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Diagnostic and Economic Analysis of Combining Blood Gene Expression, Plasma Cell-Free DNA, and Urine Chemokines to Diagnose Rejection in Kidney Transplant Recipients

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INTRODUCTION

Urine chemokines, blood-based gene expression profiling (GEP), and donor-derived cell-free DNA (dd-cfDNA) have all been shown to correlate with the presence or absence of rejection. Despite these advantages, the high cost of GEP and dd-cfDNA assays compared to urine chemokines limits their frequent and widespread use.

This challenge has motivated our investigation into the role of urine chemokines as an initial screening tool to guide a cost-effective and noninvasive diagnostic approach.

AIMS

This study aims to
1) develop and assess the reliability of a model for detecting subclinical AR using a combination of previously studied blood biomarkers: GEP, dd-cfDNA, and urine chemokines,
2) investigate stepwise models to minimize the cost while maximizing the diagnostic performance.

RESULTS

1. GEP + dd-cfDNA-based testing achieved accuracy, sensitivity, specificity, PPV, and NPV values of 0.72, 0.71 (95% CI: 0.63-0.79), 0.73 (95% CI: 0.68-0.77), 0.48 (95% CI:0.43-0.53), and 0.88 (95% CI:0.85-0.91), respectively, with improved sensitivity and NPV over the individual tests.
2. We demonstrated that urine chemokines show high specificity and NPV beyond a certain threshold.
3. In this economic framework (Figure 1), a screening threshold on CXCL9/Cr between 0.85 (0.1ng/mg) and 1.32 (0.1ng/mg) achieved an optimal balance between the false and true negatives for a reasonable false negative cost (Figure 2).
4. In addition, this approach resulted in a 48%-58% reduction in diagnostic cost ($p<0.0001$) compared to the combined GEP and dd-cfDNA test, by recommending the stage-2 test only 38.7%-48.7% of the time (Table 1)
5. We validated these screening thresholds, where a threshold of 1.32 (0.1ng/mg) on CXCL9/Cr demonstrated similar results.

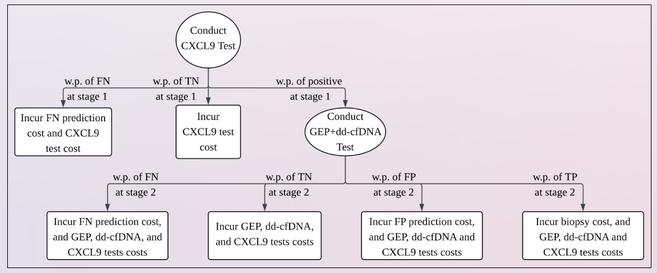

Figure 1. Decision tree-based economic analysis framework to identify the expected diagnostic and prediction costs of a two-stage model for a given screening threshold with CXCL9 as first-stage test.

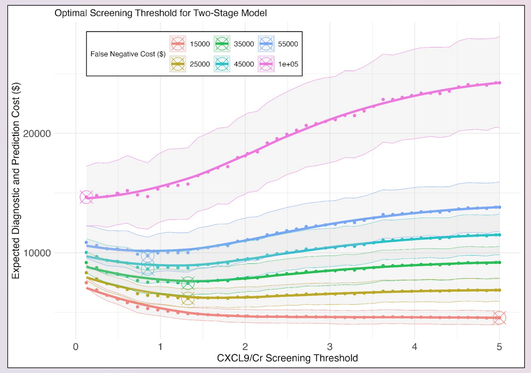

Figure 2. Expected Diagnostic and Prediction cost of a two-stage model with CXCL9 as a stage-1 test for different screening thresholds on CXCL9/Creatinine and a range of false negative outcome costs

Biomarker Model	Diagnostic Accuracy				Expected Diagnostic Cost for given screening threshold ($)
	Sensitivity	Specificity	Prevalence-adjusted NPV	Prevalence-adjusted PPV	
A single-stage CXCL9 with a threshold of 1.206 (0.1ng/mg) on CXCL9/Cr	0.64 (0.55,0.7)	0.68 (0.63,0.73)	0.84 (0.79,0.88)	0.41 (0.34,0.48)	200
A single-stage CXCL10 with a threshold of 0.355 (0.1ng/mg) on CXCL10/Cr	0.61 (0.52,0.7)	0.62 (0.56,0.67)	0.82 (0.77,0.86)	0.36 (0.3,0.43)	200
combined GEP & dd-cfDNA	0.71 (0.63,0.79)	0.73 (0.68,0.77)	0.88 (0.85,0.91)	0.48 (0.43,0.53)	5993
CXCL9-based two-stage test with a screening threshold of 1.32 (0.1ng/mg)	0.51 (0.42,0.60)	0.89 (0.85,0.92)	0.84 (0.81,0.86)	0.62 (0.54,0.70)	2521.96 (2262.53,2794.37)
CXCL10-based two-stage test with a screening threshold of 0.355 (0.1ng/mg)	0.5 (0.4,0.59)	0.87 (0.83,0.9)	0.83 (0.8,0.86)	0.57 (0.49,0.66)	2859.23 (2586.82, 3131.64)
Combined CXCL9 & CXCL10-based two-stage test with a probability threshold of 0.25	0.5 (0.41,0.58)	0.9 (0.86,0.93)	0.83 (0.81,0.86)	0.63 (0.55,0.72)	2518.19 (2258.75, 2790.6)

Table 1. Comparison of Diagnostic and Economic Performance of different two-stage models with single-stage urine chemokines and combined GEP & dd-cfDNA tests along with their 95% confidence intervals at a subclinical acute rejection prevalence rate of 26.19%.

METHODS

Study Population: Discovery dataset includes 121 subclinical acute rejection (subAR), and 341 no-rejection events (TX) from 226 subjects. Validation dataset includes 54 subAR and 92 TX events from 136 subjects.

Two-stage model development:
- Cost of CXCL9 and CXCL10: $200 each, and a blood-based GEP and dd-cfDNA test costs $5993.
- Since a false-negative cost can vary, we consider that a false-negative outcome may incur costs ranging from $15,000 to $100,000.
- For a positive outcome at Stage 2, we considered the cost of performing a biopsy ($2111.25) for definitive confirmation.

CONCLUSIONS

Our findings demonstrate that a two-stage diagnostic approach is both more cost-effective and diagnostically robust for the surveillance of subclinical AR in KT recipients when compared to current strategies. By leveraging the high NPV and affordability of urine chemokine assays to triage patients, this strategy minimizes the use of expensive blood-based tests and invasive biopsies, thereby reducing per-patient diagnostic costs while preserving clinical accuracy.

Using a decision-tree-based framework that integrates diagnostic accuracy and cost, we provide a novel framework for identifying a screening threshold in a two-stage diagnostic model.

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