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Using Urine Chemokines as a Personalized Serial Monitoring Tool for Kidney Allograft Rejection

A. Singla[1], S. Park[1], H. Pedamallu[1], K. Chen[1], B. Robelly[1], C. Rebello[1], C. Lantz[1], L. Zhao[1], R. Sinha[2], R. LaCombe[2], G. Hanna[2], S. Kleiboeker[2], S. Mehrotra[1] and J. Friedewald[1]

[1]Northwestern University, Illinois, USA

[2]Eurofins Transplant Genomics, Kansas, USA

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INTRODUCTION

Urine chemokines CXCL9 and CXCL10 are emerging biomarkers for monitoring posttransplant kidney rejection; however, their potential as a personalized, patient-specific tool has not been well studied.

We demonstrate that urine chemokines, when used as a serial monitoring tool, can provide high diagnostic and personalized insights in managing kidney rejection.

AIMS

This study aims to:

1) assess the diagnostic utility of serial urine chemokines testing over single-time point measurements for early detection of kidney rejections, and
2) generate patient-specific insights on kidney rejection using the trajectory analysis of urine chemokines.

METHODS

We analyzed longitudinal data from the multi-center CTOT-08 trial, which included urine samples from 249 kidney transplant recipients collected at 2-3, 6, 12, 15, and 24 months posttransplant, along with over 600 biopsy-paired samples.

Patient-specific CXCL9/creatinine (CXCL9/Cr) and CXCL10/creatinine (CXCL10/Cr)-based predictors—including historical averages, instantaneous values, longitudinal slopes over the past year, and baseline changes—were incorporated into a logistic regression (LR) model to predict subclinical acute rejection (subAR, 123 events) versus no rejection with stable kidney function (TX, 350 events).

RESULTS

1. Urine CXCL9/Cr and CXCL10/Cr single-time-point measurements achieved AUC values of 0.655 and 0.611, respectively, for predicting subclinical AR over no-rejection (Tables 1,2).
2. An LR model with CXCL9/Cr values, historical longitudinal slopes, and baseline changes achieved an AUC of 0.72 for predicting subAR over TX, with sensitivity, specificity, NPV, and PPV of 0.64, 0.79, 0.86, and 0.51, respectively (Table 3).
3. An LR model using CXCL10/Cr-based patient-specific predictors achieved an AUC of 0.66, with sensitivity, specificity, NPV, and PPV of 0.78, 0.52, 0.87, and 0.37, respectively (Table 3).
4. We found that when CXCL9/Cr > 1.3 and its patient-specific historical slope was > 0.04, the risk of subAR doubled compared to when CXCL9/Cr was < 1.3 (Figure 1).
5. CXCL10/Cr values significantly decrease after a subAR event. The slope of CXCL10/Cr from pre-subAR to subAR events fell within a 95% CI of -0.43 to 1.04, indicating potentially higher CXCL10/Cr levels before a subAR event (Figure 2).

Biomarkers and threshold	Accuracy	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CXCL9/Cr >1.206 (0.1 ng/mg)	0.67	0.64 (0.55,0.72)	0.68 (0.63,0.73)	0.41 (0.34,0.48)	0.84 (0.79,0.88)
CXCL10/Cr >0.355 (0.1 ng/mg)	0.61	0.61 (0.52,0.7)	0.62 (0.56,0.67)	0.36 (0.3,0.43)	0.82 (0.77,0.86)

Table 1. *Performance of single time-point urine chemokines measurements to detect subclinical acute rejection versus TX.*

Urine chemokine	OR	95% CI	p-value
CXCL9/Cr	1.05	1.01-1.09	0.01
CXCL10/Cr	1.07	0.95-1.19	0.20

Table 2. *Summary of Logistic Regression Models for urine chemokines with single time-point urine chemokines measurements to predict subclinical acute rejection over TX.*

Predictors	OR, 95% CI, p-value for CXCL9-based predictors	OR, 95% CI, p-value for CXCL10-based predictors
Single-time point measurement	1.075, 95% CI: 1.03-1.13, p=0.003	0.911, 95% CI: 0.01-1.18, p=0.49
Historical slope at the time of an event	0.062, 95% CI: 0.01-1.43, p=0.16	0.214, 95% CI: 0.01-1458, p=0.72
Baseline change	0.99, 95% CI: 0.97-1.02, p=0.7	1.23, 95% CI: 1.06-1.42, p=0.006

Table 3. *Summary of Multivariate Logistic Regression Models for CXCL9 and CXCL10 separately with single time-point urine chemokines measurements, historical slopes and baseline changes as predictors to predict subclinical acute rejection over TX.*

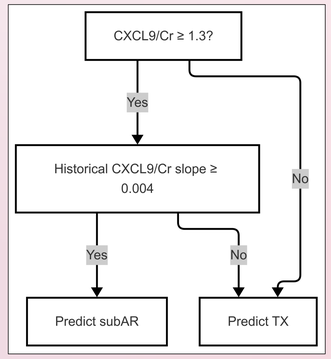

Figure 1. *Decision-tree model with CXCL9 and CXCL10-based trajectory predictors to predict subAR vs TX.*

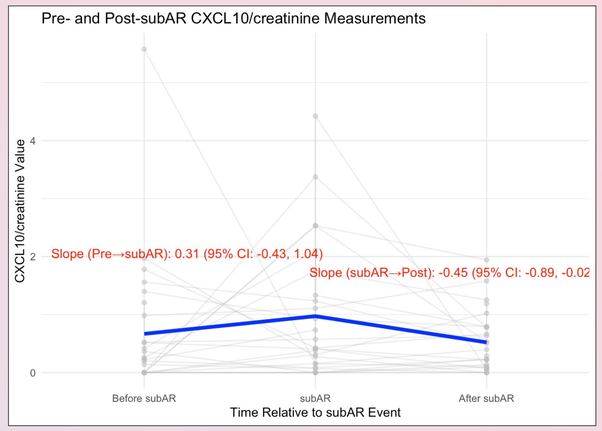

Figure 2. *Pre- and Post-subAR event CXCL10/Cr slopes.*

CONCLUSIONS

Our findings demonstrate that a serial monitoring of urine chemokines can significantly improve the diagnostic performance of predicting kidney allograft rejection over single-time point measurements.

Both CXCL9 and CXCL10 provide complementary insights into the risks of rejection. CXCL9 seems to provide better diagnostic performance, whereas, CXCL10 show early indications of rejection.

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CONTACT INFORMATION

Akhil Singla, akhilsingla@u.northwestern.edu

John J. Friedewald, john.Friedewald@nm.org

Sanjay Mehrotra, mehrotra@northwestern.edu