DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

SJJ and JJS designed the study; HZ and JS acquired data; HZ analyzed statistics and drafted tables; SJJ, JJS, HZ, JS, and SFS analyzed and interpreted data; SJJ and JJS supervised the study; SFS planned and facilitated meetings; and SFS drafted the manuscript. All authors participated in the critical revision of earlier drafts and recommendations and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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

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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.[1] It is commonly associated with chronic antibody-mediated rejection (cAMR) and is often attributed to chronic microvascular injury.[1] It has an extremely poor prognosis, resulting in kidney allograft failure within a year after diagnosis in a large number of affected patients.[1] It is estimated that approximately 5000 allografts are lost each year in the United States, primarily from TG and cAMR.[2] There are several potential options to treat TG, including plasmapheresis (PLEX), i.v. Ig, rituximab, bortezomib, and tocilizumab, or a combination thereof.[3–7] It is essential to determine the risk of allograft failure, using prognostic tools, in individual patients before subjecting patients to intensified immunosuppressive treatment measures, which have questionable benefits.

There have been multiple risk stratification tools or indices developed in the last decade, with limitations and concerns regarding practical application of such tools. Some examples include a prognostic index developed by Patri *et al*. and the iBox risk prediction scoring developed by the Paris group.[8,9] It is imperative to develop tools based on easily available clinical and histopathological factors to predict allograft failure in patients with TG. This has been previously demonstrated by Patri *et al*.[8] However, the main limitation of the Patri *et al*. study was its external validation, being conducted only in a French cohort that is not representative of the U.S. population.

The aim of our study was to externally validate a previously developed TG prognostic score by the Patri *et al*.[8] with a cohort of kidney transplant recipients of whom a majority are African Americans. Our hypothesis was that this transplant score has an excellent discrimination statistic 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 Figure 2, and the distribution between different risk groups is shown in Supplementary Figures S1–S3.

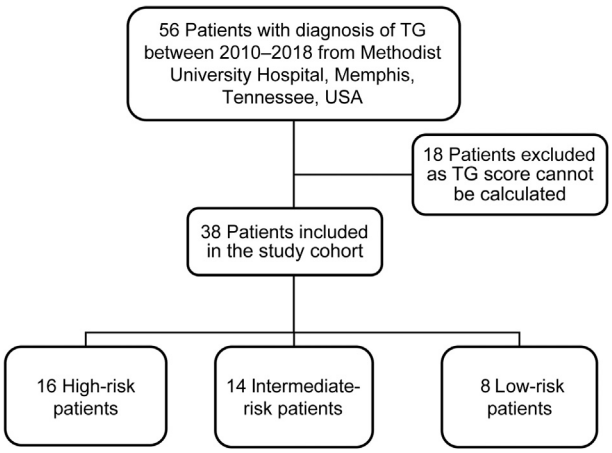

Figure 1. Flow chart of patient selection. TG, transplant glomerulopathy.

Treatment, Follow-up, and Clinical Outcome

The primary outcome of interest was graft loss within 3 years following the diagnosis of TG. During a median follow-up period of 0.83 years (minimum–maximum, 0.04–8.15 years), a total of 21 (55%) graft losses occurred (crude incidence rate, 368/1000 patient-years; 95% confidence interval [CI], 240–564). Figure 3a shows the graft survival probability over time. Close to 75% of our recipients lost their graft within 3 years after diagnosis of TG (Figure 3a).

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, 1.640.33–8.06), 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 ($P = 0.914$) 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.

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 (%)					
Diabetes	17 (46)	3 (43)	9 (64)	5 (31)	0.191
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 (454–2685)	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)	1.96 (1.02–4.30)	0.55 (0.27–1.00)	1.48 (1.02–1.92)	4.95 (3.84–6.97)	<0.001
Body mass index, kg/m^2, 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)	6 (75)	10 (71)	7 (44)	0.194
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

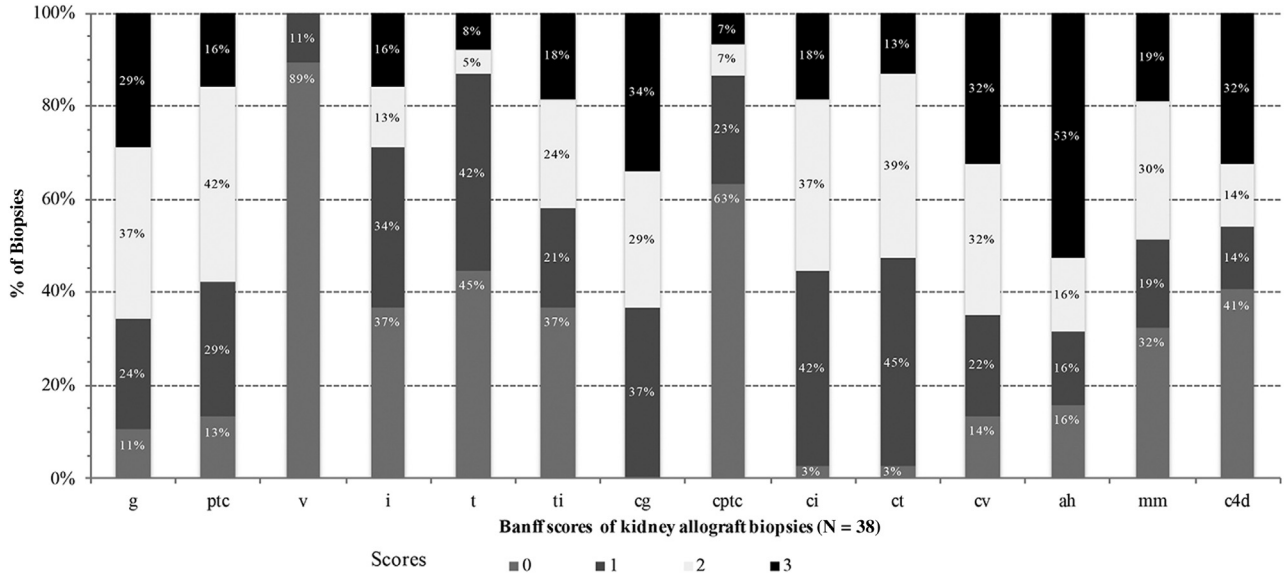

Figure 2. Histopathological characteristics of kidney transplant recipients with transplant glomerulopathy.

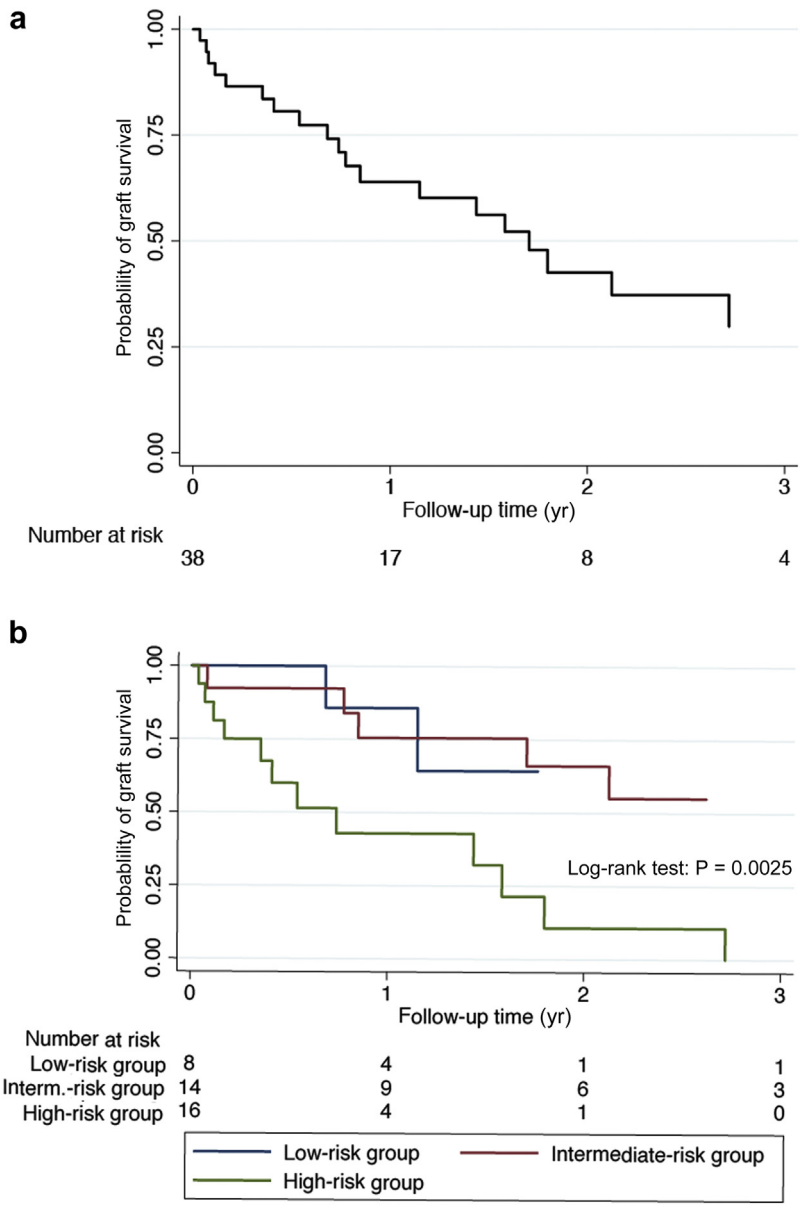

Figure 3. Probability of graft loss (a) in the entire cohort and (b) by groups with different risks using Kaplan–Meier curves.

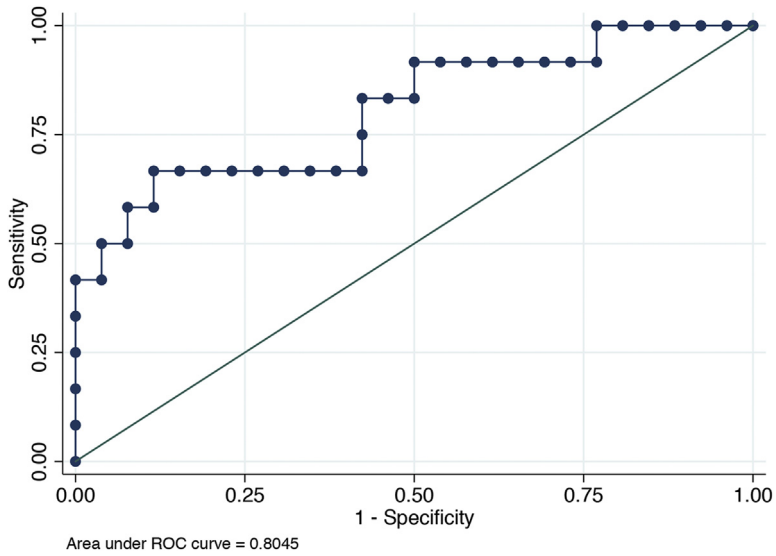

Figure 4. Receiver operating characteristic (ROC) curve of transplant glomerulopathy score for 1-year graft loss.

index score developed by Patri *et al*.[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.[S1] 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.[S2] The prognostic score developed by Patri *et al*. 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.[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.[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.[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.[S3]

Our study has several limitations. First, our sample size was small, substantially lower than in the original paper,[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*.[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.

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

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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,S1–S4] 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,S5–S8] 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,S9–S20] It has been reported that TN facilitates distance clinical care as well