The Role of Gene Expression Profile in Predicting Acute Rejection

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Introduction

Tutivia™ utilizes a next-generation sequencing assay that analyzes mRNA sequencing from peripheral whole blood and employs a validated 17-gene mRNA signature alongside a proprietary artificial intelligence derived algorithm (1). This approach classifies kidney transplant recipients as either low risk or high risk for acute rejection (AR). This analysis aims to identify the relationship between Tutivia™, incidence of allograft rejection and the overall stability of renal allograft function.

Methods

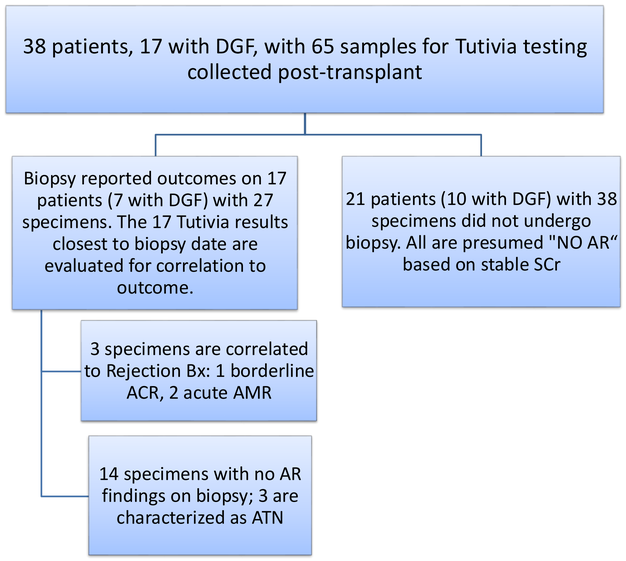
A total of 65 samples were collected from 38 patients who had undergone kidney transplants, table 1. Patients were divided into two groups. The first group consisted of patients who had a kidney biopsy and a Tutivia™ sample collected within 40 days before or after the biopsy (kidney biopsy group). The second group included patients with a Tutivia sample taken but no biopsy performed, showing stable serum creatinine levels (probable absence of AR), figure 1. Tutivia™ score of >50 is classified as a high risk for AR while a score ≤50 is classified as low risk for AR. We calculated the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for the biopsy group alone and for the combined two groups of patients (2). We calculated the odds ratio (OR) to determine the likelihood a high risk result is associated with AR in comparison to the likelihood that a low risk Tutivia™ score is associated with biopsy-proven no acute rejection or probable absence of AR (2).

Table 1: Demographics

	No biopsy n=21	Biopsy proven n=17
Age (years) mean (median)[IQR]	53 (56) [44.6-61.6]	51 (52) [43-63]
Female, n (%)	7 (33.3)	4 (23.5)
Race/Ethnicity, n (%)		
Asian	-	1 (5.8)
African American	12 (57.1)	8 (47)
Caucasian	2 (9.5)	6 (35.2)
Hispanic	7 (33.3)	2 (11.7)
DDKT, n (%)	21 (100)	16 (94.1)
PRA class I %, mean, (median) [IQR]	39 (9) [0-88]	14 (0) [0-11]
PRA class II %, mean, (median) [IQR]	31 (6) [0-54]	18 (3) [0-31]
KDPI %, mean (median) [IQR]	47 (52.5) [24.5-63]	55 (52.5) [33.7-79.5]
KDPI>84%, n (%)	2 (9.5)	1 (5.8)
DCD, n (%)	9 (42.8)	11 (64.7)
DGF, n (%)	10 (47.6)	7 (41.1)

Note: DDKT: deceased donor kidney transplant, PRA: panel reactive antibodies, KDPI: kidney disease profile index, DCD: donation after circulatory death, DGF: delayed graft function

Figure 1: Consort Chart



Conclusions

Our analysis indicates that Tutivia™ is highly effective in ruling out AR, achieving a negative predictive value of 97.9% and specificity of 90.2%, inclusive of a patient population in which nearly half have DGF.

This performance is comparable and/or superior to other existing biomarkers in the field (3, 4).

We found that a low Tutivia score is associated with excellent short-term outcomes for renal transplants, with a mean GFR of 51mL/min/1.73m*^{2}.

Further analysis is needed to better validate its role in predicting acute rejection and long-term renal allograft function.

Results

A total of 38 patients were in our study; 17 (44.7%) were patients with delayed graft function (DGF). 21 patients did not undergo a kidney biopsy but were considered stable based on serum creatinine (SCr) measures and were evaluated as presumed probable noAR. 17 patients had a kidney biopsy performed and a Tutivia test performed within +/- 40 days of the biopsy, figure 3. We obtained Tutivia test on 65 samples from the combined sets of patients: 27 samples from the biopsy group and 38 samples from the non-biopsy group, figure 2. Demographic data is presented in Table 1. In the biopsy group, Tutivia™ was correlated to histopathology defined outcomes according to current BANFF criteria based on the Tutivia test closest in time to that biopsy. Tutivia results produced and AUC of .762 and demonstrated a sensitivity of 66.7%, specificity of 85.7%, NPV of 92.3%, a PPV of 50.0%, and an overall test accuracy of 82.4%. OR for this biopsy-defined group was 12.0. When combining both biopsy proven and SCr stable groups, Tutivia™ performance resulted in an AUC of 0.784, sensitivity of 66.7%, specificity of 90.2%, NPV of 97.9%, PPV of 28.6%, and an overall test accuracy of 88.9%. OR in the combined cohorts was 18.4, p = 0.0265, table 2.

Figure 2: Tutivia Risk Score Distribution

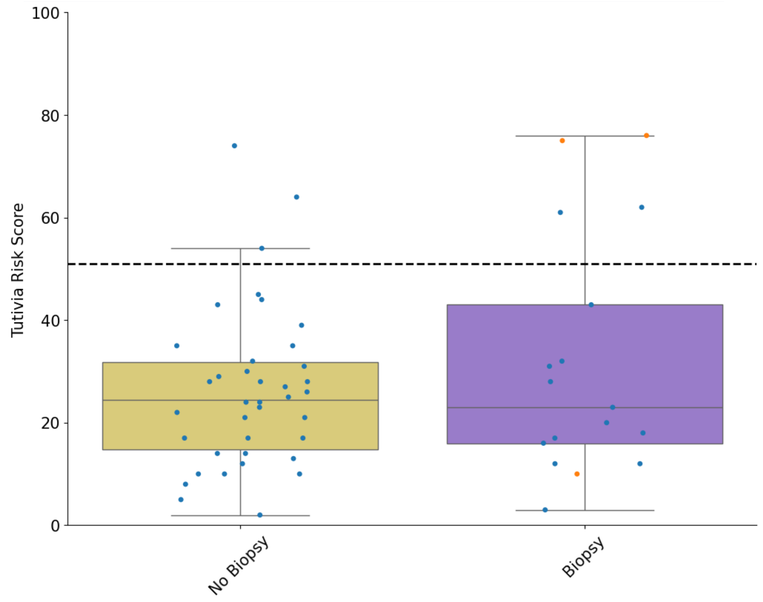
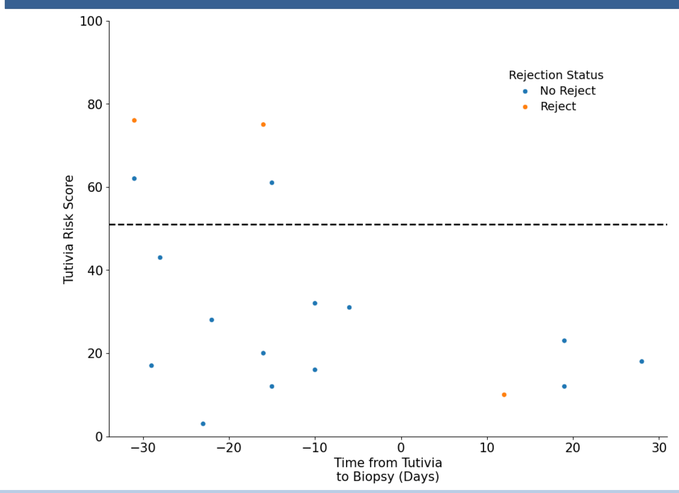


Table 2: Tutivia Performance Characteristics

	Tutivia correlated to kidney biopsy samples (95% CI)	Tutivia correlated to biopsy defined outcomes + presumed no AR samples in non-biopsy patients (95% CI)
AUC	0.762 (0.498 – 0.930)	0.784 (0.651 – 0.885)
Sensitivity %	66.7 (9.43 – 99.16)	66.7 (9.43 – 99.16)
Specificity %	85.71 (57.19 – 98.22)	90.2 (78.59 – 96.74)
NPV %	92.3 (70.48 – 98.37)	97.9 (90.25 – 99.56)
PPV %	50.0 (18.06 – 81.94)	28.6 (11.20 – 55.93)
Accuracy %	82.4 (56.57 – 96.20)	88.9 (77.37 – 95.81)
Odds Ratio	12.0, p = 0.0851	18.4, p = 0.0265

Figure 3: Tutivia Risk Score Relative to Biopsy Time



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