Validation of Prognostic Index for Allograft Outcome in Kidney Transplant Recipients With Transplant Glomerulopathy

Manish Talwar1,2,9, Vasanthi Balaraman1,2,9, Anshul Bhalla1,2, Orsolya Cseprekal3, Masahiko Yazawa1,2,4, Pradeep S.B. Podila5,6, Ambreen Azhar1,2, L. Nicholas Cossey7, James D. Eason1,2 and Miklos Z. Molnar1,2,3,8

1James D. Eason Transplant Institute, Methodist University Hospital, Memphis, Tennessee, USA; 2Division of Transplant Surgery, Department of Surgery, University of Tennessee Health Science Center, Memphis, Tennessee, USA; 3Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary; 4Division of Nephrology and Hypertension, St. Marianna University School of Medicine, Tokyo, Japan; 5Faith & Health Division, Methodist Le Bonheur Healthcare, Memphis, Tennessee, USA; 6Division of Health Systems Management & Policy, School of Public Health, The University of Memphis, Memphis, Tennessee, USA; 7Arkanalabs, Little Rock, Arkansas, USA; and 8Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Correspondence: Miklos Z Molnar, University of Tennessee Health Science Center, James D. Eason Transplant Institute, Methodist University Hospital, Methodist Transplant Epidemiology Research Group, 1211 Union Avenue, Memphis, Tennessee 38104, USA. E-mail: mzmolnar@uthsc.edu

9These authors contributed equally.

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Transplant glomerulopathy (TG) is a histological lesion of kidney allograft characterized by thickening or duplication of glomerular basement membrane, double contour formation, and mesangial interposition seen on light and electron microscopy. It is commonly associated with chronic antibody-mediated rejection (cAMR) and is often attributed to chronic microvascular injury. It has an extremely poor prognosis, resulting in kidney allograft failure within a year after diagnosis in a large number of affected patients. It is estimated that approximately 5000 allografts are lost each year in the United States, primarily from TG and cAMR. There are several potential options to treat TG, including plasmapheresis (PLEX), i.v. Ig, rituximab, bortezomib, and tocilizumab, or a combination thereof.

The aim of our study was to externally validate a previously developed TG prognostic score by the Patri et al. study. Our hypothesis was that this transplant score has an excellent discriminatory capacity in our cohort and can be used for prediction in these patients.

**RESULTS**

**Baseline Recipient, Donor, and Transplantation Characteristics**

Of the 38 recipients, 16, 14, and 8 had high-risk, intermediate-risk, and low-risk scores, respectively (Figure 1). As shown in Table 1, the mean age at the time of biopsy was 41 ± 17 years, 66% were male, and 61% were African American. The recipients with higher TG scores were significantly younger and also had worse graft function and proteinuria at the time of diagnosis (Table 1). The distribution of the histopathological features in the entire group is shown in Table 1. The incidence rate of graft loss was similar (P = 0.914) between recipients who received antirejection treatment for TG (n = 13; 50%; crude incidence rate, 382/1000 patient-years; 95% CI, 222–657) versus recipients who did not receive treatment (n = 8; 67%; crude incidence rate, 347/1000 patient-years; 95% CI, 174–694), as shown in Supplementary Figure S4.

The crude mortality rate was significantly different between groups, as shown in Figure 3B. The lowest incidence rate of graft loss (n = 2; 25%) occurred (crude incidence rate, 130 per 1000 patient-years; 95% CI, 33–522) in the low-risk group; a total of 7 (50%) graft losses occurred (crude incidence rate, 233/1000 patient-years; 95% CI, 111–490) in the intermediate-risk group; and the highest incidence rate of graft loss (n = 12, 75%) occurred (crude incidence rate, 1019/1000 patient-years; 95% CI, 579–1794) in the high-risk group (P = 0.0025).

Compared to patients with a low-risk TG score, patients with an intermediate-risk TG score had similar risk of graft loss over time (hazard ratio, 1.64; 95% CI, 1.640–8.06), whereas recipients with a high-risk TG score had significantly higher risk of graft loss (hazard ratio, 6.69; 95% CI, 1.39–32.23) using an unadjusted Cox proportional risk regression model.

The incidence rate of graft loss was similar (P = 0.941) between recipients who received antirejection treatment for TG (n = 13; 50%; crude incidence rate, 382/1000 patient-years; 95% CI, 222–657) versus recipients who did not receive treatment (n = 8; 67%; crude incidence rate, 347/1000 patient-years; 95% CI, 174–694), as shown in Supplementary Figure S4.
Table 1. Baseline characteristics of the patients

| Characteristics                        | Total cohort (N = 38) | Low-risk group (n = 8) | Intermediate-risk group (n = 14) | High-risk group (n = 16) | P value |
|----------------------------------------|-----------------------|------------------------|----------------------------------|--------------------------|---------|
| Demographics                           |                       |                        |                                  |                          |         |
| Age, yr, mean (SD)                     | 41 (17)               | 46 (21)                | 49 (12)                          | 30 (15)                  | 0.008   |
| Sex, n (%)                             |                       |                        |                                  |                          | 0.564   |
| Male                                   | 25 (66)               | 6 (75)                 | 10 (71)                          | 9 (56)                   |         |
| Female                                 | 13 (34)               | 2 (25)                 | 4 (29)                           | 7 (44)                   |         |
| Race, n (%)                            |                       |                        |                                  |                          | 0.081   |
| White                                  | 13 (34)               | 5 (63)                 | 2 (14)                           | 6 (38)                   |         |
| African American                       | 23 (61)               | 2 (25)                 | 12 (86)                          | 9 (56)                   |         |
| Asian                                  | 2 (5)                 | 1 (13)                 | 0                                | 1 (6)                    |         |
| Marital status, n (%)                  |                       |                        |                                  |                          | 0.223   |
| Divorced                               | 1 (3)                 | 0                      | 0                                | 1 (6)                    |         |
| Married                                | 15 (39)               | 5 (63)                 | 5 (36)                           | 5 (31)                   |         |
| Single                                 | 21 (55)               | 2 (25)                 | 9 (64)                           | 10 (63)                  |         |
| Widowed                                | 1 (3)                 | 1 (13)                 | 0                                | 0                       |         |
| Insurance, n (%)                       |                       |                        |                                  |                          | 0.331   |
| Medicare                               | 27 (71)               | 5 (63)                 | 12 (86)                          | 10 (63)                  |         |
| TennCare                                | 2 (5)                 | 0                      | 0                                | 2 (13)                   |         |
| Other                                  | 9 (24)                | 3 (38)                 | 2 (14)                           | 4 (25)                   |         |
| Comorbidities, n (%)                   |                       |                        |                                  |                          | 0.191   |
| Diabetess                              | 17 (46)               | 3 (43)                 | 9 (64)                           | 5 (31)                   |         |
| Hypertension                           | 37 (97)               | 8 (100)                | 14 (100)                         | 15 (94)                  | 0.494   |
| CAD                                    | 3 (8)                 | 0 (0)                  | 1 (7)                            | 2 (13)                   | 0.559   |
| Time between transplantation and biopsy, d, median (IQR) | 2051 (1123–4602)      | 1286 (1098–3720)       | 1961 (674–3449)                 | 3383 (1927–6225)         | 0.059   |
| Dialysis vintage, d, median (IQR)      | 1002 (454–2865)       | 1074 (594–2618)        | 533 (431–2752)                  | 1215 (613–2324)          | 0.790   |
| Laboratory parameters                  |                       |                        |                                  |                          |         |
| Serum creatinine, mg/dl, mean (SD)     | 2.74 (1.12)           | 1.99 (0.66)            | 2.53 (0.84)                      | 3.30 (1.27)              | 0.006   |
| UPCR, median (IQR)                     | 1.98 (1.02–4.30)      | 0.55 (0.27–1.00)       | 1.48 (1.02–1.02)                 | 4.96 (3.84–6.97)         | <0.001  |
| Body mass index, kg/m², mean (SD)      | 27.5 (7.3)            | 26.6 (12.4)            | 28.8 (4.9)                       | 26.6 (5.3)               | 0.239   |
| Maintenance immunosuppressive therapy, n (%) |                       |                        |                                  |                          |         |
| Tacrolimus                              | 36 (95)               | 8 (100)                | 14 (100)                         | 14 (88)                  | 0.234   |
| Cyclosporin                             | 3 (8)                 | 1 (13)                 | 0                                | 2 (13)                   | 0.387   |
| mTOR inhibitors                         | 1 (3)                 | 0                      | 0                                | 1 (7)                    | 0.494   |
| Prednisone                              | 36 (95)               | 8 (100)                | 14 (100)                         | 14 (88)                  | 0.234   |
| Mycophenolate mofetil                   | 25 (66)               | 4 (50)                 | 11 (79)                          | 10 (63)                  | 0.372   |
| Mycophenolic acid                       | 23 (61)               | 8 (75)                 | 10 (71)                          | 7 (44)                   | 0.184   |
| Azathioprine                            | 3 (8)                 | 1 (13)                 | 0 (0)                            | 2 (13)                   | 0.387   |
| Treatment for TG, n (%)                 |                       |                        |                                  |                          |         |
| Received treatment                      | 26 (68)               | 7 (88)                 | 9 (64)                           | 10 (63)                  | 0.424   |
| PLEX                                    | 22 (58)               | 6 (75)                 | 8 (57)                           | 8 (50)                   | 0.503   |
| i.v. Ig                                 | 25 (66)               | 6 (75)                 | 9 (64)                           | 10 (63)                  | 0.822   |
| Rituximab                               | 2 (5)                 | 1 (13)                 | 0 (0)                            | 1 (6)                    | 0.483   |
| Bortezomib                              | 3 (8)                 | 1 (13)                 | 2 (14)                           | 0 (0)                    | 0.303   |
| Thymoglobulin                           | 9 (24)                | 2 (25)                 | 4 (29)                           | 3 (19)                   | 0.815   |
| Tocilizumab                             | 5 (13)                | 3 (38)                 | 2 (14)                           | 0 (0)                    | 0.037   |
| Steroid                                 | 29 (76)               | 5 (63)                 | 13 (93)                          | 11 (69)                  | 0.176   |
| ACEI/ARB                                | 28 (74)               | 5 (63)                 | 11 (79)                          | 12 (75)                  | 0.704   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; IQR, interquartile range; mTOR, mammalian target of rapamycin; PLEX, plasma exchange; TG, transplant glomerulopathy; UPCR, urine protein:creatinine ratio.

Performance, Discrimination, and Calibration of Prognostic Score
The Harrel c-index, which is the measure of discrimination, was 0.69, which indicates good discrimination of the model. Figure 4 shows the receiver operating characteristic curve of the transplant glomerulopathy prediction score for using 1-year graft loss as the gold standard outcome with an area under the curve of 0.80. Supplementary Table S1 presents a detailed report of sensitivity, specificity, positive, and negative likelihood ratio of different cut points.

DISCUSSION
In this retrospective, single-center, observational study, we have externally validated the TG prognostic
Figure 2. Histopathological characteristics of kidney transplant recipients with transplant glomerulopathy.

Figure 3. Probability of graft loss (a) in the entire cohort and (b) by groups with different risks using Kaplan–Meier curves.
index score developed by Patri et al.\textsuperscript{8} in a cohort of kidney transplant recipients largely comprising African American individuals. In our cohort, we used the TG score to stratify the patients, and were able to show that this stratification has acceptable discrimination and calibration statistics, therefore enabling accurate prediction of their graft outcomes.

It has been previously shown that African Americans have worse renal allograft survival compared to patients who are not African American.\textsuperscript{5,2} Stratification of these patients is necessary to decide which patients should be exposed to further aggressive immunosuppressive treatments. A data-driven archetypes approach can refine the diagnostic and prognostic features associated with TG; however, this might be difficult to use at the bedside, and it was developed based on French and Canadian patients.\textsuperscript{5,2} The prognostic score developed by Patri et al.\textsuperscript{5} for TG was developed and validated previously in a non–African American majority cohort, and it needed to be validated in this high-risk population.

In our cohort, the TG score showed acceptable discrimination and calibration statistics. We found no statistical difference in the incidence of graft loss in the low-risk and intermediate-risk group, which was seen in the developmental cohort. There are several potential explanations why our result was different from that in the original developmental and validation cohort.\textsuperscript{8} First, this could have been due to our small sample size. Second, in our cohort there was a high number of African Americans, which might explain the observed differences. Third, the treatment pattern and practice might be different in our center from those in the original centers; however, in both our cohort and the original cohorts, the graft survival rate was similar in patients who received treatment versus those who did not.\textsuperscript{8} Finally, differences in immunological risk and treatment adherence might be contributing factors.

We found no difference in graft outcomes in the treatment group versus the no-treatment group, similarly to the original cohorts.\textsuperscript{8} In our cohort, we found that patients in the high-risk group were younger than those in the low-risk and intermediate-risk groups. This observation echoes the previous findings where younger age has been associated with increased risk of renal allograft rejection.\textsuperscript{5,3}

Our study has several limitations. First, our sample size was small, substantially lower than in the original paper,\textsuperscript{8} with relatively fewer patients in the low-risk group; however, we were still able to perform statistical comparison in this group, although our analysis was most likely underpowered. Second, we did not have a standardized approach to the treatment of TG; however, we did not see any difference in the treatment arm versus the no-treatment arm. Finally, we did not have information about the proximal cause of graft failure, and the follow-up time was only 3 years.

In conclusion, the transplant glomerulopathy prognostic index score developed by Patri et al.\textsuperscript{8} showed an acceptable discrimination and calibration statistic in an independent U.S. cohort largely comprising African Americans.

**DISCLOSURE**

All the authors declared no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods.
Table S1. Detailed report of sensitivity and specificity.
Figure S1. Histopathological characteristics of kidney transplant recipients with low-risk score for transplant glomerulopathy.
Figure S2. Histopathological characteristics of kidney transplant recipients with intermediate-risk score for transplant glomerulopathy.
Figure S3. Histopathological characteristics of kidney transplant recipients with high-risk score for transplant glomerulopathy.
Figure S4. Probability of Graft Loss by Treatment using Kaplan-Meier curves.

Supplementary References.

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Using Telenephrology to Improve Access to Nephrologist and Global Kidney Management of CKD Primary Care Patients

Carlos Zuniga1,2,3, Cecilia Riquelme4, Hans Muller2,3, Gerardo Vergara5, Camila Astorga4 and Manuel Espinoza5

1School of Medicine, Universidad Catolica de la Santisima Concepcion, Bio Bio, Chile; 2Service of Nephrology, Hospital Las Higueras, Talcahuano, Chile; 3School of Medicine, Universidad de Concepcion, Bio Bio, Chile; 4Servicio Salud Concepcion, Hospital Regional of Concepcion, Bio Bio, Chile; 5Telemedicine Unit, Hospital Las Higueras, Talcahuano, Chile; and 6Faculty of Medicine, Pontificia Universidad Catolica, Santiago, Chile

Correspondence: Carlos Zuniga, Service of Nephrology, Hospital Las Higueras, 777 Alto Horno Av, Talcahuano 4270918, Chile. E-mail: czunigasm2002@yahoo.com

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Most chronic kidney disease (CKD) clinical guidelines recommend that patients with CKD stage 3b to 5 be referred to a nephrologist for specialized evaluations and treatment.1–3,51–53 Unfortunately, this recommendation is difficult to follow because of a lack of specialists, a problem especially critical in developing nations, where scarcity has reached a critical level.4,5,53–58 The consequences include long waiting lists, lack of opportune diagnosis and/or treatment, and impaired health outcomes.

Telenephrology (TN), also known as telehealth in nephrology, is digital connectivity strategy to improve access to specialists.6–9,59–62 It has been reported that TN facilitates distance clinical care as well