# Development and validation of a prognostic index for allograft outcome in kidney recipients with transplant glomerulopathy

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**We studied 92 patients with transplant glomerulopathy to develop a prognostic index based on the risk factors for allograft failure within five years of diagnosis (Development cohort). During 60 months (median) follow-up, 64 patients developed allograft failure. A chronic-inflammation score generated by combining Banff ci, ct and ti scores, serum creatinine and proteinuria at biopsy, were independent risk factors for allograft failure. Based on the Cox model, we developed a prognostic index and classified patients into risk groups. Compared to the low-risk group (median allograft survival over 60 months from diagnosis), patients in the medium risk group had a hazard ratio of 2.83 (median survival 25 months), while those in the high-risk group had a hazard ratio of 5.96 (median survival 3.7 months). We next evaluated the performance of the prognostic index in an independent external cohort of 47 patients with transplant glomerulopathy (Validation cohort). The hazard ratios were 2.18 (median survival 19 months) and 16.27 (median survival 1.6 months), respectively, for patients in the medium and high-risk groups, compared to the low-risk group (median survival 47 months). Our prognostic index model did well in measures of discrimination and calibration. Thus, risk stratification of transplant glomerulopathy based on our prognostic index may provide informative insight for both the patient and physician regarding prognosis and treatment.**

*Kidney International* advance online publication, 30 September 2015; doi:10.1038/ki.2015.288

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**Received 10 April 2015; revised 5 July 2015; accepted 31 July 2015**

KEYWORDS: antibody-mediated rejection; kidney allograft biopsy; kidney transplant outcome; prognostic index; transplant glomerulopathy

Transplant glomerulopathy (TG), defined, as a morphological lesion of kidney allograft characterized on light microscopy by the duplication of glomerular basement membrane in the absence of immune complex deposition, is an important cause of late allograft failure.[1–4] The strong association with circulating antibodies directed against donor human leukocyte antigen (HLA) and prior acute antibody-mediated rejection, as well as new research pointing towards a possible crosstalk between endothelial cells and HLA antibody, implies chronic alloantibody mediated injury as a plausible cause of TG.[1,5–7]

Kidney recipients with TG have poor allograft survival compared with those who do not have TG.[8] However factors associated with allograft failure have not been clearly defined.[9] Recognizing such factors and risk stratification of patients is important and may help improve outcomes. The objective of our research was to develop a prognostic index (PI) based on the risk factors for allograft failure within 5 years of diagnosis and validate the PI in an independent external cohort of kidney transplant recipients with TG.

## RESULTS

### Characteristics of the study cohort

The study cohort (Development cohort) contained 92 clinically indicated kidney allograft biopsies from 92 kidney transplant recipients with TG from Cornell. We reviewed the results of 1606 consecutive clinically indicated kidney allograft biopsies at our center between January 2000 and June 2011

**Table 1 | Characteristics of kidney allograft recipients**

| Variables | N = 92 patients |
|---|---|
| *At the time of transplant* | |
| Age (years), mean (s.d.) | 44 (15) |
| Women, N (%) | 37 (40) |
| Racial categories (black), N (%) | 25 (27) |
| Cause of end-stage kidney disease, N (%) | |
| Diabetes | 19 (21) |
| Hypertension | 18 (20) |
| Polycystic kidney disease | 6 (7) |
| IgA nephropathy | 5 (5) |
| Lupus nephritis | 5 (5) |
| Focal and segmental glomerulosclerosis | 4 (4) |
| Other glomerular diseases | 9 (10) |
| Others or unknown | 26 (28) |
| Deceased donor organ, N (%) | 48 (52) |
| Cold ischemia time, hours, deceased donor, mean (s.d.) | 26 (10) |
| Human leukocyte antigen mismatches, mean (s.d.) | 5 (2) |
| Donor information available, N (%) | 73 (79) |
| Age (years), mean (s.d.) | 44 (15) |
| Women, N (%) | 38 (52) |
| Racial categories (black), N (%) | 13 (18) |
| Previous transplants, N (%) | 16 (17) |
| PRA, data available, N (%) | 69 (73) |
| Peak PRA %, median (IQR) | 11 (0–100) |
| Pre-transplant PRA %, median (IQR) | 0 (0–80) |
| CDC cross match, data available, N (%) | 92 (100) |
| T-cell positive, N (%) | 0 (0) |
| B-cell positive, N (%) | 10 (11) |
| Flow cytometry cross match, data available, N (%) | 30 (33) |
| T-cell positive | 11 (37) |
| B-cell positive | 14 (47) |
| Luminex platform DSA, data available, N (%) | 17 (18) |
| DSA negative (MFI of the highest rank donor-specific bead <1000) | 11 (65) |
| DSA positive (MFI of the highest rank donor-specific bead >1000) | 6 (35) |
| Received desensitization therapy, N (%) | 15 (16) |
| Induction Immunosuppression, N (%) | 62 (67) |
| Antithymocyte globulin | 54 (87) |
| Interleukin receptor-2 antibodies | 8 (13) |
| *After transplant and before the index allograft biopsy* | |
| Delayed graft function, N (%) | 15 (16) |
| Calcineurin inhibitor based maintenance immunosuppression, N (%) | 89 (97) |
| Early corticosteroid withdrawal | 39 (42) |
| Thrombotic microangiopathy, N (%) | 4 (4) |
| Hepatitis C virus, N (%) | 15 (16) |
| Acute rejection, N (%) | 23 (25) |
| Acute rejection episodes, N | 28 |
| Acute T-cell mediated rejection episodes, N (%) | 13 (46) |
| Acute antibody-mediated rejection episodes, N (%) | 7 (25) |
| Mixed acute T-cell and antibody-mediated rejection episodes, N (%) | 8 (29) |
| *At the time of index allograft biopsy* | |
| Age, mean (s.d.) | 48 (14) |
| Time from transplantation to biopsy (months), median (IQR) | 43 (16–83) |
| Luminex platform DSA, data available, N (%) | 37 (40) |
| DSA negative (MFI of the highest rank donor-specific bead <1000) | 11 (30) |
| DSA positive (MFI of the highest rank donor-specific bead >1000) | 26 (70) |
| Serum creatinine (mg/dl), median (IQR) | 2.75 (2.15–4.14) |
| Proteinuria >1 g/day, N (%) | 63 (68) |

Abbreviations: CDC, complement-dependent cytotoxicity; DSA, donor HLA-specific IgG antibodies; IQR, interquartile range; MFI, mean fluorescence intensity; PRA, panel reactive antibodies.

from 842 kidney transplant recipients and identified these 92 (6%) biopsies (Table 1). For patients with multiple allograft biopsies only the first biopsy with TG was included. Results on staining for complement split product 4d (C4d) were available on all and electron microscopy were available in 85 (92%) specimens. A single pathologist (SVS) evaluated the biopsies and categorized them using the Banff '07 update of the Banff '97 classification.

The median (interquartile range, IQR) time from transplantation to biopsy was 43 (16–83) months. The main reason for biopsy was an increase in serum creatinine in 64 (70%) and proteinuria in 28 (30%) patients. At the time of biopsy, serum creatinine was 2.75 (2.15–4.14) mg/dl, and the proteinuria was >1 g/day in 63 (69%) patients. The distribution of the histopathological features is shown in Figure 1. Sixty-nine of the 92 patients (75%) had evidence for chronic active antibody-mediated rejection; 38 with serological evidence of alloantibodies that included positive cross matches or Luminex platform-detected IgG antibodies directed against donor HLA; 34 with positive staining for peritubular capillary C4d and 56 with at least moderate microvascular inflammation (Banff score g+ptc ≥ 2).

### Treatment, follow-up and clinical outcome

Patients diagnosed with TG were treated at the discretion of their transplant physician. Treatment consisted of anti-rejection therapy in 46 (50%) patients that included various combinations of high dose corticosteroids, intravenous immunoglobulin, plasmapheresis, antithymocyte globulin, rituximab, and bortezomib with or without additional therapy with drugs that block the renin-angiotensin system. The other 46 (50%) patients did not receive anti-rejection therapy but were treated with addition of new or dose adjustment of their maintenance immunosuppressive medicines and drugs that block the renin-angiotensin system.

The primary outcome was allograft failure within 60 months following the diagnosis of TG. During a median follow-up of 60 months from the diagnosis, 64 (70%) patients developed graft failure, 9 (3–26) months from the diagnosis. The 28 (30%) patients who did not have allograft failure were followed for 59 (37–60) months from the diagnosis. Time from transplantation to diagnosis was 48 (19–90) months in patients who eventually had allograft failure and was 37 (14–69) months in those who did not have allograft failure.

There was no difference in the outcome between patients who did and who did not receive anti-rejection therapy (Figure 2). Because patients were not randomly assigned to the two groups (anti-rejection therapy vs. no anti-rejection therapy), we did propensity score (PS) analysis to mimic a quasi-randomized trial using the observational data. We used the baseline variables to generate PS, defined as the probability of receiving anti-rejection therapy. The resulting concordance index of the model was 0.89 suggesting that the model discriminated the two groups well. We then used the PS as a covariate in the Cox analysis. The difference in allograft outcome between the two groups, adjusted for the PS, was not statistically significant (hazard ratio (HR) 0.89, 95% confidence interval (0.45–1.76), $P = 0.74$).

### Statistical analyses of risk factors

We included 19 variables at the time of the index biopsy in a univariate Cox regression analysis to determine the