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Original Paper

Proteinuria, Estimated Glomerular Filtration Rate and Urinary Retinol-Binding Protein as Clinical Predictors of Long-Term Allograft Outcomes in Transplant Glomerulopathy

Xue Li Jinsong Chen Dongrui Cheng Rong Wang Wei Wang
Mingchao Zhang Feng Xu Jiqiu Wen Zheng Tang

National Clinical Research Center of Kidney Diseases, Jinling Hospital, Medical School of Nanjing University, Nanjing, China

Key Words
Transplant glomerulopathy • Renal survival • Risk factors • Urinary retinol-binding protein

Abstract
Background/Aims: We aimed to explore the associations between clinical parameters and long-term allograft outcomes in transplant glomerulopathy (TG) in a large retrospective cohort with long follow-up. ***Methods:*** Clinical and laboratory data at biopsy from 180 cases of TG with an estimated glomerular filtration rate (eGFR)>15ml/min/1.73m^2 from January 2004 to December 2016 at our center were retrospectively analyzed. The main outcome of this study was initiation of replacement therapy or an eGFR declined to <15 ml/min/1.73m^2. ***Results:*** During a median follow-up of 5 years (interquartile range 2.6-8.2 years), 117 cases (65.0%) achieved the combined event. Kaplan-Meier method yielded the 1-year and 5-year cumulative renal allograft survival rates after a histopathologic diagnosis of TG were 84% (95% confidence interval [CI] 81-87%) and 33% (95% CI 27–39%) respectively. In univariate analysis, allograft outcome differed significantly by eGFR, proteinuria, blood hemoglobin level, urinary retinol-binding protein (urRBP) and urinary N-acetyl-β-D-glucosaminidase (urNAG) level at the time of biopsy. Multivariate Cox analysis revealed that a higher level of eGFR was the most powerful predictor of allograft survival. Compared with those with eGFR≥60, the hazard ratio (HR) increased from 4.50 (95% CI: 1.03-19.71, p=0.0462) for patients with eGFR between 30 and 59 ml/min/1.73m^2 to 9.14 (95% CI 1.97-42.45, P=0.0047) when eGFR decreased to 15 to 29 ml/min/1.73m^2. Additionally, proteinuria and higher urRBP values (≥2.85mg/dl) were found to confer much worse survival rates for TG patients in multivariate Cox analysis. Male sex (HR 0.48,

Zheng Tang, MD, PhD
and Jiqiu Wen, MD, PhD

National Clinical Research Center of Kidney Diseases, Jinling Hospital,
Medical School of Nanjing University, 305 East Zhong Shan Road, Nanjing (China)
Tel. +86 13913009285, +86 15905143922, E-Mail tang_dr@163.com; wjqkidney@hotmail.com

P=0.02) and HCV infection (HR 1.78, P=0.0499) were also found to be independent risk factors for worse allograft survival. ***Conclusion:*** Five clinical features—impaired renal function, higher proteinuria, higher urRBP level, male sex and HCV infection—are independent predictors of an unfavorable renal allograft outcome. urRBP is a simple and useful parameter that can add invaluable information for the clinical follow-up of patients with TG.

Introduction

Transplant glomerulopathy (TG), which is histologically characterized by double contours of the glomerular basement membrane (GBM) without concomitant immuno-complex deposition, is a histomorphologic pattern frequently seen in patients presented with late allograft dysfunction several years or decades after kidney transplantation [1, 2]. Although it has been elucidated that chronic antibody-mediated rejection accounts for the majority of cases with a morphologic diagnosis of TG, other pathoetiologies such as hepatitis C virus (HCV) infection and thrombotic microangiopathy (TMA) could also incur allograft chronic injury with a morphologic manifestation of TG [3]. It is sometimes difficult if not impossible to ascertain the exact etiology for TG in an individual case. Regardless of the underlying etiology, endothelial cell injury and subsequent remodeling has been demonstrated to be the essential pathophysiology for the formation of double contours in TG [1].

Although clinical symptoms of TG were commonly characterized by proteinuria and serum creatinine (Scr) elevation, the symptoms of individual TG patients were heterogeneous, with some severe histological TG have stable graft function while rapidly deteriorating graft function in histologically mild TG [4]. The identification of clinical characteristics at the time of TG diagnosis that are predictable of future renal allograft dysfunction would greatly facilitate clinical prognostication for individual TG patient, which would ideally be explored in a large representative cohort. However, a few studies available were limited by their small sample size, short follow-up time and discordant conclusions [5, 6].

Several previous studies have suggested that urinary retinol-binding protein (urRBP), which is a biomarker of renal tubular injury, could potentially serve as a biomarker that predicts allograft survival in TG patients [7-9]. The advantage that urRBP is routinely measured in our center enabled us to characterize the relationship between urRBP and allograft survival in a large cohort of TG patients.

Thus, in this study, the authors aimed to explore the relationship between baseline clinical variables at the time of TG diagnosis and future allograft function decline in a population of 180 TG patients with a median follow-up time of 60 months.

Materials and Methods

Study cohort

This single-center retrospective study was carried out after Institutional Review Board approval and performed in accordance with the Principles of the Declaration of Istanbul. Electronic medical records of patients sought medical attention and biopsied with a pathologic diagnosis of TG at National Clinical Research Center of Kidney Diseases during January 2004 to December 2016 were identified. TG patients with an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m^2 at biopsy were excluded. The main outcome of this study was initiation of replacement therapy or an eGFR declined to <15 ml/min/1.73m^2. Relevant demographic information, clinical history and laboratory test results at the time of biopsy were retrieved from electronic medical records.

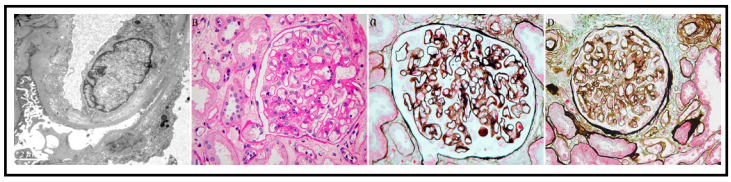

Fig. 1. Representative images of transplant glomerulopathy (TG). A: In TG with Banff cg1a, capillary loop duplication could only be observed under electron microscopy. B: When capillary loop duplication observed under light microscopy accounts for less than 25%, cg score is cg1b (Periodic acid-Schiff stain, 200×). C: cg2 designates capillary loop duplication that exceeds 25% but less than 50% (Jones stain, 400×). D: Widespread (>50%) capillary loop duplication in cg3 in TG (Jones stain, 200×).

Allograft biopsy and pathologic interpretation

There were 167 for-cause biopsies and 13 protocol-biopsies at an overall median allograft age of 91 months (range 50-124mo.) included in this study. Frequent indications for indicative biopsies included proteinuria, allograft dysfunction or appearance of anti-HLA antibodies. Biopsy materials were routinely processed for light microscopic, immunofluorescence and electron microscopic studies. Allograft biopsy slides were retrieved and re-evaluated by two experienced nephropathologists (X.F & Z.M.C) according to the 2015 Banff Classification [10]. TG was diagnosed when double contours of the GBM was identified by light microscopy or electron microscopy (Fig. 1). Attention was exercised to exclude cases that share overlapping morphologic features with TG, especially membranoproliferative glomerulonephritis. Specifically, cases with a morphologic pattern of double contours were examined for the presence of IgG and immuno-deposits by immunofluorescence and electron microscopy respectively. Cases with either IgG or immuno-deposits were excluded.

Definitions

Hematuria under light microscope was defined as a red blood cell count 10, 000/ml in urinary sediment. Proteinuria was defined as urine protein 0.4 g/24 hours. The urNAG enzyme was normal when it was less than 16.5 U/g per creatinine. The normal range for urRBP is less than 0.5 mg/dl. Hypoproteinemia was defined as serum albumin level <35 g/L. A hemoglobin level <130 g/L in men and < 120 g/L was defined as anemia. eGFR was calculated from the Chronic Kidney Disease Epidemiology formula [11].

Statistical analysis

Statistical analysis was performed using commercially available SPSS 22.0 software (IBM, Armonk, NY) and the *Hmisc, rms, survival* ROC package in R, version 3.0.2 (http://www.r-project.org/). Results were presented as mean ± standard deviations for measurement data or ratio for enumeration data. We employed Kaplan–Meier analysis to calculate patient and graft survival, and adopted the Mantel-Cox log-rank test to compare survival between groups. In the Cox regression analysis, we included variables that showed significant associations (P<0.2) in the univariable model. Variables for survival analyses included sex, age, allograft age, eGFR, anemia, proteinuria, hypoproteinemia, urRBP, urNAG, HCV and panel reactive antibody (PRA) status. The optimal cut-off for allograft age, urRBP and urNAG were calculated based on "maximally selected rank statistics" as proposed by Lausen and Schumacher [12]. This method allows the distinction of a low and high risk group of patients by offering the selection of a cut-off point in the predictor without the problem of multiple testing. The result of the statistical analysis is shown in Fig. 2. This cut-off value was used to dichotomize allograft age, urRBP and urNAG as variables for Cox regression and Kaplan Meier survival analyses. All tests were two-sided and confidence intervals (CIs) were reported at the 95% level. P values < 0.05 were considered statistically significant.

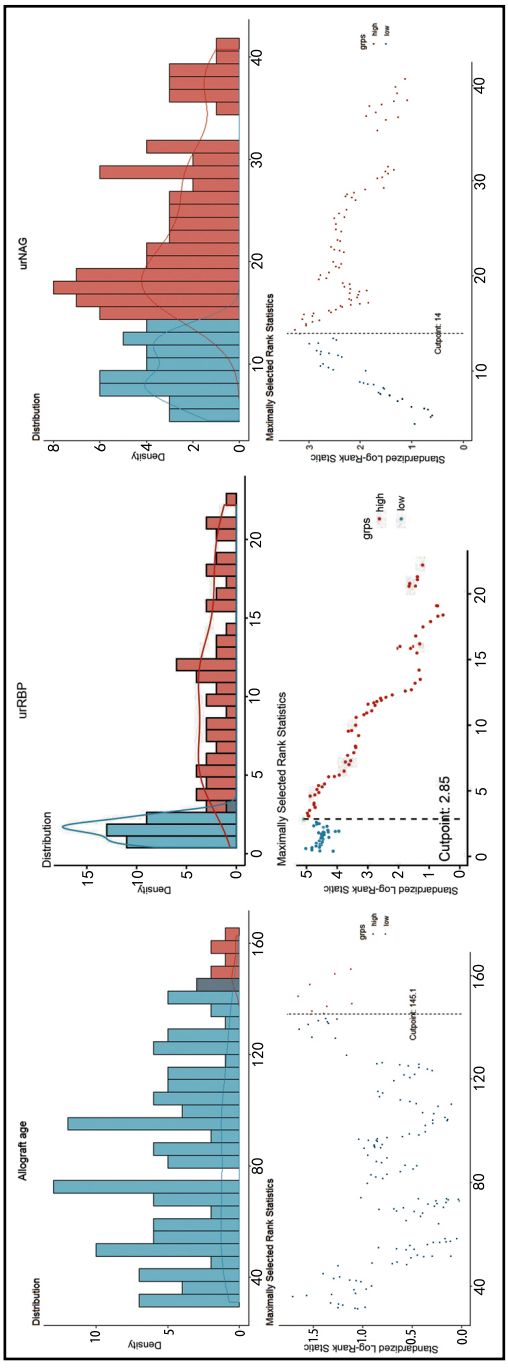

Fig. 2. The optimal cut-off for allograft age, urinary retinol-binding protein and urinary N-acetyl-β-D-glucosaminidase were based on "maximally selected rank statistics". Abbreviations: urRBP: urinary retinol-binding protein; urNAG: urinary N-acetyl-β-D-glucosamidase.

Results

Patient demographics and characteristics at the time of biopsy

Patient demographics and characteristics were summarized in Table 1. From January 2004 to December 2016, a total of 1587 allograft biopsies were performed, resulting in an incidence of 11.3% for TG. Histologic score for glomerular capillary duplication (cg) as determined by Banff is as follows: cg1a 6 cases, cg1b 14 cases, cg2 42 cases and cg3 118 cases. All the included TG patients were first-time non-sensitized kidney transplant recipients. The great majority of patients received a triple baseline immunosuppressive protocol consisting of prednisone, mycophenolate mofetil, tacrolimus (41.7%) or cyclosporine (47.8%). Hepatitis C DNA-positivity was present in 38 (21.1%) patients. PRA-I or PRA-II positivity was observed in 109 (64.5%) among 169 patients for whom PRA data were available. The distribution of patients stratified by eGFR at baseline was as follows: 13.9% within Stage 2, 46.1% within Stage 3, 40.0% within Stage 4. Proteinuria in the majority of the patients was subnephrotic with only 19.4% patients exceeded 3g/d.

Clinical outcomes of the cohort during follow-up

During a median follow-up of 5 years (interquartile range, 2.6-8.2 years), 20 cases (11.1%) deceased, of which ten patients died of infections with functional renal allografts and 117 cases (65.0%) achieved the combined event (initiation of replacement therapy or eGFR<15ml/min/1.73m^2). Kaplan-Meier methods yielded the 1-year and 5-year cumulative renal allograft survival rates after a histopathologic diagnosis of TG were 84% [95% confidence interval (CI), 81-87%] and 33% (95% CI, 27–39%), respectively (Fig. 3).

Univariate analysis for risk factors predicting graft survival

In univariate analysis, higher proteinuria (P<0.005), impaired eGFR (P<0.0001), higher urRBP and urNAG level (P<0.0001 and P=0.003 respectively), anemia (P<0.0001) and hypoproteinemia (P<0.002) at the time of biopsy were negative predictors of allograft outcome for TG patients. Interestingly, HCV

and PRA status did not seem to have statistically significant influence on graft survival for TG patients (Fig. 4).

Multivariate Cox model for allograft survival

Patients were divided into three groups on the basis of their peak proteinuria: <1 g/d (group 1), 1 to 3 g/d (group 2), and >3 g/d (group 3). As illustrated in Fig. 4, the greater the proteinuria, the worse the renal survival. Multivariate analysis revealed that patients in either group 2 (HR 3.66, P<0.001) or group 3 (HR 5.01, P<0.001) had a significantly more rapid rate of renal function decline than patients in group 1. Similar observations had been made regarding eGFR: for those with an eGFR between 30 to 59 at the time of biopsy, the hazard ratio for worse allograft outcome was 4.50 (95% CI 1.03-19.71, P=0.0462) as compared with those with initial eGFR≥60, which further increased to 9.14 (95% CI 1.97-42.45, P<0.0047) when eGFR decreased to 15-29 at the time of biopsy. Additionally, higher urRBP (>2.85mg/dl) was found to confer a much worse survival rate for TG patients (hazard ratio 2.13, P=0.009) in multivariate Cox analysis. Furthermore, multivariate analysis also indicated that male sex (HR 0.48, P=0.02) and HCV infection (HR 1.78, P=0.0499) were associated with a worse allograft survival rate. Nonetheless, NAG, hypoproteinemia and anemia that were associated with allograft survival rate in univariate analysis were not found to be statistically significant by multivariate Cox analysis (Table 2).

Table 1. Demographic and clinical features at biopsy. Abbreviations: PRA, panel-reactive antibody; MMF, mycophenolate mofetil; Pred, prednisolone; Tac, Tacrolimus; CsA, cyclosporine A; eGFR: estimated glomerular filtration rate; urNAG: urinary N-acetyl-β-D-glucosamidase; urRBP: urinary retinol-binding protein; HCV: hepatitis C virus; cg: chronic glomerulopathy

Characteristics	N=180 patients
Gender, male (%)	143 (79.4)
Age (years)	43.9±10.7
Donor age (years)	40.3±7.3
Positive pre-transplant PRA (n)	0
Previous transplant(n)	0
Baseline immunosuppressants, N (%)	
MMF+Tac+Pred	75 (41.7)
MMF+CsA+Pred	86 (47.8)
Others	19 (10.6)
Time from transplantation to biopsy (months), median (IQR)	85 (50-124)
Serum creatinine (mg/dl), median (IQR)	2.27 (1.60-2.79)
eGFR (ml/min/1.73m²), median (IQR)	35.42 (25.3-49.3)
≥60 (%)	25 (13.9)
30-59 (%)	83 (46.1)
15-29 (%)	72 (40.0)
Proteinuria (g/d), median (IQR)	1.90 (0.67-2.71)
<1.0g/d (%)	69 (38.3)
1 to<3 g/d(%)	76 (42.2)
≥3 g/d(%)	35 (19.4)
Hematuria (%)	20 (11.1)
urNAG (U/g*cr), median (IQR)	17.4 (10.4-28.6)
urRBP (mg/L), median (IQR)	4.33 (1.28-12.63)
Albumin (g/L)	35.88±5.90
Hemoglobin (g/dl)	10.18±1.74
Uric acid (ummol/L)	482±107
HCV infection, N (%)	38 (21.11)
PRA, data available, N (%)	169 (93. 9)
PRA I positive, N (%)	28 (16.6)
PRA II positive, N (%)	94 (55.6)
PRA I or II positive, N (%)	109 (64.5)
CD3, median (IQR)	1140 (873-1491)
CD4, median (IQR)	650 (452-955)
CD8, median (IQR)	420 (314-556)
CD4/CD8, median (IQR)	1.50 (1.16-1.99)

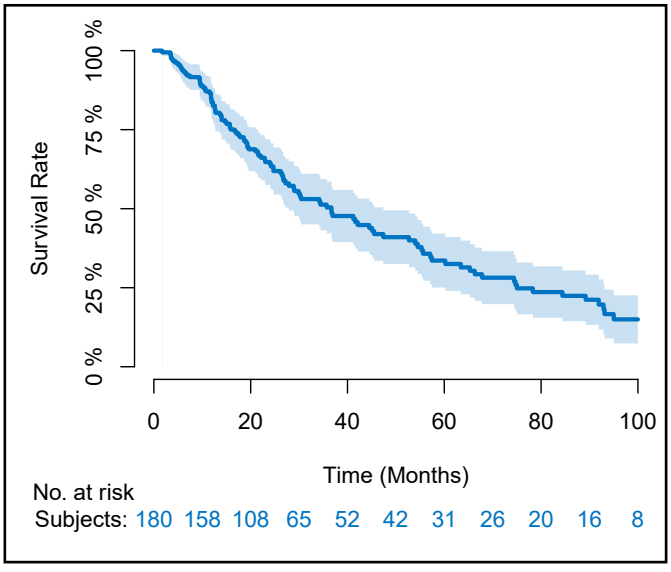

Fig. 3. The Kaplan-Meier renal survival curve of 180 patients with transplant glomerulopathy.

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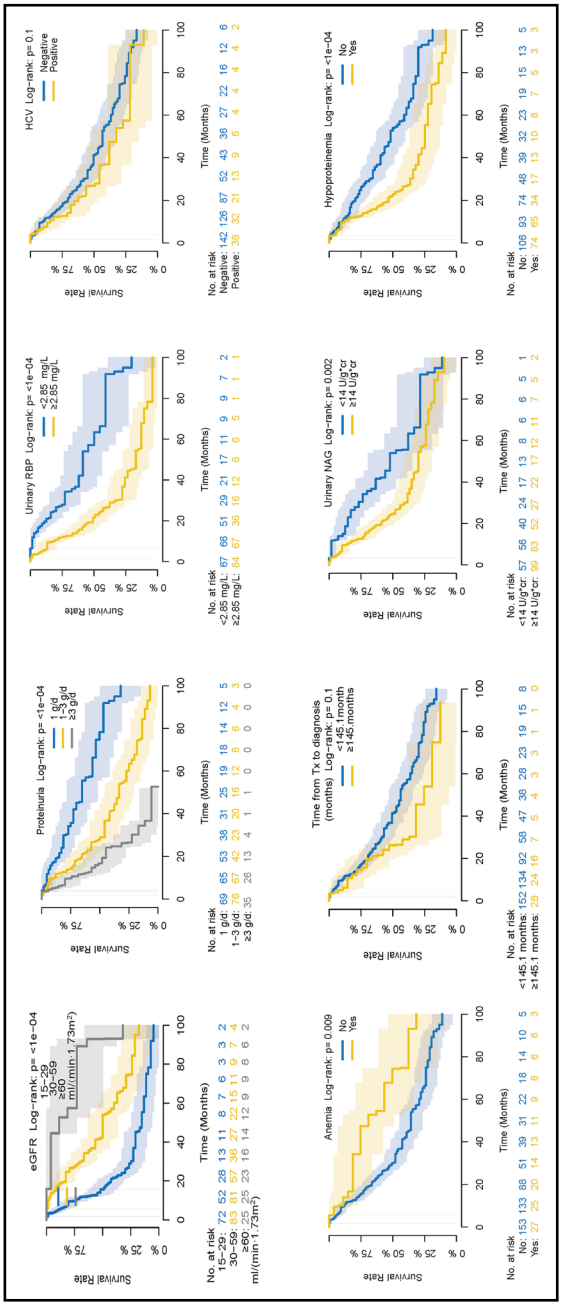

Fig. 4. Kaplan–Meier curves showing time to graft loss after transplantation in transplant glomerulopathy patients. Abbreviations: eGFR: estimated glomerular filtration rate; NAG: urinary N-acetyl-β-D-glucosamidase; RBP: urinary retinol-binding protein; HCV: hepatitis C virus; Tx: transplantation.

Discussion

This large retrospective study with long-term follow-up identified several clinical parameters as risk factors for renal allograft loss in patients with TG. We demonstrated that at the time of biopsy, impaired renal allograft function (as indicated by lower eGFR), higher level of proteinuria, higher urRBP level, HCV infection and male sex were independent risk factors for long-term allograft survival.

Proteinuria has been established as a risk factor that confers poor outcome for a variety of kidney diseases both in the native kidneys and renal allografts [13-15]. Chronic endothelial injury and remodeling account for the main mechanism for proteinuria in TG, the severity of which as assessed by histologic score of cg does not necessarily correlated with proteinuria degree clinically, though. We found in this study that increasing levels of proteinuria were inversely associated with graft survival rate, which is compatible with other investigations. In a previous study, Amer and associates reported even minimal proteinuria (<0.5 g/24h) was associated with a 4-fold increased risk for renal allograft failure when compared with those without proteinuria, which further increased to 19-fold when proteinuria was in nephrotic-range. In another study, Banfi et al. demonstrated that TG patients with a daily proteinuria >2.5 g were twice more likely to return to dialysis than those with lower proteinuria [16]. Since eGFR is frequently within normal range in early stages of TG and the only clinical indicator of allograft dysfunction is minimal to mild proteinuria, the results of this study highlighted the importance of early biopsy to improve long-term allograft survival.

Urinary metabolites produced or excreted by the proximal tubules actively or under the regulations of various hormones [17-19] have been demonstrated to be of prognostic significance in various renal conditions. Retinol binding protein is a low-molecular

Table 2. Factors at biopsy influencing by univariate and multivariate Cox regression. Abbreviations: eGFR: estimated glomerular filtration rate; urNAG: urinary N-acetyl-β-D-glucosamidase; urRBP: urinary retinol-binding protein; HCV: hepatitis C virus

Parameter	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
eGFR (ml/min/1.73m^2)				
≥60	Reference		Reference	
30-59	3.13 (1.40-6.99)	0.005	4.50 (1.03-19.71)	0.0462
15-29	8.60 (3.89-19.01)	<0.0001	9.14 (1.97-42.45)	0.0047
proteinuria (g/24h)				
<1	Reference		Reference	
1 to <3	2.50 (1.61-3.88)	<0.0001	3.66 (1.87-7.16)	<0.001
≥3	6.22 (3.58-10.79)	<0.0001	5.01 (2.19-11.48)	<0.001
urRBP (≥2.85 vs. <2.85mg/L)	3.05 (1.95-4.78)	<0.0001	2.13 (1.21-3.75)	0.0091
sex (male vs. female)	1.47(0.90-2.38)	0.125	2.08 (1.11-4.00)	0.0214
HCV infection	1.38 (0.90-2.11)	0.144	1.78 (1.00-3.15)	0.0499
anemia	2.08 (1.19-3.57)	<0.0001	2.13 (0.82-6.26)	0.1186
allograft age (≥145.1 vs. <145.1month)	1.47 (0.90-2.42)	0.127	1.25 (0.67-2.32)	0.4882
urNAG (≥14 vs. <14U/g*cr)	1.27 (2.00-3.14)	0.003	1.16 (0.65-2.06)	0.6244
hypoproteinemia	2.12 (1.46-3.08)	<0.0002	1.06 (0.57-1.99)	0.8456

weight protein produced in the liver, excreted by the glomeruli and reabsorbed in the proximal convoluted tubules, therefore whose excretion in the urine is a noninvasive biologic marker of proximal tubule injury [20]. It has been found that urRBP was an independent risk factor of renal outcome in patients with macroalbuminuric diabetic nephropathy [21] and a prognostic marker for various glomerulopathy [22]. urRBP has also been demonstrated to be predictable of normal allograft histology when it and urinary albumin, IgM were within normal range [8]. In an earlier study with 183 kidney transplant recipients, Hosaka et al. noticed that urRBP level higher than 0.6 mg/L had the best predictive value for diagnosing allograft dysfunction at 1 year post-transplantation [20]. The finding that higher urRBP level is associated with worse allograft survival rate is in line with the study of Câmara et al. [23], who reported that high urRBP level could identify those at risk for developing chronic allograft nephropathy and thus decreased allograft survival time.

Contrary to RBP, NAG is a high molecular-weight enzyme produced predominantly in the proximal tubules and thus serves as a sensitive marker for tubular impairment. The predictive value of urNAG for allograft survival has been conducted in two studies with conflicting results. In a study involving 33 patients, Kotanko et al. found that paradoxically lower urNAG excretion is associated with reduced graft survival [24]. In a subsequent investigation, Ferdau et al. demonstrate that urNAG level is positively associated with graft failure [13-15]. However, this predictive value disappeared when adjusted for albuminuria which had been demonstrated to be the best predictor of allograft failure. In our study, we noticed urNAG is a negative predictor of allograft survival in univariate analysis while urNAG level no longer predicts allograft survival in the multivariate analysis.

There are conflicting results regarding the predictive value of PRA for kidney graft survival in previous published studies. Abreau et al. [5] demonstrated that PRA class II was associated with graft failure while Julie et al. [25] and Layla et al. [6] consistently showed that allograft survival/failure was independent of PRA levels. We failed to find PRA predictive of allograft survival in both univariate and multivariate analysis, which did not necessarily negate previous findings. The follow-up time of this study is so long that antibody-detection method in our center underwent dramatic change from flow cytometry to Luminex solid-phase assay. Therefore, the inconsistency of PRA and DSA information prevented us from analyzing whether different cause of TG possessed disparate allograft survival, which is a limitation of this study.

Interestingly, we found HCV infection decreased allograft survival compared with those without HCV infection. Although as much as 21.1% of patients included in this analysis were infected with HCV, it is extremely difficult if possible to differentiate between TG caused by chronic antibody reaction or those caused by HCV infection [26]. Additionally, the effect of HCV infection on TG prognosis as analyzed by multivariate Cox regression was marginal, therefore the intimate association between HCV infection and TG entails further scrutiny. It remains elusive whether treatment for HCV improves kidney allograft survival in TG patients. The finding that male sex serves an independent prognostic factors for the progression to allograft failure is in line with previous studies which reported that recipient male gender confers a worse prognosis for allograft survival in a large retrospective cohort [27]. This gender differences may partially be explained by the fact that women are protected by hormones and appear to be more compliant than male recipients [28, 29]. Other clinical parameters predicting outcome at the univariate analysis, i.e. the time from transplantation to biopsy, anemia and hypoproteinemia, lost their prognostic value at the multivariate Cox analysis.

Our study has some limitations inherent to any retrospective study. Although we have analyzed the associations of variables at the time of biopsy with long-tern allograft outcome, therapeutic influences and pathologic factors that may also influence allograft survival were not accounted for in this study. However, recent studies have indicated that currently available treatment modalities for TG is ineffective to improve kidney allograft survival [5, 30, 31]. Additionally, patients included in this study are predominantly composed of for-cause biopsy. It remains undetermined whether early detection of TG (as is often the case in protocol-biopsy) improves allograft outcome. Another limitation of this study is that histologic predictors of allograft survival were not assessed. Although RBP has been found to be an noninvasive marker of interstitial fibrosis/tubular atrophy(IFTA) that has been demonstrated to be the most important histologic predictors of allograft survival [20, 32], it remains to be determined whether RBP possessed the same predictive value as histologic lesions of interstitial fibrosis and/or tubular atrophy.

Conclusion

The cumulative renal allograft survival was 84% within 1 years, 33% within 5 years in this cohort of Chinese adult patients with TG. Five clinical features at the time of allograft biopsy- impaired allograft function, higher proteinuria, higher urRBP level, male sex and HCV infection are independent predictors of an unfavorable outcome. urRBP is a simple and useful parameter that adds invaluable information for the clinical follow-up of patients with TG.

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This single-center retrospective study was carried out after Institutional Review Board approval and performed in accordance with the Principles of the Declaration of Istanbul.

Disclosure Statement

The authors declare no competing interests.

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