Supplementary Appendix for

Urinary CXCL10 independently improves non-invasive diagnosis of antibody-mediated kidney allograft rejection

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SUPPLEMENTARY RESULTS

Sensitivity analysis

In the sensitivity analysis, we assessed the robustness of our study results by investigating the diagnostic accuracy of the urine biomarkers separately in the subgroup of non-sensitized patients (e.g., patients with no identified preformed DSA) and in a subgroup analysis that included only the first biopsy of each patient.

We first evaluated the performance of the biomarkers in predicting AR and ABMR while restricting the analysis in the subgroup of non-sensitized patients. This subgroup analysis included 119 patients with no rejection, 2 patients with TCMR, 13 patients with pure ABMR and 16 patients with mixed rejections. **Supplemental Figure 2** shows that the four protein biomarkers accurately predicted AR (**Supplemental Figure 2A**) and ABMR (**Supplemental Figure 2B**), with CXCL10 (AUC=0.78; 95% CI: 0.70-0.87; P=1.3E-06) and CXCL10: Cr (AUC=0.78; 95% CI: 0.69-0.86; P=1.9E-06) yielding the best AUC values for ABMR prediction.

Second, 37 patients were biopsied more than once in the study period; therefore, the performance of urinary biomarkers was evaluated in predicting AR and ABMR, while the analysis was restricted to only the first biopsy of each patient. This subgroup analysis included 171 patients with no rejection, 8 patients with TCMR, 35 patients with pure ABMR and 30 patients with mixed rejections. Again, the four protein biomarkers accurately predicted AR (**Supplemental Figure 2C**) and ABMR (**Supplemental Figure 2D**), and CXCL10 (AUC=0.74; 95% CI: 0.67-0.81; P=4.0E-09)) and CXCL10: Cr (AUC=0.75; 95% CI: 0.68-0.82; P=1.0E-09) still showed the best AUC values for ABMR prediction.

Does normalization by urine creatinine improve biomarker diagnostic performance?

Because the need for normalization of protein biomarkers with urine creatinine remains debatable, we compared the accuracy of CXCL9 and CXCL10 in noninvasively diagnosing AR with and without normalization with urine creatinine. The results shown in **Figure 1B** confirm the strong correlation between CXCL9 and the CXCL9: Cr ratio (r_s=0.85, P<2.2E-16) and between CXCL10 and the CXCL10: Cr ratio (r_s=0.90, P<2.2E-16). A comparison of ROC curves of markers, normalized or not to urine creatinine, in predicting AR revealed similar results (**Figure 2B, 2C, 2D and Supplemental Table 3**). Taken together, these results suggest that urine creatinine normalization does not significantly improve the diagnostic performance of the evaluated biomarkers. As the prognostication of graft survival after ABMR seemed better when using the CXCL10: Cr ratio (see below), we considered this ratio as the best marker of ABMR and showed all subsequent data using this ratio.

Analysis of confounding factors

We examined whether the urine CXCL10: Cr ratio is diagnostic of ABMR under different conditions that may affect the value of this ratio independently of rejection. The urinary CXCL10: Cr ratio distinguished ABMR from DNR independently of the donor type, recipient age, recipient gender, history of delayed graft function, time post-transplantation, and coexisting scaring lesions on the kidney allograft (**Supplemental Table 4)**. However, significant leukocyturia (>10^4/mL) was found to increase the urinary CXCL10: Cr ratio in patients with no rejection (2.0$\pm$0.3 vs. 0.9$\pm$0.1, P=5.1E-4). The impact of leukocyturia on the performance of CXCL10: Cr in diagnosing ABMR remained minimal, and the exclusion of samples with significant leukocyturia only improved the AUC from 0.755 to 0.765 (P=0.84).

SUPPLEMENTARY DISCUSSION

Normalization of proteins using urine creatinine

Certain other aspects of the study warrant highlighting. First, whether urinary protein levels should be normalized to urine creatinine to correct for urine concentration remains debatable. Urinary values of protein biomarkers are usually reported in relation to urine creatinine, and the implicit assumption is that creatinine excretion is constant across and within individuals, such that changes in the ratio will reflect changes in biomarker excretion. This general rule has been applied in several studies in the field of biomarker discovery for renal allograft rejection,[1-3] but not in all studies.[4-8] Several studies questioned the validity of normalizing urinary protein levels to creatinine. For instance, Waikar et al challenged the assumption that normalization to creatinine can be used in the acute state of acute kidney injury, in which creatinine clearance is, by definition, changing acutely.[9] We therefore decided to compare urinary biomarkers with and without normalization with urine creatinine to investigate this question in kidney transplant patients with acutely dysfunctional kidney allografts. We showed that normalization to urine creatinine had very little benefit, if any, in diagnosing AR. Nevertheless, the CXCL10: Cr ratio provided not only better diagnostic but also prognostic insight, and we recommend the use of CXCL10: Cr as the best noninvasive predictor of ABMR.

Leukocyturia as a confounding factor

Our study also identified a confounding factor in the assessment of urine chemokine levels. We showed that leukocyturia increased the levels of CXCL10 (**Supplemental Table 4**) and CXCL9 (data not shown). Urinary tract infection is often considered a potential confounding factor in the field of urinary biomarkers of AR, although few data are available.

Several studies claim that urinary tract infection does not significantly alter CXCL9 and CXCL10 levels;[8] however, results remain inconclusive due to the small number of affected subjects [10] or the lack of data. [3, 6] Notably, in the Hricik study, a small group of 7 patients with concomitant infection, five of whom had bacterial urinary tract infections, was studied.[5] Our subgroup analysis revealed that leukocyturia may increase urinary chemokine levels. This point will need to be considered when implementing these new monitoring tools in clinical practice, and urinary tract infections will need to be ruled out to facilitate accurate interpretation of the biomarker results.

SUPPLEMENTARY REFERENCES

1. Dubinski B, Boratynska M, Kopec W, Szyber P, Patrzalek D, Klinger M: Activated cells in urine and monocyte chemotactic peptide-1 (MCP-1)--sensitive rejection markers in renal graft recipients. *Transpl Immunol* 18: 203-207, 2008
2. Peng W, Chen J, Jiang Y, Wu J, Shou Z, He Q, Wang Y, Chen Y, Wang H: Urinary fractalkine is a marker of acute rejection. *Kidney international* 74: 1454-1460, 2008
3. Schaub S, Nickerson P, Rush D, Mayr M, Hess C, Golian M, Stefura W, Hayglass K: Urinary CXCL9 and CXCL10 levels correlate with the extent of subclinical tubulitis. *Am J Transplant* 9: 1347-1353, 2009
4. Hauser IA, Spiegler S, Kiss E, Gauer S, Sichler O, Scheuermann EH, Ackermann H, Pfeilschifter JM, Geiger H, Grone HJ, Radeke HH: Prediction of acute renal allograft rejection by urinary monokine induced by IFN-gamma (MIG). *J Am Soc Nephrol* 16: 1849-1858, 2005
5. Hricik DE, Nickerson P, Formica RN, Poggio ED, Rush D, Newell KA, Goebel J, Gibson IW, Fairchild RL, Riggs M, Spain K, Ikle D, Bridges ND, Heeger PS: Multicenter validation of

urinary CXCL9 as a risk-stratifying biomarker for kidney transplant injury. *Am J Transplant* 13: 2634-2644, 2013

6. Hu H, Aizenstein BD, Puchalski A, Burmania JA, Hamawy MM, Knechtle SJ: Elevation of CXCR3-binding chemokines in urine indicates acute renal-allograft dysfunction. *Am J Transplant* 4: 432-437, 2004
7. Hu H, Kwun J, Aizenstein BD, Knechtle SJ: Noninvasive detection of acute and chronic injuries in human renal transplant by elevation of multiple cytokines/chemokines in urine. *Transplantation* 87: 1814-1820, 2009
8. Matz M, Beyer J, Wunsch D, Mashreghi MF, Seiler M, Pratschke J, Babel N, Volk HD, Reinke P, Kotsch K: Early post-transplant urinary IP-10 expression after kidney transplantation is predictive of short- and long-term graft function. *Kidney Int* 69: 1683-1690, 2006
9. Waikar SS, Sabbisetti VS, Bonventre JV: Normalization of urinary biomarkers to creatinine during changes in glomerular filtration rate. *Kidney international* 78: 486-494, 2010
10. Hirt-Minkowski P, Amico P, Ho J, Gao A, Bestland J, Hopfer H, Steiger J, Dickenmann M, Burkhalter F, Rush D, Nickerson P, Schaub S: Detection of clinical and subclinical tubulo-interstitial inflammation by the urinary CXCL10 chemokine in a real-life setting. *Am J Transplant* 12: 1811-1823, 2012

Supplementary Table 1: Banff scores (mean±SD) and percent of patients with histology scores >0 based on 281 indication biopsies

Banff elementary scores	Dysfunction with no rejection group (N=203)					TCMR (N=10)	Pure ABMR (N=37)	Mixed rejection (N=31)
	All DNR (N=203)	Acute tubular injury (N=43)	Borderline changes (N=17)	IF/TA (N=140)	Recurrence (N=3)			
Glomerulitis (g)								
% with g score>0	57 (28.5%)	9 (20.9%)	5 (33.3%)	41 (29.5%)	2 (66.7%)	2 (25.0%)	33 (94.3%)	28 (100.0%)
g score, mean±SD	0.3±0.6	0.3±0.6	0.3±0.5	0.3±0.5	1.3±1.2	0.2±0.5	1.7±0.9	2.3±0.8
Peritubular capillaritis (ptc)								
% with ptc score>0	36 (17.9%)	1 (2.3%)	7 (43.8%)	26 (18.7%)	2 (66.7%)	5 (55.6%)	27 (73.0)	29 (96.7)
pct score, mean±SD	0.2±0.5	0±0.2	0.5±0.6	0.2±0.5	1.0±1.0	0.8±0.8	1.3±1.1	2.1±0.8
Interstitial infiltrates (i)								
% with i score>0	7 (3.6%)	0 (0.0%)	7 (50.0%)	0 (0.0%)	0 (0.0%)	8 (88.9%)	0 (0.0%)	11 (50.0%)
i score, mean±SD	0.0±0.2	0.0±0.0	0.5±0.5	0.0±0.0	0.0±0.0	2.1±0.9	0.0±0.0	1.0±1.3
Tubulitis (t)								
% with t score>0	37 (18.3%)	1 (2.3%)	16 (100%)	20 (14.3%)	0 (0.0%)	10 (100.0%)	0 (0.0%)	25 (92.6%)
t score, mean±SD	0.3±0.8	0.1±0.5	2.1±1.0	0.2±0.6	0.0±0.0	2.9±0.3	0.0±0.0	2.0±1.0
Vasculitis (v)								
% with v score>0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (9.7%)	6 (26.1%)
v score, mean±SD	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.3±0.8	0.5±0.9
Allograft glomerulopathy (cg)								
% with cg score>0	10 (5.0%)	0 (0.0%)	0 (0.0%)	9 (6.5%)	1 (33.3%)	1 (10.0%)	19 (51.4%)	10 (34.5%)
cg score, mean±SD	0.1±0.5	0.0±0.0	0.0±0.0	0.1±0.5	1.0±1.7	0.1±0.3	1.1±1.3	0.7±1.1
Mesangial expansion (mm)								
% with mm score>0	84 (42.0%)	10 (23.3%)	8 (50%)	64 (46.4%)	2 (66.7%)	2 (20.0%)	28 (80.0%)	14 (56.0%)
mm score, mean±SD	0.7±1.0	0.3±0.6	0.7±0.9	0.8±1.0	1.7±1.5	0.3±0.7	1.5±1.1	1.0±1.1
Interstitial fibrosis (ci)								
% with ci score>0	154 (76.6%)	0 (0.0%)	12 (75%)	139 (100.0%)	3 (100.0%)	7 (77.8%)	35 (94.6%)	20 (87.0%)
ci score, mean±SD	1.5±1.1	0.0±0.0	1.7±1.2	1.9±0.8	2.0±1.0	1.9±1.4	1.9±0.9	2.0±1.1
Tubular atrophy (ct)								
% with ct score>0	152 (75.2%)	0 (0.0%)	12 (75.0%)	137 (97.9%)	3 (100.0%)	7 (77.8%)	35 (94.6%)	19 (79.2%)

ct score, mean±SD	1.5±1.1	0.0±0.0	1.7±1.2	1.9±0.9	2.0±1.0	1.8±1.3	1.8±0.9	1.8±1.2
Chronic vascular changes (cv)								
% with cv score>0	154 (90.1%)	29 (74.4%)	8 (88.9%)	114 (95.0%)	3 (100.0%)	9 (90.0%)	29 (96.7%)	18 (81.8%)
cv score, mean±SD	1.9±1.0	1.4±1.0	1.6±1.0	2.1±0.9	1.7±0.6	2.2±0.9	1.9±0.7	1.8±1.1
Arteriolar hyalinosis (ah)								
% with ah score>0	169 (83.7%)	31 (72.1%)	12 (75.0%)	123 (87.9%)	3 (100.0%)	9 (90.0%)	33 (89.2%)	20 (71.4%)
ah score, mean±SD	1.5±1.0	1.0±0.9	1.7±1.2	1.7±1.0	2.3±1.2	1.7±0.9	2.1±1.0	1.6±1.2

Supplementary Table 2: Biomarker levels in 281 urine samples from 244 patients

	DNR group (N=203)					TCMR (N=10)	Pure ABMR (N=37)	Mixed Rejection (N=31)
	All DNR (N=203)	Acute tubular injury (N=43)	Borderline changes (N=17)	IF/TA (N=140)	Recurrence (N=3)			
CXCL10								
Mean±SD	52.8±99.8	53.2±85.9	87.6±126.9	48.7±101.2	36.9±10.8	1345.2±3954.4	112.9±141.7	182.5±187.1
Median (IQR)	22.3 (41.1)	21.9 (56.2)	37.6 (60.0)	20.3 (33.8)	34.7 (10.7)	63.2 (112.7)	47.5 (99.3)	117.1 (192.3)
Min - Max	0.8 - 683.2	0.8 - 395.9	0.8 - 411.9	0.8 - 683.2	27.3 - 48.6	10.3 – 12595.0	0.8 - 587.9	0.8 – 796.0
CXCL10 : Cr								
Mean±SD	7.5±12.8	8.7±15.3	9.0±10.5	7.0±12.4	4.2±1.6	262.7±774.0	15.1±18.9	30.8±38.7
Median (IQR)	3.1 (5.9)	2.9 (7.1)	3.4 (8.3)	3.0 (4.7)	4.7 (1.5)	16.3 (15.1)	7.7 (13.8)	16.9 (28.6)
Min - Max	0.1 - 78.7	0.1 - 78.7	0.2 - 36.9	0.1 – 69.0	2.5 - 5.5	3.5 - 2464.8	0.4 - 76. 5	0.5 - 182.2
CXCL9								
Mean±SD	72.6±272.5	91.5±272.0	68.5±71.3	68.6±291.5	7.0±0.0	538.5±1119.8	92.0±146.4	463.3±537.4
Median (IQR)	7.0 (34.7)	7.0 (44.9)	34.7 (139.4)	7.0 (0.0)	7.0 (0.0)	197.3 (199.5)	21.2 (96.9)	286.3 (617.1)
Min - Max	7.0 – 3178.0	7.0 – 1326.0	7.0 – 180.0	7.0 – 3178.0	7.0 – 7.0	7.0 – 3704.0	7.0 – 699.7	7.0 – 1886.0
CXCL9 : Cr								
Mean±SD	10.8±36.3	14.1±47.0	9.7±10.5	10.0±35.0	0.8±0.2	102.6±219.7	13.5±22.8	77.3±99.6
Median (IQR)	1.6 (4.4)	1.9 (3.9)	5.3 (13.8)	1.6 (3.8)	0.8 (0.2)	33.2 (45.2)	4.9 (11.4)	37.6 (116.2)
Min - Max	0.3 - 370.8	0.4 - 263.6	0.3 - 30.1	0.3 - 370.8	0.6 - 0.9	4.0 - 724.9	0.4 - 95.5	0.5 - 431.6

Supplementary Table 3: Comparison of the accuracy of the different biomarkers in diagnosing acute rejection of any type, T cell-mediated rejection, mixed rejection (antibody-mediated rejection with i+t score≠0), and pure antibody-mediated rejection (ABMR with i+t score=0). P values for the comparison between the AUC of ROC curves are shown.

Biomarkers	All rejection	TCMR	Mixed rejection	Pure ABMR
CXCL10: Cr vs. CXCL10	0.311	0.044	0.824	0.985
CXCL9: Cr vs. CXCL9	0.833	0.137	0.632	0.513
CXCL10 vs. CXCL9	0.442	0.076	0.970	0.062
CXCL10: Cr vs. CXCL9: Cr	0.179	0.087	0.710	0.046

TCMR: T cell-mediated rejection; ABMR: antibody-mediated rejection

Supplementary Table 4: Subgroup analysis of the urinary CXCL10: Cr ratio as a diagnostic marker of ABMR

Variables	No. of samples	Ln(CXCL10: Cr) (mean±SEM)		P Value
		ABMR (n=68)	DNR (n=203)	
Donor type				
Living	12	2.5±0.3	0.8±0.2	5.5E-04
Deceased	56	2.4±0.2	1.2±0.1	2.3E-07
P-value		0.7416	0.0652	
Donor age				
<60	46	2.5±0.2	1.0±0.1	8.6E-09
≥60	18	2.2±0.3	1.1±0.2	1.1E-02
P-value		0.5992	0.5437	
Donor category				
Standard criteria donor	44	2.5±0.2	1.1±0.1	1.1E-08
Expanded criteria donor	22	2.1±0.3	1.1±0.2	6.5E-03
P-value		0.3542	0.9405	
Recipient gender				
Men	41	2.4±0.2	1.1±0.1	7.5E-07
Women	27	2.3±0.2	1.0±0.2	1.3E-04
P-value		0.5091	0.9091	
History of delayed graft function				
Yes	19	2.3±0.3	1.5±0.2	4.1E-02
No	45	2.4±0.2	0.9±0.1	6.2E-09
P-value		0.7708	0.0367	
Biopsy within 1 mo of transplantation				
Yes	58	2.3±0.2	1.1±0.1	8.3E-08
No	10	2.9±0.4	1.0±0.2	2.5E-04
P-value		0.1054	0.9395	
Biopsy within 12 mo of transplantation				
Yes	47	2.2±0.2	0.9±0.1	2.7E-07
No	21	2.7±0.3	1.2±0.1	3.2E-05
P-value		0.0946	0.3198	
Leukocyturia (>10^4/mL) at biopsy				
Yes	10	3.1±0.3	2.0±0.3	6.4E-02
No	54	2.3±0.2	0.9±0.1	4.5E-09
P-value		0.0581	0.0005	
Concomitant IF/TA, moderate to severe				
Yes	41	2.3±0.2	1.0±0.1	1.4E-06
No	20	2.5±0.3	1.1±0.1	1.8E-04
P-value		0.5990	0.7579	

Supplementary Table 5: Clinical, biological, and immunological factors associated with the diagnosis of ABMR (univariate logistic regression analysis)

Variable	No. of biopsies	No. of events	Odds ratio (95% CI)	P value
Clinical factors				
Recipient age	271	68	0.98 (0.96-1.00)	2.0E-02
Donor type				
Living donor	62	12	1	
Deceased donor	209	56	1.53 (0.78-3.19)	0.238
Extended criteria donor	128	22	1	
Standard criteria donor	138	44	2.26 (1.27-4.09)	6.2E-3
Cold ischemia time, hr	262	65	1.03 (1.00-1.06)	3.3E-2
Donor age, years	260	64	0.98 (0.96-0.99)	3.4E-3
Recipient gender				
Male	170	41	1	
Female	101	27	1.15 (0.65-2.01)	0.631
Graft rank	271	68	1.47 (0.92-2.31)	0.099
Delayed graft function	67	19	1.34 (0.70-2.48)	0.364
Time post-transplantation per 100 days	271	68	1.03 (1.02-1.05)	2.3E-04
Biological factors				
Serum creatinine at biopsy	271	68	1.00 (1.00-1.00)	0.326
Proteinuria	266	66	1.21 (0.98-1.53)	0.076
Leukocyturia				
$\leq 10^4$/mL	223	54	1	
$>10^4$/mL	35	10	1.25 (0.54-2.70)	0.580
Ln(CXCL9)	267	67	1.59 (1.35-1.89)	5.1E-08
Ln(CXCL9: Cr)	267	67	1.56 (1.32-1.86)	3.0E-07
Ln(CXCL10)	271	68	1.88 (1.52-2.38)	3.9E-08
Ln(CXCL10: Cr)	271	68	2.03 (1.62-2.62)	6.6E-09
Immunological factors				
Pre-transplant DSAs	78	20	1.41 (0.73-2.70)	0.296
DSAs at the time of biopsy	107	47	6.17 (3.34-11.89)	1.7E-08
MFI of immunodominant DSAs at biopsy				
0	151	17	1	
<1000	34	7	2.04 (0.73-5.25)	0.150
1000-3000	21	7	3.94 (1.34-11.96)	9.6E-03
>3000	50	31	12.86 (6.12-28.24)	5.1E-11

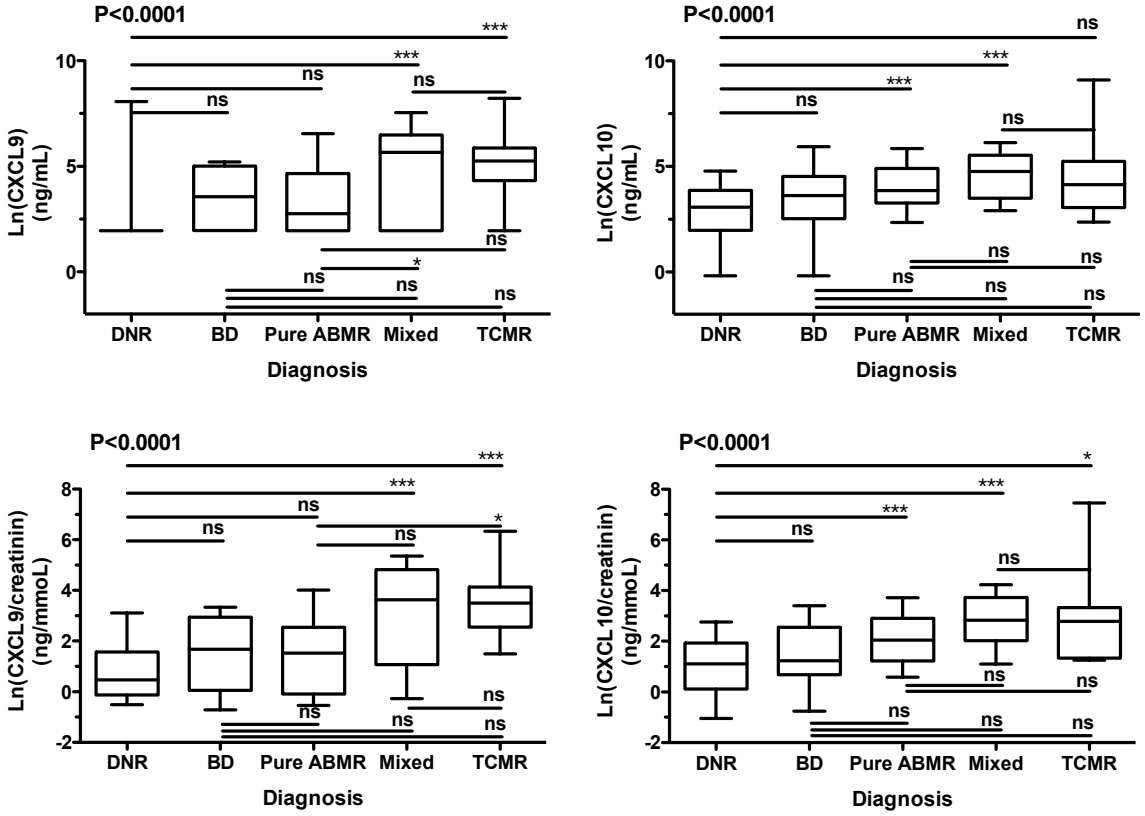
MFI, mean fluorescence intensity; DSA: anti-HLA donor-specific antibody

Supplementary Table 6: Determinants of kidney transplant graft outcome after acute antibody-mediated rejection (univariate Cox proportional analysis)

Variable	Hazard ratio (95% CI)	P value
Clinical factors		
Recipient age, year	0.97 (0.93-1.00)	4.7E-02
Donor age, year	0.97 (0.95-1.00)	5.2E-02
Donor type		
Living donor	1	
Deceased donor	2.45 (0.32-18.70)	0.389
Recipient gender		
Male	1	
Female	1.56 (0.55-4.45)	0.406
Biological factors		
Serum creatinine at biopsy	1.00 (1.00-1.01)	4.0E-03
Proteinuria at biopsy	1.63 (1.29-2.06)	4.0E-05
Leukocyturia>10^4, /mL	2.28 (0.62-8.37)	0.213
Immunological factors		
DSAs at the time of biopsy	1.84 (0.40-8.39)	0.432
MFI of immunodominant DSAs at biopsy		
0	1	
<1000	0.93 (0.08-10.26)	0.949
1000-3000	2.78 (0.39-19.75)	0.307
>3000	1.65 (0.33-8.16)	0.542
Histological factors		
Glomerulitis (g) score	1.28 (0.60-2.75)	0.521
Peritubular capillaritis (ptc) score	1.10 (0.66-1.85)	0.717
Vasculitis (v) score	1.60 (0.97-2.62)	0.064
Interstitial inflammation (i) score	2.10 (1.34-3.29)	1.3E-03
Tubulitis (t) score	1.21 (0.81-1.81)	0.358
Transplant glomerulopathy (cg) score	1.34 (0.88-2.05)	0.171
C4d Banff score	1.09 (0.69-1.70)	0.713
Arterial fibrous intimal thickening (cv) score	0.97 (0.43-2.18)	0.938
Arteriolar hyalinosis (ah) score	2.37 (1.14-4.94)	2.1E-02
Interstitial fibrosis/tubular atrophy score	2.20 (1.01-4.76)	4.6E-02
Urinary biomarkers		
Ln(CXCL9)	1.26 (0.95-1.67)	0.106
Ln(CXCL9: Cr)	1.39 (1.03-1.87)	3.1E-02
Ln(CXCL10)	1.34 (0.87-2.05)	0.182
Ln(CXCL10: Cr)	1.87 (1.13-3.11)	1.6E-02

MFI, mean fluorescence intensity; DSA: anti-HLA donor-specific antibody

Supplemental Figure 1: Box-and-whisker plots of the log (natural)-transformed urinary biomarker levels in 186 matched urine/biopsy samples from patients with allograft dysfunction but no rejection (DNR), 17 matched urine/biopsy samples from patients with borderline changes (BD), 10 matched urine/biopsy samples from patients with T cell-mediated rejection (TCMR), 37 matched urine/biopsy samples from patients with pure antibody-mediated rejection (Pure ABMR) and 31 matched urine/biopsy samples from patients with mixed rejection (Mixed). P values are based on the Kruskal-Wallis test. Stars depict pairwise group comparisons by means of Dunn's post-test (** P<0.01; *** P<0.001).



Supplemental Figure 2: Receiver operating characteristic curves for the urinary chemokines. The fraction of true-positive results (sensitivity) and the fraction of false-positive results (1 – specificity) for urinary CXCL9 and CXCL10 levels, normalized or not by urine creatinine, as diagnostic biomarkers of acute rejection (both T cell-mediated rejection and antibody-mediated rejection), compared with the fractions in the group of patients with allograft dysfunction but no rejection (DNR) (A. and C.) and antibody-mediated rejection compared with DNR (B. and D.) among non-sensitized patients (A. and B.) and while restricting analysis only on the first biopsy of each patient (C. and D.). 95% confidence intervals were generated by 2,000 stratified Bootstrap replicates.