression-based biomarker test of rejection in evaluating the risk of rejection in the setting of lowered immunosuppression in KTR with BKVAN or at risk of BKVAN.

Methods

The Tutivia test has been previously described in a validation study (1). Tutivia risk scores are provided as numerical values between 1-100 and defined as high-risk (score > 50) and low-risk score ≤ 50) for acute rejection. We retrospectively studied all 46 KTR who had Tutivia tests done at our center. There were 56 specimens from the 46 patients, and specimens were characterized as to rejection and BK status based on allograft biopsy findings or BK viral load testing of peripheral blood (Table 1); patients with BK viremia >1,000IU/mL were characterized as BKVAN. Patients with stable creatinine but without biopsy were characterized as presumed no rejection, Figure 1. The cohort included 16 patients who have undergone multiple transplants, including 1 HKT, 2 KLT, 1 SPKT who also had a failed KT, 8 patients with a single previous failed KT, 3 with two previous failed KT and 1 with 3 previous failed KT.

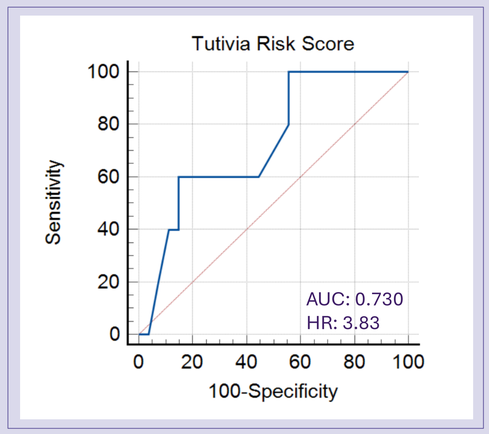
Figure 1: Consort Chart



Results

Tutivia performance in 32 samples with biopsy proven outcomes resulted in an AUC of 0.730, an accuracy of 78.13% and hazard ratio of 3.83, figure 2/table 2. In 15 specimens from 11 patients with proven or presumed BKVAN, 14 (93.3%) were low-risk Tutivia, resulting in an NPV of 100%, and overall, 48 of 56 (85.7%) patients had low-risk Tutivia results, figures 3-4. Examining Tutivia risk scores in patients with BK viremia at any level and in comparison to patients with rejection is shown in figure 5. A subset of patients, n=8, had at least 2 Tutivia tests over the course of time, range 63-312d, 6 patients experienced no rejection, while patients 11 and 9 experienced rejection, 1A and cAMR, respectively, figure 6. A single patient with high BK viremia and BKVAN on biopsy had 4 Tutivia measures over the course of IS adjustment for BK, figure 7. This patient demonstrates consistently low-risk Tutivia, ranging between 39-50, during the 5 month period culminating in improved BK viral load without occurrence of AR. The subset of patients with multiple transplants is plotted in comparison to first time kidney transplants, patients with rejection findings on biopsy are plotted in red, figure 8.

Figure 2: ROC in biopsy defined outcomes



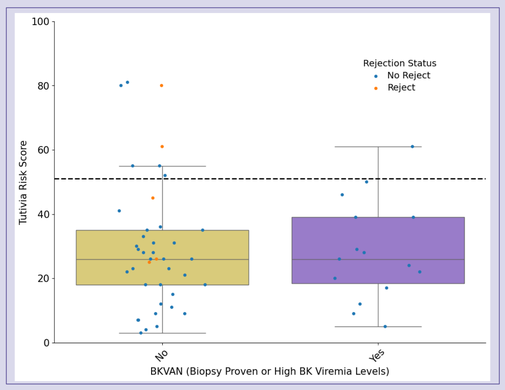


Figure 3: Tutivia Risk Scores in Patients with and without BK

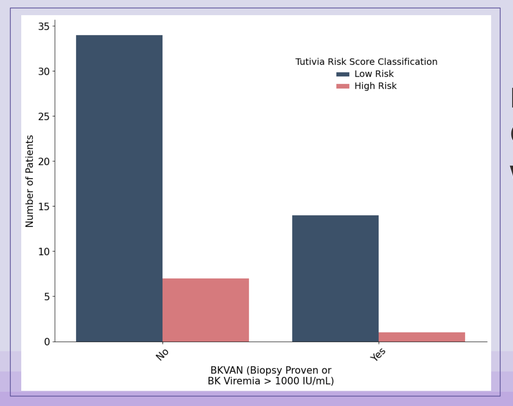


Figure 4: Tutivia Risk Classification in Patients with and without BK

Table 1: AR Outcomes in BK+/BK- Patients

		Rejection	
		No-Rejection	Rejection
BK Positivity	Positive (>0)	22	0
	Negative (0)	29	5

Table 2: Tutivia Performance

	Performance (%)	95% CI
Sensitivity	40.0	5.3 - 85.3
Specificity	85.2	66.3 - 95.8
PPV	33.3	10.9 - 67.1
NPV	88.5	78.7 - 94.1
Accuracy	78.13	60.0 - 90.7

Figure 6: Patients with Sequential Tutivia

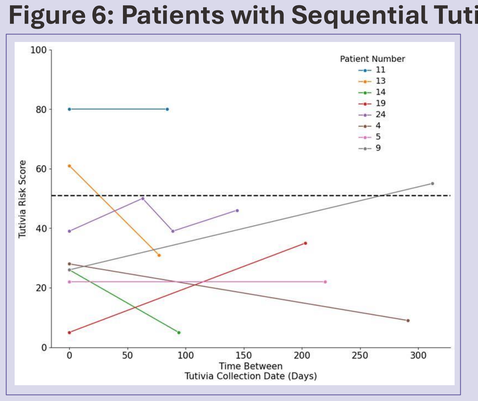


Figure 7: Single Patient with IS Changes

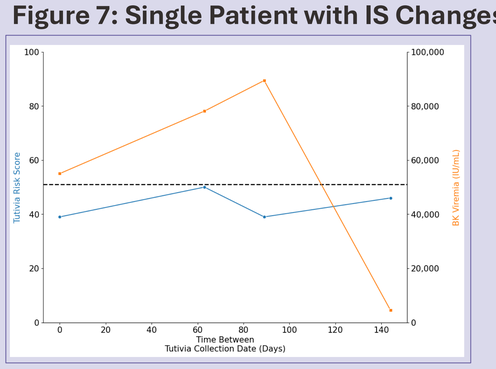
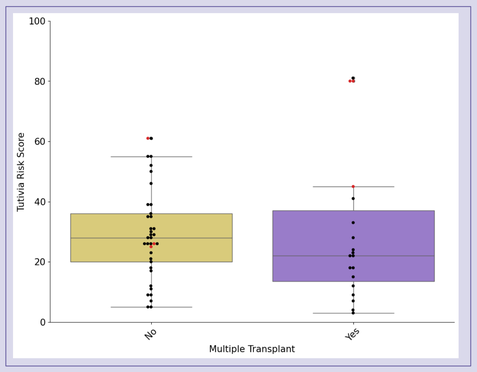


Figure 8: Tutivia in Multiple Transplants



Conclusions

Tutivia, a novel gene expression-based biomarker test of rejection in kidney transplant recipients performs, in the real-word, similar to that reported in the validation study (1). Furthermore, recipients with BKVAN or at risk thereof had low-risk Tutivia scores consistently. Tutivia test NPV of 100% for rejection in these patients will aid clinicians in decisions regarding performing a biopsy to rule out underlying rejection and managing BK infection by progressively lowering immunosuppression with confidence, guided by serial Tutivia monitoring.

References

1. Bestard O, et al. *Am J Transplant*. 2024;24(3):436-447.