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Impact of Glomerulitis on Long-term Outcomes After Kidney Transplantation

Morgan Whigham, MD,[1] Raymond L. Heilman, MD,[2,3] Sumi Sukumaran Nair, MBBS, MD,[2,3] Matthew R. Buras, MS,[4] Elisabeth S. Lim, MPH,[4] Andres Jaramillo, PhD,[5] Daniel S. Ramon, PhD,[5] Margaret S. Ryan, MD,[6] and Girish K. Mour, MBBS, MD[2,3]

Background. The Banff classification scheme provides a framework for interpreting transplant kidney biopsies and has undergone various updates in the past 2 decades especially related to antibody-mediated rejection. The clinical significance of early glomerulitis seen within 4 mo on protocol biopsies has received limited attention. We hypothesized that early glomerulitis seen on protocol biopsies will lead to significant adverse outcomes as assessed by histopathology and allograft outcome. **Methods.** A single-center retrospective study of a cohort of patients who underwent protocol biopsies within 4 mo after transplantation with timely follow-up protocol biopsies were assessed. Patients with recurrent glomerulonephritis were excluded. **Results.** We calculated glomerulitis (g) scores for 2212 biopsy specimens and identified 186 patients with glomerulitis ($g>0$) and 2026 patients without glomerulitis ($g=0$). The progression to chronic transplant glomerulopathy at 1 and 2 y was higher in patients with $g>0$ as compared with $g=0$ (year 1, 10.7% versus 2.3% [$P<0.001$], respectively; year 2, 17.2% versus 4.3% [$P<0.001$], respectively) with no difference in other chronic lesions. The death-censored graft failure rate was higher in patients with $g>0$ as compared with $g=0$ (hazard ratio, 1.68 [95% CI, 1.07-2.65]; $P=0.02$). We did not find any difference in outcomes in glomerulitis group based on donor-specific antibody. **Conclusion.** Our findings suggest that early glomerulitis (seen within 4 mo after transplantation) may lead to clinically significant long-term changes and thus could be a target for early intervention therapies.

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INTRODUCTION

The past 2 decades have seen tremendous improvements in the technologies used to detect and characterize anti-HLA alloantibodies and those used to promptly recognize and treat acute and chronic forms of rejection. The use of Luminex bead-based immunoassays has improved the accuracy of HLA antibody detection, and these tests have become a routine part of transplant evaluations and subsequent donor-specific antibody (DSA) screening.

Significant developments also have occurred in terms of recognizing patterns of acute and chronic rejection. Several seminal studies prompted modification of the Banff criteria to encompass the complex spectrum of antibody-mediated rejection (AMR).[1-6] Based on criteria from the Banff 2017 kidney meeting, active AMR requires histological evidence of acute tissue injury (microvascular inflammation [MVI], acute thrombotic microangiopathy, arteritis, or acute tubular injury), evidence of antibody interaction with vascular

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[1] Resident (Whigham), Mayo Clinic School of Graduate Medical Education, Mayo Clinic College of Medicine and Science, Scottsdale, AZ, USA.

[2] Division of Nephrology, Mayo Clinic Hospital, Phoenix, AZ, USA.

[3] Transplant Center, Mayo Clinic Hospital, Phoenix, AZ, USA.

[4] Division of Clinical Trials and Biostatistics, Mayo Clinic, Scottsdale, AZ, USA.

[5] Department of Laboratory Medicine and Pathology, Mayo Clinic Hospital, Phoenix, AZ, USA.

[6] Department of Laboratory Medicine and Pathology (Ryan), Mayo Clinic, Scottsdale, AZ, USA.

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Correspondence: Girish K. Mour, MBBS, MD, Division of Nephrology, Mayo Clinic Hospital, 5777 E Mayo Blvd, Phoenix, AZ 85054 (mour.girish@mayo.edu).

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endothelium through C4d staining or MVI score of 2 or higher in the absence of glomerulonephritis (GN), and serologic evidence of DSA. Notably, the presence of C4d staining or validated transcripts or classifiers may now substitute for DSA because of studies that have shown specificity in conjunction with appropriate histologic morphology for AMR.[7-9]

Although criteria for AMR have been well defined, areas of ambiguity remain in patients with MVI (calculated as peritubular capillaritis [ptc] score plus glomerulitis [g] score). In the absence of C4d staining and DSA, the clinical significance of isolated glomerulitis or isolated peritubular capillaritis remains debatable. The impact of glomerulitis on graft outcomes has been evaluated previously[10-14]; however, most studies assessed patients who required biopsies in the setting of impaired graft function, and recurrent GN as a cause of glomerulitis was not excluded.

Overall, there is a paucity of evidence to interpret the prognostic value of glomerulitis that is identified with routine follow-up surveillance biopsies (termed *protocol biopsies*). The aim of this study was to determine the effect of early glomerulitis (defined as a g score >0 within 4 mo of transplantation) that was identified with protocol biopsies. We assessed the outcomes of death-censored graft failure and progression to chronic glomerulopathy (cg; defined as cg score >0).

MATERIALS AND METHODS

The study protocol was approved by the Mayo Clinic Institutional Review Board (protocol 18-004465). The Institutional Review Board waived the requirement for informed consent from patients who authorized use of their health records for research.

Study Population

We retrospectively studied patients undergoing solitary kidney transplantation from July 1, 2003, through August 31, 2018. Patients were treated at Mayo Clinic (Phoenix, AZ). Recipients of combined organ transplants and patients with recurrent GN were excluded from the analysis. Our clinical protocol included surveillance biopsies at 1 mo (until April 2014), 4 mo, 1 y, and 2 y. Clinically indicated biopsies were performed as needed for allograft dysfunction or proteinuria. Posttransplant donor-specific anti-HLA antibody tests were obtained routinely with surveillance biopsies, starting in August 2011.

All patients received induction immunosuppression. Before 2011, all recipients underwent rabbit-antithymocyte globulin induction. Starting in 2011, the induction regimen was tailored to the recipient age and sensitization. Alemtuzumab was used for all patients younger than 65 y, with corticosteroid withdrawal by postoperative day 5. Corticosteroids were continued if calculated panel-reactive antibodies (PRA) was 80% or higher. Basiliximab with corticosteroid maintenance was used throughout the study for patients with a history of solid-organ cancer (except for nonmelanoma skin cancer without metastasis) and for patients who were age 65 y and older. Rabbit-antithymocyte globulin induction was reserved for patients who had DSA with a mean fluorescence intensity (MFI) of 2000 or higher at the time of transplantation; it also could be used at the physician's discretion, depending on the patient's history. Immunosuppression was maintained with tacrolimus and mycophenolate mofetil. Tacrolimus therapy invariably started on posttransplant day 1, with trough goals of 8–10 ng/mL for the first 30 d and 6–8 ng/mL afterward. Delayed graft function (DGF) was defined as needing dialysis within the first 7 d after transplantation. The change in estimated glomerular filtration rate (ΔeGFR) was calculated as the difference between the last available measured creatinine level and that at 4 mo. The eGFR was calculated by using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) formula.[15]

Histologic Analysis

Light microscopy samples were evaluated with routine histologic stains, including hematoxylin and eosin, periodic acid–Schiff, methenamine Jones silver, and trichrome stains. Quantification of glomerulitis (g score), ptc score, and cg score were determined according to Banff criteria.[6] All samples underwent immunohistochemical staining with C4d antibodies to evaluate the peritubular capillaries. Inclusion in the glomerulitis cohort required a g score >0.

Detection of Anti-HLA Antibodies

Recipient and living-donor HLA typing was determined by using the reverse sequence–specific oligonucleotide probe method (LABType SSO, One Lambda, Inc). HLA typing results were reported as serologic equivalents. Pretransplant HLA antibody screening and posttransplant monitoring of DSA were performed by using single-antigen bead immunoassays (Luminex). Anti-HLA antibodies were evaluated by using the Flow PRA Single-Antigen HLA class I and class II assays (One Lambda, Inc) (2003–2009) and the LABScreen Single-Antigen HLA class I and class II assays (One Lambda, Inc) (2009–2018). Since June of 2016, sera were treated with ethylenediaminetetraacetic acid (5%, Sigma-Aldrich) and fetal bovine serum (5%, Sigma-Aldrich) to remove complement proteins, immunoglobulin M proteins, heterophile antibodies, and other serum components that interfere with solid-phase anti-HLA antibody assays.[16-18] An MFI value of 1000 was used as the positivity threshold for anti-HLA antibodies and DSA. Deceased-donor HLA typing data were obtained from United Network for Organ Sharing. Non-HLA antibodies were not routinely tested.

Statistical Analysis

Categorical variables are described with counts and percentages, and numeric variables are described with means and standard deviations and with medians and ranges (both are reported to help clarify the direction of the skewness of the distribution, if any). For the comparative group characteristic analysis, we used the chi-square test for categorical data and the Wilcoxon rank-sum test for numeric data, unless otherwise stated.

A patient with DSA before transplantation was categorized as having pretransplant DSA (preDSA). A patient without detectable DSA before transplantation and detectable DSA after transplantation was categorized as having de novo DSA (dnDSA). DSA positivity in our study was defined as an MFI of 1000 or higher. We performed a subgroup analysis on the basis of DSA testing, stratifying patients into 3 categories: patients who did not undergo DSA testing (before 2011), patients whose DSA test results were negative (MFI < 1000), and patients whose DSA test results were positive (MFI ≥ 1000).

Glomerulitis groups were defined as follows: the *g > 0 group* had patients with g scores >0 that were identified

by protocol biopsies within 4 mo after transplantation; patients in the *g = 0* group had no histologic findings of glomerulitis. No imputations were done to address missing data. Patients with missing data were excluded from analyses (if data were missing for at least 1 variable, then those patients were not considered in the adjusted models, etc). Missing values were not recoded as "0" or "No" and so do not appear in the tables on a variable-by-variable basis (ie, only the count and percentage of "Yes" responses are reported in the tables).

Between-group comparisons for death-censored graft failure were performed with the log-rank test for the difference in unadjusted Kaplan–Meier curves or the likelihood ratio test for adjusted models by using a Cox proportional hazards model.[19] All hypotheses were 2-sided, with the threshold for statistical significance set at $P < 0.05$. Analyses were conducted with SAS v9.4 (SAS Institute Inc).

RESULTS

Baseline Demographic Characteristics

Entire Cohort

We identified 2212 kidney transplant recipients. Patients were stratified by g score at 4 mo, and 186 patients (8.4%) were in the g > 0 group. HLA information was available for 1115 patients (50.4%). We included 219 patients with preDSA in the analysis after excluding 11 patients with recurrent GN or chronic transplant glomerulopathy (cg) within 4 mo after transplantation. All transplants were ABO-compatible, and flow cytometry crossmatch was negative for all except 22 patients.

At baseline, we observed no difference between groups (g = 0 versus g > 0) for age at transplant, recipient Black race, sex, Kidney Donor Profile Index, cold ischemia time (CIT) in deceased donors, induction regimen, or DGF. De Novo DSA was significantly higher in g > 0 group ($P < 0.001$). Dialysis vintage (length of time on dialysis before transplantation) was significantly longer in the g > 0 group ($P < 0.001$). Fourteen percent of patients in the g > 0 group had a previous kidney transplant graft failure compared with 9% in the g = 0 group ($P = 0.02$). The g > 0 group had more deceased-donor kidney transplantations ($P = 0.048$) and more patients with PRA >20% ($P = 0.02$). However, the degrees of HLA mismatch were similar in both groups (data not shown). Other baseline demographic characteristics are summarized in Table 1. We noted similar trends among patients whose HLA information was not available (before 2011) (Table S1, SDC, http://links.lww.com/TXD/A452).

DSA Cohort

This patient group had some differences compared with the aforementioned trends. Among DSA-negative patients, the g > 0 group had significantly more Black patients than the g = 0 group (22% versus 8%; $P = 0.005$), although the number of patients was quite low. Interestingly, dialysis vintage, type of transplant, prior kidney transplantation, and PRA were not different for the DSA-positive and DSA-negative groups. CIT

TABLE 1.

Baseline demographic characteristics, stratified by g score[a]

Characteristic	Total (N = 2212)	g = 0 (n = 2026)	g > 0 (n = 186)	*P*
Recipient variable				
Age at transplantation, mean (SD), y	54.4 (13.6)	54.3 (13.6)	55.7 (12.8)	0.21
Female sex, no. (%)	903(40.8)	820 (40.5)	83 (44.6)	0.27
Black race, no. (%)	187 (8.5)	172 (8.5)	15 (8.1)	0.84
Cause of end-stage renal disease, no. (%)				
Diabetes	789 (35.7)	711 (35.1)	78 (41.9)	0.06
Hypertension	286 (29.1)	267 (29.5)	19 (24.4)	0.34
Pretransplant dialysis, no. (%)	1673 (75.6)	1525 (75.3)	148 (79.6)	0.19
Duration of dialysis, d, median (IQR)	1114.5 (585–1687)	1084 (56–1646)	1387 (802–1898)	<0.001
Previous kidney transplantation, no. (%)	206 (9.3)	180 (8.9)	26 (14.0)	0.02
Body mass index, mean (SD)	28.7 (5.9)	28.6 (5.9)	29.1 (6.0)	0.31
Number of HLA mismatches, mean (SD)	3.8 (1.7)	3.8 (1.7)	3.8 (1.7)	0.66
Panel-reactive antibody >20%, no. (%)	473 (21.5)	421 (20.9)	52 (28.1)	0.02
Pretransplant DSA with mean fluorescence intensity ≥1000, no. (%)	185 (16.6)	172 (16.2)	13 (25.0)	0.09
De novo DSA (post transplant) (%)	87 (7.8)	75 (7.1)	12 (23.1)	<0.001
Induction, no. (%)				0.10
Basiliximab	524 (23.7)	481 (23.7)	43 (23.1)	
Alemtuzumab	1,017 (46.0)	943 (46.5)	74 (39.8)	
Thymoglobulin	671 (30.3)	602 (29.7)	69 (37.1)	
Corticosteroid avoidance, no. (%)	1265 (57.2)	1157 (57.1)	108 (58.1)	0.80
Delayed graft function, no. (%)	658 (29.7)	611 (30.2)	47 (25.3)	0.16
Donor variable				
Age, mean (SD), y	41.6 (15.1)	41.7 (15.1)	40.9 (16.0)	0.57
Kidney donor profile index, mean (SD), %	52.3 (27.1)	52.5 (27.0)	50.2 (27.7)	0.38
Deceased donor, no. (%)	1361 (61.5)	1234 (60.9)	127 (68.3)	0.048
Donation after circulatory death, no. (%)	242 (17.3)	224 (17.6)	18 (14.2)	0.33
Cold ischemia time for deceased donors, mean (SD), h	18.1 (7.4)	18.2 (7.4)	17.6 (7.4)	0.31

[a]No imputations were done to address missing data, and patients were excluded from specific analyses if their data were missing. Only the count and percentage of "Yes" responses are reported.
DSA, donor-specific antibody; g, glomerulitis; IQR, interquartile range.

was significantly higher in the g > 0 group compared with the g = 0 group for DSA-negative patients ($P = 0.045$), but it was similar for DSA-positive patients ($P = 0.12$) (data not shown).

Glomerulitis Outcomes

Entire Cohort

Progression to transplant glomerulopathy (cg score > 0) at years 1 and 2 was significantly higher in the g > 0 group than the g = 0 group (year 1, 10.7% versus 2.3% [$P < 0.001$]; year 2, 17.2% versus 4.3% [$P < 0.001$]) (Table 2). We did not find any difference in other chronic lesions or arteritis at year 1 and year 2 between the 2 groups. Significantly more patients had ptc scores >0 in the g > 0 group than the g = 0 group (68% versus 9%; $P < 0.001$). C4d deposition also was significantly more common in the g > 0 group (13% versus 1%; $P < 0.001$). Interestingly, both chronic interstitial fibrosis (ci) and chronic tubular atrophy (ct) biopsy scores were also significantly higher in the g > 0 group. The percentage of patients with intimal arteritis (v) scores >0 was higher in the g > 0 group (8.9% versus 1.7%; $P < 0.001$). The mean MVI score was 3.1 when analyzed as g > 0 plus ptc > 0. C4d deposition was not significantly different when comparing patients with isolated glomerulitis (g > 0 and ptc = 0) and isolated peritubular capillaritis (g = 0 and ptc > 0) (Table S2, SDC, http://links.lww.com/TXD/A452). We also analyzed if c4d was associated with death-censored graft failure in subjects with g > 0 but did not find any significant difference, which could be because of low number of events (Figure S1, SDC, http://links.lww.com/TXD/A452).

Subcohort Findings

Within the glomerulitis cohort, we observed similar outcomes for patients without available HLA information. However, in the cohort of patients with HLA information, we noted some differences. In the DSA-positive group, the progression to chronic glomerulopathy at year 1 was not significantly different for the g > 0 versus g = 0 groups ($P = 0.09$), whereas in the DSA-negative group, the g > 0 group had significant progression to chronic glomerulopathy at year 1 ($P < 0.001$). However, both DSA-positive and DSA-negative groups had significant progression to chronic glomerulopathy at year 2. We analyzed glomerulitis progression in DSA-positive versus DSA-negative patients and saw no difference in progression to cg at year 1 and 2 between the 2 groups (Table 3).

Isolated Glomerulitis

We identified 31 patients with isolated glomerulitis. These patients did not have a significantly different progression to chronic glomerulopathy at years 1 or 2 compared with patients with glomerulitis plus peritubular capillaritis (Table 4). Electron microscopy is not performed routinely in our biopsies, and data were not included.

Long-Term Follow-Up

The baseline eGFR for the entire cohort was lower in the g > 0 group than the g = 0 group (53.4 versus 56.8 mL/min; $P = 0.02$). However, there was no difference in ΔeGFR ($P = 0.66$) at the end of follow up (Table 2). Among patients without HLA

TABLE 2.

Patient outcomes, stratified by g score[a]

Outcome	Total (N = 2212)	g = 0 (n = 2026)	g > 0 (n = 186)	P
cg score >0, no. (%)				
Year 1	46 (2.9)	33 (2.3)	13 (10.7)	<0.001[b]
Year 2	55 (5.4)	40 (4.3)	15 (17.2)	<0.001[b]
ci > 0, no. (%)				
Year 1	1153 (72.5%)	1056 (72.0%)	97 (77.6%)	0.21[b]
Year 2	811 (79.7%)	741 (79.5%)	70 (81.4%)	0.78[b]
ct > 0, no. (%)				
Year 1	1314 (82.7%)	1207 (82.4%)	107 (85.6%)	0.45[b]
Year 2	868 (85.2%)	795 (85.2%)	73 (84.9%)	0.87[b]
cv > 0, no. (%)				
Year 1	727 (46.1%)	675 (46.5%)	52 (42.3%)	0.39[b]
Year 2	508 (50.0%)	466 (50.2%)	42 (48.3%)	0.82[b]
v > 0, no. (%)				
Year 1	16 (1.0%)	15 (1.0%)	1 (0.8%)	>0.99[b]
Year 2	6 (0.6%)	5 (0.5%)	1 (1.2%)	0.41[b]
Outcomes at month 4				
ptc score > 0, no. (%)	186 (12.9)	120 (8.9)	66 (68.0)	<0.001[b]
Biopsy positive for C4d, no. (%)	41 (2.4)	23 (1.4)	18 (12.9)	<0.001[b]
eGFR, mean (SD), mL/min	56.6 (20.1)	56.8 (20.0)	53.4 (21.6)	.02
ΔeGFR, mean (SD), mL/min	−0.4 (3.8)	−0.4 (3.7)	0.1 (4.4)	.66
ci score, mean (SD)	0.7 (0.7)	0.7 (0.7)	0.8 (0.7)	.002
ct score, mean (SD)	0.8 (0.6)	0.8 (0.6)	0.9 (0.7)	.008
cv score, mean (SD)	0.5 (0.7)	0.5 (0.7)	0.6 (0.7)	.13
cg score, mean (SD)	0 (0)	0 (0)	0 (0)	>0.99
v score > 0, no. (%)	45 (2.3)	30 (1.7)	15 (8.9)	<0.001[b]

[a]No imputations were done to address missing data, and patients were excluded from specific analyses if their data were missing. Only the count and percentage of "Yes" responses are reported.
[b]Fisher exact test.
cg, chronic glomerulopathy; ci, chronic interstitial fibrosis; ct, chronic tubular atrophy; cv, fibrous intimal thickening; ΔeGFR, change in estimated glomerular filtration rate; g, glomerulitis; ptc, peritubular capillaritis; v, intimal arteritis.

data, eGFR values were not different between the g = 0 and g > 0 groups at baseline ($P = 0.37$; at 4 mo), and the ΔeGFR values also were not different ($P = 0.18$). Among patients with HLA data, eGFR values at baseline (at 4 mo) were significantly lower in the g > 0 group than the g = 0 group when patients were negative for DSA (42.0 versus 55.3 mL/min; $P < 0.001$). However, during follow-up, we did not observe a difference in ΔeGFR ($P = 0.88$). In the DSA-positive group, eGFR values at baseline were not different (56.9 mL/min in g = 0 versus 52.2 mL/min in g > 0; $P = 0.26$), but at the end of follow-up, ΔeGFR was significantly higher in the g > 0 group ($P = 0.02$). However, we found no difference in median ΔeGFR values ($P > 0.99$) after adjusting for the differences in follow-up time between the 2 groups.

Kaplan–Meier analysis showed that the death-censored graft failure rate was significantly higher in the g > 0 group than the g = 0 group (hazard ratio, 1.68 [95% CI, 1.07-2.65]; $P = 0.02$) (Figure 1). We developed 2 models for multivariable analysis of death-censored graft failure, stratified by g score. Both models adjusted for age at transplantation, C4d status at 4 mo, DGF, and donor type. Additionally, in the first model, we adjusted for PRA of 20% or higher but not pretransplant DSA status, and in the second model, we adjusted for pretransplant DSA with MFI of 1000 or higher but not PRA. Both models showed similar outcomes (Table 5).

TABLE 3.

Outcomes of patients with glomerulitis (g Score > 0), stratified by DSA status[a]

Patients with cg score > 0	Total (n = 52)	DSA-positive, MFI ≥ 1000 (n = 20)	DSA-negative or MFI < 1000 (n = 32)	*P* value[b]
Year 1, no. (%)	5 (13.9)	2 (11.8)	3 (15.8)	>0.99
Year 2, no. (%)	8 (33.3)	5 (50.0)	3 (21.4)	0.20

[a]No imputations were done to address missing data, and patients were excluded from specific analyses if their data were missing. Only the count and percentage of "Yes" responses are reported.
[b]Fisher exact text.
cg, chronic glomerulopathy; DSA, donor-specific antibody; g, glomerulitis; MFI, mean fluorescence intensity.

TABLE 4.

Outcomes of patients with isolated glomerulitis (g Score > 0), stratified by ptc score[a]

Patients with cg score > 0	Total (n = 97)	ptc score = 0 (n = 31)	ptc score > 0 (n = 66)	*P* value[b]
Year 1, No. (%)	5 (7.9)	0 (0)	5 (12.2)	0.15
Year 2, No. (%)	9 (20.0)	1 (7.1)	8 (25.8)	0.23

[a]No imputations were done to address missing data, and patients were excluded from specific analyses if their data were missing. Only the count and percentage of "Yes" responses are reported.
[b]Fisher exact test.
cg, chronic glomerulopathy; g, glomerulitis; ptc, peritubular capillaritis.

Subsequent AMR Risks

Overall risk of developing subsequent AMR including MVI in patients with g > 0 was 21%. Twenty-six patients developed MVI with negative c4d in all and negative DSA in 19 patients (7 patients with DSA not available). Thirteen patients with MVI were either c4d positive or had positive DSA. A total of 73% developed graft loss from progressive chronic lesions, infections, etc., and 27% of graft loss had mix of ACR with AMR with or without c4d deposition. DSA data were not available in majority except for 1 patient.

DISCUSSION

The Banff criteria for AMR have been revised since 1997, and the latest classification approach removes DSA as a requisite for diagnosis. MVI in the absence of C4d and DSA is suggestive of AMR, but *early* glomerulitis with or without peritubular capillaritis has received limited attention and thus was the main focus of the current study. In this retrospective study, 186 patients developed glomerulitis on protocol biopsy done within 4 mo of transplantation and identified a cohort of patients who are at a higher risk for progression to chronic

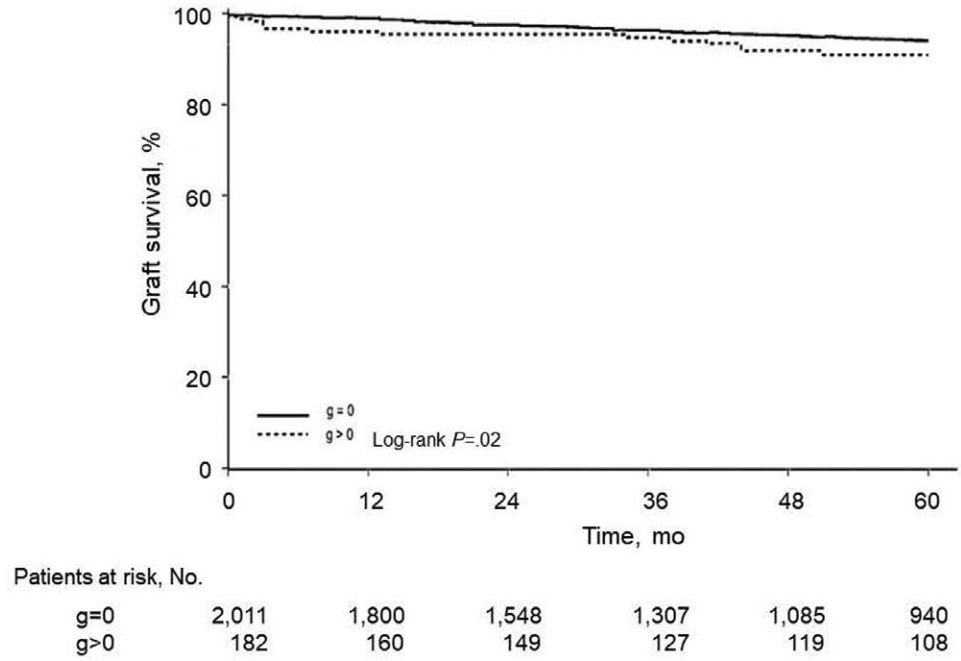

FIGURE 1. Death-censored graft failure. Patients were stratified by glomerulitis (g) score.

TABLE 5.

Multivariable Cox model for death-censored graft failure with PRA and pretransplant DSA

Variable	HR	CI	*P*
PRA			
g > 0	1.07	(0.54-2.1)	0.84
PRA > 20%	0.49	(0.27-0.92)	0.02
Delayed graft function	1	(0.6-1.64)	0.99
Donor type, deceased	2.16	(1.29-3.61)	0.003
c4d	1.8	(0.8-4.05)	0.15
Age at transplant, in decades	0.76	(0.65-0.88)	<0.001
Pretransplant DSA			
g > 0	0.88	(0.2-3.9)	0.86
Pretransplant DSA	1.68	(0.78-3.65)	0.18
Delayed graft function	1.31	(0.64-2.71)	0.45
Donor type, deceased	2.96	(0.95-9.18)	0.06
c4d	2.28	(0.29-17.99)	0.43
Age at transplant, in decades	0.84	(0.66-1.07)	0.14

95% CI, 95% confidence interval; DSA, donor-specific antibody; HR, hazard ratio; PRA, panel-reactive antibodies.

transplant glomerulopathy at 1 and 2 y when compared with patients who did not have glomerulitis, irrespective of DSA. There was no difference in other chronic lesions between the 2 groups. We also observed a significantly increased risk of death-censored graft failure for patients who had glomerulitis within 4 mo (compared with patients without glomerulitis). However, when adjusted for age, donor type, DGF, presence of C4d at 4 mon, calculated PRA, and pretransplant DSA, there was no difference in death-censored graft failure rates. Our strength is the large dataset of patients, which confirms that even early transplant glomerulitis can lead to inferior graft survival and adds to our knowledge in this patient population.

Data remain conflicted regarding role of glomerulitis. Previous studies have included outcomes on glomerulitis at later time points, small number of patients at earlier time points, lack of timely follow-up biopsies, or were based on clinically indicated biopsies.[13,14,20-26] Such an approach is unsuitable for following the natural course of glomerulitis. Our study is unique in assessing the role of early glomerulitis with adverse long-term outcomes with timely follow-up later on with surveillance biopsies, which is not been studied before. Our study addresses the aforementioned limitations in a large database as we perform protocol (surveillance) biopsies at various intervals, which more accurately characterize the incidence and outcomes of glomerulitis. Interestingly, although patients with early glomerulitis had progression to chronic glomerulopathy, we did not observe significant differences in progression when comparing DSA-positive versus DSA-negative patients as compared with the study from Gloor et al[27] Our finding is also different from the Belgian group,[25] who found that DSA-negative AMR had better prognosis as compared with DSA-positive AMR. This could be because of our study design focusing on glomerulitis within 4 mo of transplant as compared with theirs, in which index biopsy post transplant was used to diagnose AMR, different DSA cut off with preponderance of preformed DSA in Belgian study. However, we agree that our finding indicates that there could be some other mechanism of progression, such as a non-HLA antibody–mediated mechanism irrespective of DSA. Furthermore, in our study, the g > 0 group (from the entire cohort) had a significantly higher number of deceased-donor transplantations and higher 4 mo ci and ct scores, possibly indicating ischemia reperfusion injuries, although the CIT and DGF were not different between these 2 groups. It is important to note that we excluded patients with recurrent GN from this cohort.

Papadimitriou et al[13] evaluated 240 biopsies that were performed 12 mo or more after transplantation and reported that the g score was significantly associated with transplant glomerulopathy. However, allograft failure was not associated with severity of glomerulitis after adjusting for C4d status and ptc score. In our cohort, glomerulitis that was observed within a few mo after transplantation was associated with adverse outcomes. Similarly, Buob et al[20] evaluated 20 protocol biopsies with isolated transplant glomerulitis at 3 mo and predicted 3-y outcomes. In their study, isolated transplant glomerulitis was not associated with a decrease in eGFR or graft failure at 3 y. However, about half the patients with glomerulitis did not have a follow-up biopsy and thus, limits our ability to assess progressive changes.

Few studies have shown an increased association of glomerulitis with death-censored graft failure. Gonzales et al[21] used the Birmingham risk model with 1-y allograft data to predict 5-y outcomes. The death-censored graft failure rate was significantly associated with glomerulitis, chronic interstitial fibrosis, and HLA class II DSA in patients whose histology and DSA data were available at 1 y. However, only glomerulitis at 1 y was associated with an increased overall risk of graft failure. Nabokow et al[14] evaluated 24 patients with isolated glomerulitis, identified with biopsies performed for clinical indications, and assessed development of chronic glomerulopathy (cg score > 0) and graft survival. They reported that graft survival rates among patients with isolated glomerulitis, AMR, or glomerulitis plus T-cell–mediated rejection (TCMR) were low and similar, but they were worse than that of patients with TCMR alone or no rejection. Sis et al[28] evaluated MVI from patients who mostly underwent biopsy for clinical indications. They reported that glomerulitis (g score > 0) was associated with AMR and DSA formation. Our study had 21% incidence of subsequent AMR in g > 0 group. Majority were c4d negative and DSA negative. Majority of graft loss were non-rejection-related. There is no difference in chronic scores besides chronic transplant glomerulopathy. Although we acknowledge lack of DSA data pre 2011 because of evolving practice patterns, we still believe that this is large dataset with no difference in outcomes in glomerulitis based on DSA.

Transplant glomerulopathy is associated with chronic AMR and poor graft survival.[27,29-31] The current study emphasizes the concept that glomerulitis may be associated with progression to chronic transplant glomerulopathy. We further analyzed a cohort of patients with subclinical isolated glomerulitis as there remains an ambiguity regarding the significance of glomerulitis and long-term outcomes.[13,20,21] We did not find isolated glomerulitis was significantly associated with increased progression to chronic transplant glomerulopathy. The lack of progression could be because of small cohort in isolated glomerulitis group despite a large dataset. However, we looked at outcomes based on numeric g scores. We found significant difference in death-censored graft failure based on g scores. We think this is because of higher number of events in a small cohort of g3 patients resulting in difference early on (Figure S2, SDC, http://links.lww.com/TXD/A452). We do not have protocol for treating isolated glomerulitis

and practice has evolved over last 2 decades. This is clinician dependent and may include no treatment; augmentation of immunosuppression, if not optimized; or treat with high-dose steroids. Because treatment is quite variable, we were unable to analyze outcomes based on treatment. It will be interesting to see how many centers treat patients with isolated glomerulitis and report their outcomes. Further studies are also required to determine whether isolated glomerulitis is indicative of a missed AMR because limited evidence suggests that it may lead to clinically significant long-term changes.

Strengths and Limitations

The strength of this study is the longitudinal follow-up with protocol biopsies of patients with glomerulitis. This study was limited by its single-center analysis and retrospective nature. We acknowledge lack of HLA information in half the cohort due practice patterns before 2011 and changes in HLA methodology detection over this time period of time. We did not compare differences between patients with pretransplant DSA versus de novo DSA because of small sample size. However, the study is still novel because it addresses outcomes of patients, stratified by g score early post transplant, who underwent protocol biopsies, and had HLA information in 1115 patients, which makes one of the largest studies to date. Non-HLA antibodies were not assessed because such evaluations are not part of routine testing. We did not evaluate concurrent glomerulitis and TCMR, nor did we determine whether v scores were associated with progression in this cohort because of low patient numbers. Some outcomes in the glomerulitis group could be because of higher MVI scores.

CONCLUSION

Development of early glomerulitis may be a risk factor for chronic transplant glomerulopathy and inferior graft survival, irrespective of DSA status. These findings require further evaluation in prospective studies that include analysis of non-HLA antibodies.

Data requests should be directed to the corresponding author. Data will be made available upon reasonable request.

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