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Original Article

The impact of pathological diagnosis and histological damage in indicated biopsy on predicting long-term graft survival in renal transplant patients

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Purpose: The relative impact of histological diagnoses and changes on renal allograft outcome remains elusive. To investigate the relative effects of histopathological lesions on graft kidney survival.

Methods: In a single-center observational study, we examined the histopathological findings of allograft biopsies in kidney transplant recipients who achieved either a doubling of the creatinine level or graft failure.

Results: The three most common biopsy diagnoses were Borderline acute cellular rejection (18.95%), mixed rejection (16.53%), and calcineurin inhibitor toxicity (15.73%). Similarly, transplant glomerulopathy with microvascular injury (88.89%) and microvascular injury alone (75%) were the most common clinical diagnoses achieving the graft endpoint. Conversely, calcineurin inhibitor toxicity had the lowest percentage of reaching the endpoint (20.51%). Finally, a strong association between chronicity score in histology and graft loss ratio has been noted using Kaplan–Meier estimates in this study.

Conclusion: Microvascular injury and transplant glomerulopathy, two distinctive histological indicators of antibody-mediated rejection (ABMR), have a dramatic impact on graft renal loss. The impact of CNI toxicity on long-term graft survival was also overemphasized as it did not cause as much graft failure. Better diagnostic, monitoring, and therapeutic strategies for ABMR should be evolved to minimize graft renal loss.

Keywords: Antibody-mediated rejection; Renal transplant; Calcineurin inhibitors; Microvascular injury; Transplant glomerulopathy

1. Introduction

Under the influence of etiologies such as hypertensive nephropathy, glomerulonephritis, diabetic nephropathy, and obstructive nephropathy, incidents of end stage renal disease (ESRD) have increased dramatically worldwide over the past few years. Although medical treatments such as dialysis relieve the uremic symptoms, renal transplantation has emerged as one of the most cost-effective and favorable approach for long term ESRD management. (1) The expenses associated with patient therapy through hemodialysis in end-stage renal disease are nearly three and a half times higher than the costs involved in transplantation and subsequent maintenance therapy.(2) The numbers of renal allograft transplantation have therefore increased significantly and almost doubled in countries such as Japan (1) and Iran (3) in the past decade.

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However, patients who received allograft transplantation may suffer from graft dysfunction. Researches have suggested that common causes such as rejections, recurrence or de novo glomerulonephritis, thrombotic microangiopathy and other histopathological changes have contributed to the graft dysfunction.(4) Chronic damages from antibody medicated rejection (ABMR) resulting in transplant glomerulopathy (TG), arterial intimal fibrosis, and interstitial fibrosis/ tubular atrophy(IF/TA) may eventually lead to graft kidney failure.(5-9) Other concerns such as Calcineurin inhibitors (CNIs), which were used as immunosuppressive therapy, have caused renal toxicity and might result in graft kidney dysfunction(10).

Due to its complexity, the true cause of a graft failure often requires a histopathological analysis from biopsy samples to confirm a definite diagnosis. Rejections have been classified into antibody medicated rejection and T-cell medicated rejection (TCMR). Banff classification, a standardized method for interpreting renal transplant pathologies established in 1991. It was constantly reviewed and Banff 2018 was consisted of the following six categories: [1] normal, [2] ABMR, [3] borderline changes, [4)]TCMR, [5] interstitial fibrosis and tubular atrophy (IF/TA), and [6] other changes.(11) With limited data available, we focused on the impact of histopathological and clinical diagnosis to identified their association with the long-term renal graft survival.

2. Methods

In this study, a total of 284 allograft patients indicated for renal biopsy at a medical center (Chung San University H.) between 2008 and 2013 were enrolled. Histological examination data from the biopsies was collected. Patients with inadequate biopsy tissue, those undergoing ABO-I treatment, or those without regular follow-up were excluded from the study. The remaining patients who participated in the study were monitored and followed up until they reached the primary endpoint, which was defined as achieving a doubling of the creatinine level or experiencing graft failure. Because large long-term changes in serum creatinine are thought to reflect a structural renal function decline, the doubling of the serum creatinine is well-accepted as an endpoint.(12)

The collected data was further categorized based on their histological examination, including acute cellular rejection (ACR), borderline ACR, microvascular injury (MI), transplant glomerulopathy with MI, mixed cellular or antibody-mediated rejection, calcineurin inhibitor (CNI) toxicity, BK-virus nephropathy (BKN), recurrent glomerulonephritis (GN), no major abnormalities, and others. Additionally, a multivariate Cox proportional hazards analysis was conducted with additional variables including age and creatinine levels at the time of biopsy.

3. Results

The clinical demographics of the 284 patients were demonstrated in the Table 1. As can be seen from the table, there were 162 males (65%) and 86 females (35%) involved in the study. Approximately a half of the candidates had diabetes mellitus and hypertension, occupying 50.4% and 41.53% of the study population respectively. Hepatitis B viral (HBV) and Hepatitis C viral (HCV) infections were not as common among the patients, which were only 16.13% and 7.66% respectively. The average creatinine level was 2.6 mg/dl. Lastly, the average time between biopsy to graft endpoint was 50.7months

As observed in Table 2, it displays the total number of various histopathological diagnoses and the cases that reached a graft endpoint. Among the histopathological diagnoses in the study group, Borderline ACR, mixed rejection, and CNI toxicity were the most frequently encountered, accounting for 18.95%, 16.53%, and 15.73%, respectively. In contrast, TG with MI and BKN were less commonly observed, representing only 3.63% and 3.23%, respectively. Interestingly, although TG with MI and MI were less common, they exhibited a higher likelihood of reaching the graft endpoint, with 88.89% in the TG with MI group and 75% in the MI group.

Conversely, although CNI toxicity was a common finding in the study group, it had the lowest percentage of reaching the endpoint at 20.51%. ACR (29.63%) and Borderline ACR (25.53%) did not result in a high graft failure rate as initially expected. Other causes such as mixed rejection, BKN, and GN achieved approximately

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Table 1. Demographic and clinical characteristics of the transplant patients (N=248)

Patient demographics	
Mean age	47 (15-74)
Gender (male)	162/248 (65%)
Hepatitis B virus	40/248 (16.13%)
Hepatitis C virus	19/248 (7.66%)
Diabetes mellitus	125/248 (50.40%)
Hypertension	187/248 (41.53%)
Mean creatinine level at biopsy (mg/dl)	2.6
Time between biopsy to graft endpoint (months)	50.7(1-193)
Immunosuppressant	
Tacrolimus	217/248 (87.5%)
Cyclosporine	29/248 (11.69%)
Mycophenolate mofetil/mycophenolic acid (MMF/MPA)	237/248 (95.56%)
mTOR	27/248 (10.89%)

Table 2. The association between the histopathological diagnosis and graft loss in the 284 patients

Patient demographics	Total n=248	%	Graft to endpoint n=101	% of Graft to endpoint in each cohort
ACR	27	10.89	8	29.63
Borderline ACR	47	18.95	12	25.53
MI	24	9.68	18	75
TG+MI	9	3.63	8	88.89
Mixed rejection	41	16.53	22	53.66
CNI toxicity	39	15.73	8	20.51
BKN	8	3.23	4	50
GN	19	7.66	12	63.16
No major abnormalities	20	8.06	4	20
Others	14	5.65	5	35.71

ACR: acute cellular rejection; MI: Microvascular injury; TG: transplant glomerulopathy; CNI: calcineurin inhibitor; BKN: BK-virus nephropathy; GN: recurrent glomerulonephritis;

a 50% graft failure rate.

The significance of clinical diagnoses associated with graft loss was analyzed using multivariate Cox proportional hazard analysis (Table 3). ACR was used as the reference, and the Hazard ratio was adjusted. Among these diagnoses, MI and GN showed statistical significance with a P-value less than 0.05, followed by TG with a P-value of 0.088.

The association of renal endpoint with histopathological diagnosis was further examined using statistical

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Table 3. Multivariate Cox proportional hazards analysis of histopathological diagnosis associated with graft loss, with additional variables including age and creatinine level at biopsy

	Crude HR (95% C.I.)	p value	Adjusted HR (95% C.I.)	p value
Histopathological diagnosis				
ACR	Reference		Reference	
Borderline ACR	0.71 (0.29-1.73)	0.450	1.32 (0.38-4.60)	0.664
Microvascular injury	3.70 (1.60-8.56)	0.002	4.06 (1.10-15.01)	0.036
TG+Microvascular injury	4.79 (1.79-12.83)	0.002	4.30 (0.81-22.92)	0.088
Mixed rejection	1.89 (0.84-4.24)	0.124	1.57 (0.53-4.69)	0.420
CNI toxicity	0.59 (0.22-1.58)	0.297	1.64 (0.35-7.57)	0.528
BKN	1.67 (0.50-5.55)	0.403	3.25 (0.87-12.10)	0.079
GN	2.18 (0.89-5.33)	0.088	3.83 (1.01-14.59)	0.049
No major abnormalities	0.53 (0.16-1.76)	0.299	1.84 (0.35-9.67)	0.471
Others	1.02 (0.33-3.12)	0.970	1.78 (0.38-8.38)	0.469
Age	1.00 (0.98-1.02)	0.860	1.01 (0.99-1.03)	0.555
Cre level at Biopsy	0.93 (0.83-1.04)	0.197	0.99 (0.86-1.14)	0.918

ACR: acute cellular rejection; TG: transplant glomerulopathy; CNI: calcineurin inhibitor; BKN: BK-virus nephropathy; GN: recurrent glomerulonephritis; Cre: creatinine

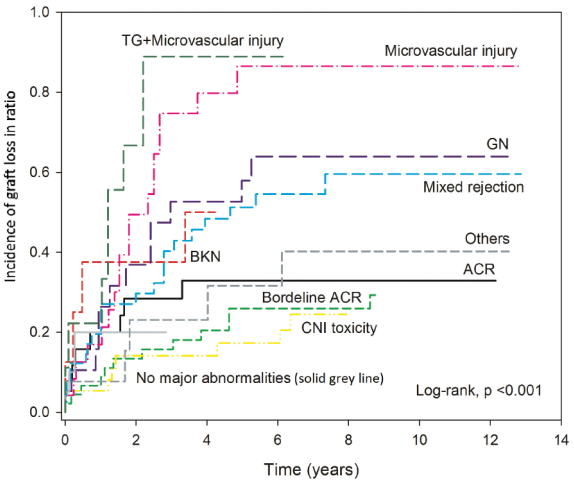


Figure 1. Association of renal graft loss and histopathological diagnosis, by Kaplan–Meier estimates

Kaplan-Meier estimates and is presented in Figure 1. TG with MI exhibited the steepest slope, resulting in the highest graft loss ratio within the shortest time interval (approximately 2 years). The MI curves and GN curve ranked second and third in terms of graft loss ratio. In contrast, CNI toxicity and no major abnormalities had the flattest curves and resulted in the lowest graft loss ratio.

As illustrated in Figure 2, we observe the association between individual histopathological changes and graft survival in Kaplan-Meier estimates of graft survival. It is evident from the figures that the graft loss ratio increases over time. A higher chronicity score is associated with a higher graft loss ratio within the same time interval. However, significant overlaps

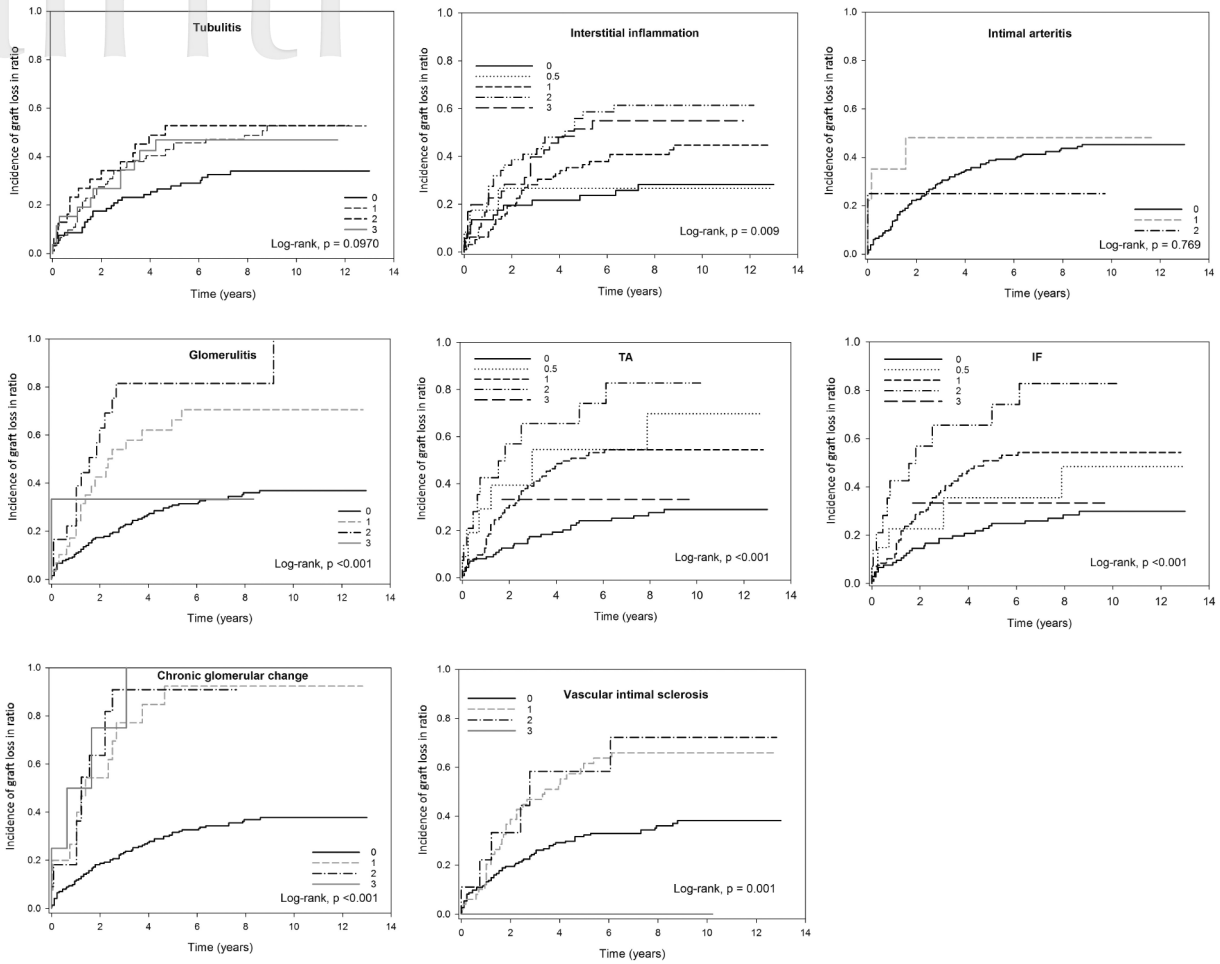


Figure 2. The association between the individual histopathological change and graft survival in Kaplan–Meier estimates
IF: interstitial fibrosis; TA: tubular atrophy

are observed among the curves in the tubulitis, chronic glomerular change, and vascular intimal sclerosis subgroups. In the IF/TA groups, score 3 also does not exhibit a higher ratio of renal loss, contrary to the expectations from the other figures.

4. Discussion

With rapid advancements of rejection mechanisms and their management with more effective immunosuppressants, there has been an astounding uptick in the success rate of kidney transplants. With the implementation of modern protocols, the incidence of hyperacute rejection leading to graft failure has become exceedingly rare, and the rates of acute cellular rejection (ACR) have decreased to less than 10% in the first year after transplantation.(13) In the United States, the longevity of a typical deceased donor kidney, as measured by its half-life, has significantly increased by nearly 50% (13). In comparison, in 1989, the average was at 10.6 years, whereas by 2005, it had increased to 15.5 years. A similar positive trend was observed in a living donor transplantation as well. Conversely, there has been only a modest improvement in long-term graft survival.(14)

Recent cohort studies have indicated that renal allograft loss is multifactorial and preceded by a combination of TCMR, ABMR, de novo or recurrent glomerulopathy, or polyomavirus-associated nephropathy (PVAN), together with chronic histological damage.(15) Antibody-mediated rejection (ABMR) emerged as the most frequent cause, contributing to 40% of graft failures, with a peak occurrence of a 6-year mark post-transplant.(16) Transplant

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glomerulopathy, a distinctive histological indicator of chronic ABMR, has become responsible for 17% of graft failures, predominantly occurring after 6-7 years post-transplant. Furthermore, the persistence of chronic changes and the less understood mechanisms related to TG and IF/TA might pose challenges to extend the survival of transplanted organs.

Our study has highlighted the significant role of antibody-mediated rejection by revealing a high rate of renal graft loss associated with MI, a major criterion defining ABMR according to the 2018 Banff consensus.(11) The combination of MI and TG further have accelerated the progression of graft failure and worsening the outcome. The significance of MI was further confirmed by the Cox proportional hazard analysis (Table 3) where ACR was used as the reference and the Hazard ratio was adjusted. The MI, as well as GN, had shown their significance with a p-value less than 0.005, indicating that both were important factors that contributed to graft renal failure. Previously the chronic allograft nephropathy that resulted from the nephrotoxic effects of calcineurin inhibitors (CNIs) was regarded as the primary cause of death-censored graft loss.(10) Our study has shown that although CNI toxicity has a high prevalence, it did not lead to renal graft failure in comparison to other histopathological diagnoses. This suggests that while calcineurin inhibitors may have played a role in contributing to long-term graft survival, they may not be the most dominant factor in this regard.

The significance of the chronic histopathological change in association with renal graft loss is portrayed in Figure 2. In general, the ratio of graft loss increased in accordance with the chronicity scores in the Kaplan-Meier estimates analysis. A high score would result in a distinctive higher rate of graft loss. This is a strong indication that renal graft loss is potentially associated with chronic histopathological changes. One study had also reached a similar conclusion where the prognosis is determined by the development of subsequent chronic damage rather than the occurrence of rejection itself.(15) In tubulitis, chronic glomerular change, and vascular intimal sclerosis subgroups, there is much overlap amongst the curves. This indicates that these histopathological changes might contribute to a similar degree of renal damages.

IF/TA represents a culminating convergence of numerous independent and interconnected molecular and cellular pathways.(17) Currently, there is no unanimous agreement on the mechanism or treatment for IF/TA, although chronic immune rejection and inflammation are significant factors under consideration.(18) An interesting observation was made in the IF/TA subgroup, where score 3 did not exhibit a higher ratio of renal loss as expected. One possible explanation might be due to the limited study size with insufficient patients that progressed to score 3, resulting in a misleading trend.

Our study revealed the impact of the ABMR on the long-term graft survival. Much focus has been emphasized on the prevention and management of ABMR. While treatments with plasmapheresis, intravenous immunoglobulin (IVIG) or combination of plasmapheresis with low-dose IVIG and rituximab have already been used in desensitization protocols for ABMR today(19), some studies have revealed that these treatments might not achieve a favorable outcome against ABMR as expected.(20, 21) However, novel therapeutic approaches, including the use of agents designed to target B cell activation (such as atacicept and belimumab), anti-CD20 antibodies (such as ofatumumab and ocrelizumab), anti-CD22 antibody (epratuzumab), and the utilization of an Anti-C5 antibody (eculizumab) or their combinations are currently under further investigation.(22, 23)

Despite the comprehensive nature of the study on renal allograft transplantation and its impact on long-term graft survival, several limitations should be considered. Firstly, the study's exclusive focus on patients from a single medical center (Chung San University H.) between 2008 and 2013 raises concerns about the generalizability of the findings to a broader population. Moreover, the relatively small sample size of 284 patients might limit the statistical power of the study, and the absence of an in-depth exploration of therapeutic interventions leaves questions about the optimal management strategies for the identified histopathological changes. Lastly, the study's temporal scope, ending in 2013, may not fully capture recent advancements in transplantation practices, potentially impacting the relevance of the findings to current medical standards.

In summary, the clinical diagnosis of MI was significantly associated with the worse renal graft

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survival. The combination of MI with TG in histology would result in an even worse clinical outcome. The chronicity scores of a graft kidney also plays an important role in predicting the long-term renal graft survival. The impact of CNI toxicity on long-term graft survival was overemphasized. The immunosuppression strategy for avoidance of CNI toxicity previously employed should be reconsidered. As a sequence, better diagnostic, monitoring, and therapeutic strategies for ABMR were required to improve the life-span of a transplant kidney.

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