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Impact of Subclinical and Clinical Kidney Allograft Rejection Within 1 Year Posttransplantation Among Compatible Transplant With Steroid Withdrawal Protocol

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Background. Early acute kidney rejection remains an important clinical issue. **Methods.** The current study included 552 recipients who had 1–2 surveillance or indication biopsy within the 1 y posttransplant. We evaluated the impact of type of allograft inflammation on allograft outcome. They were divided into 5 groups: no inflammation (NI: 95), subclinical inflammation (SCI: 244), subclinical T cell–mediated rejection (TCMR) (SC-TCMR: 110), clinical TCMR (C-TCMR: 83), and antibody-mediated rejection (AMR: 20). Estimated glomerular filtration rate (eGFR) over time using linear mixed model, cumulative chronic allograft scores/interstitial fibrosis and tubular atrophy (IFTA) ≥2 at 12 mo, and survival estimates were compared between groups. **Results.** The common types of rejections were C-TCMR (15%), SC-TCMR (19.9%), and AMR (3.6%) of patients. Eighteen of 20 patients with AMR had mixed rejection with TCMR. Key findings were as follows: (i) posttransplant renal function: eGFR was lower for patients with C-TCMR and AMR ($P<0.0001$) compared with NI, SCI, and SC-TCMR groups. There was an increase in delta-creatinine from 3 to 12 mo and cumulative allograft chronicity scores at 12 mo ($P<0.001$) according to the type of allograft inflammation. (ii) Allograft histology: the odds of IFTA ≥2 was higher for SC-TCMR (3.7 [1.3-10.4]; $P=0.04$) but was not significant for C-TCMR (3.1 [1.0-9.4]; $P=0.26$), and AMR (2.5 [0.5-12.8]; $P=0.84$) compared with NI group, and (iii) graft loss: C-TCMR accounted for the largest number of graft losses and impending graft losses on long-term follow-up. Graft loss among patient with AMR was numerically higher but was not statistically significant. **Conclusions.** The type of kidney allograft inflammation predicted posttransplant eGFR, cumulative chronic allograft score/IFTA ≥2 at 12 mo, and graft loss.

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INTRODUCTION

Kidney transplantation remains the treatment of choice for patients with end-stage renal disease.[1] Acute rejection of kidney allografts negatively impacts graft survival.[2] Kidney allograft pathology findings can subcategorize into: no inflammation (NI), subclinical inflammation (SCI), clinical T cell–mediated rejection (C-TCMR), subclinical TCMR (SC-TCMR), and antibody-mediated rejection (AMR) or mixed rejection (MR). It is believed that AMR and MR are associated with the worst outcomes, whereas TCMR is reversible without impacting long-term outcome.[3–5]

Natural history and evolution of subclinical rejection (SCR) and SCI through surveillance biopsies and their

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significance have been described with different types of immunosuppressive agents.[6–8] A recent registry analysis has shown that acute rejection, including TCMR, can impact transplant outcome.[9] The GoCAR study identified 13 genes correlating with allograph chronicity at 1 y.[10] CTOT-08 study found that a combination of clinical phenotype and blood biomarkers correlated with a composite clinical outcome (renal function, biopsy-proven acute rejection [BPAR], interstitial fibrosis, and tubular atrophy) and development of de novo donor-specific antibody (DSA).[11]

Increasing awareness of allograft rejection prompted us to analyze the spectrum of allograft inflammation in kidney allograft biopsies within 1 y posttransplantation to various outcomes. We hypothesized that the prevalence of C-TCMR and SC-TCMR within 1 y posttransplant would be higher than AMR and MR; and the type of inflammation would have a differential impact on outcome. We evaluated the differences in allograft chronicity at 12 mo, long-term renal function, development of posttransplant DSA, rejection after 1 y, and long-term survival among patients with SCI, SC-TCMR, C-TCMR, and AMR/MR versus NI diagnosed by biopsy within 1 y posttransplantation.

MATERIALS AND METHODS

Study Population

This single-center prospective study of 802 adult kidney transplant recipients was performed between January 2013 and December 2016, followed until July 2020.

Inclusion and Exclusion Criteria

We included adult kidney transplant recipients of all sex, racial, and ethnic groups who underwent either deceased donor (DD) or living donor (LD) kidney only transplants. The study included recipients who had either (1) a surveillance biopsy at 3 and 12 mo posttransplant, or (2) a for-cause biopsy within 1 y posttransplant. The study included a total of 552 of 802 recipients and 250 were excluded because they did not undergo biopsy and inadequate sample (n = 135), had dual-organ kidney transplants (n = 51), allograft loss <1 y (n = 36), or had recurrent glomerulonephritis/BKV nephritis (n = 28) as shown in Figure 1.

Study Groups

Among the 552 recipients who had biopsies within 1 y, 394 had biopsies at both 3 and 12 mo posttransplant. Patients were divided into 5 groups per renal histology: NI found in all biopsies (n = 95), SCI in at least 1 biopsy (n = 244), SC-TCMR in at least 1 biopsy (n = 110), C-TCMR in at least 1 biopsy (n = 83), and AMR/MR (N = 20) in at least 1 biopsy. Patients with pure AMR (n = 2) and those with MR (n = 18) were classified as the AMR/MR group.

Kidney Transplantation

All recipients underwent ABO compatible transplantation without desensitization and with a negative T/B flow crossmatch. Thymoglobulin induction (total dose 6 mg/kg) with rapid steroid withdrawal over 7 d and mycophenolate mofetil (MMF) and tacrolimus (TAC) maintenance therapy were used in the majority of patients. Trough serum TAC level was targeted to 8–12 ng/mL for the first 6 mo and 6–10 ng/mL thereafter. Mycophenolic acid levels were not performed. Maintenance prednisone of 5 mg daily was used for patients with calculated panel reactive antibody (cPRA) >90%.

Immunosuppression

The mean and median doses of MMF and mycophenolate acid (MPA) at 3 and 12 mo and trough TAC levels using mixed models were compared across groups.

Renal Biopsy and Histological Classification

Surveillance allograft biopsies were obtained at 3 and 12 mo posttransplant and for-cause biopsies when indicated. Patients were classified into groups based on interstitial (i), tubular (t), vascular (v), glomerular (g) scores: NI (i0, t0, v0) or (i1, t0, v0); SCI (i > 0 with t > 0, v0) through surveillance biopsy and did not meet the criteria for Banff IA; SC-TCMR (i2, t ≥ 2, v ≥ 0) or (i. ≥ 0, t ≥ 0, v > 0) through surveillance biopsy; C-TCMR (i2, t ≥ 2, v ≥ 0) or (i.>0, t ≥ 0, v > 0) through for-cause biopsy, and AMR (i ≥ 0, t ≥ 0, v ≥ 0, g ≥ 0) with PTC^+, $C4d^+$, or $C4d^-$ and with circulating DSA.

Renal Allograft Histological Scores

The histological diagnosis of acute rejection was based on the 2017 Banff classification.[12] The SCI group included surveillance biopsies patients who have combination of interstitial inflammation and tubulitis that did not meet the criteria for Banff IA rejection or AMR. C-TCMR was defined per histological criteria among those who had renal dysfunction. The cumulative allograft histological scores including acute (i, t, g, v), chronic (ci + ct + cg + cv), and interstitial fibrosis and tubular atrophy (IFTA) (ct + ci) scores were recorded for all study recipients, and the mean cumulative acute and chronic scores, as well as the prevalence of IFTA ≥2 were compared at both 3 and 12 mo posttransplant. Biopsy adequacies were assessed per Banff criteria before including them for the study.

Allograft Biopsy Beyond 1 Year Posttransplantation

For-cause allograft biopsies were performed beyond 1 y posttransplant for renal dysfunction.

DSA Testing

HLA antibodies were detected by single antigen bead assay (One Lambda LAB Screen) and have been discussed before.[13] Mean fluorescence intensity value of >1000 was considered significant. We screened for DSA at 1, 3, 6, 12, 18, 24, 36, 48, and 60 mo posttransplant.

Treatment of SC and C-TCMR

Recipients with C-TCMR and SC-TCMR (Banff grade—1A and 1B) were treated with intravenous solumedrol (250 mg × 3) and the addition of maintenance prednisone 5 mg/d. Banff grade ≥2A rejections were treated with thymoglobulin 1.5 mg/kg/d (total of 6 mg/kg). Patients with AMR/MR were treated with steroids as well as PLEX/IVIG. The doses of MPA and Tac were optimized upon detection of acute rejection to achieve therapeutic TAC levels.

Renal Allograft Function

Renal function was defined as the mean eGFR (mL/min) calculated using the Chronic Kidney Disease Epidemiology Collaboration formula at 3, 6, 12, 18, 24, 36, 48, and 60 mo posttransplant and at last follow-up. Recipients who had

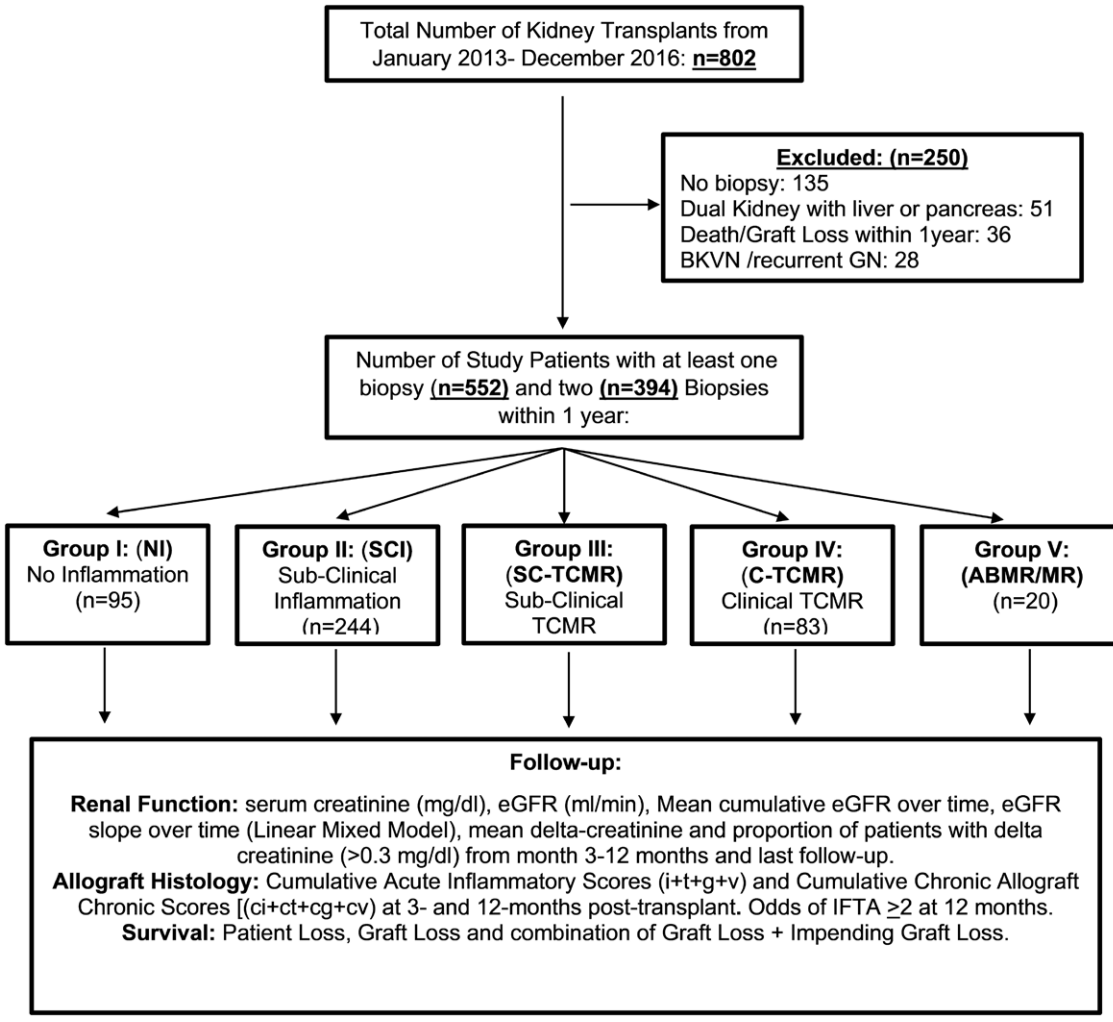

FIGURE 1. Flowchart of kidney transplant recipients at the study center including the number of recipients eliminated, study patients with at least 1 biopsy with 5 groups (NI, SCI, SC-TCMR, C-TCMR, and AMR/MR) within 1 y posttransplant and follow-up of patients with various outcome measures (renal function, renal progression, allograft chronicity, and survival) used for the study. ABMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; eGFR, estimated glomerular filtration rate; g, glomerular; i, interstitial; IFTA, interstitial fibrosis and tubular atrophy; MR, mixed rejection; NI, no inflammation; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection; t, tubular; TCMR, T cell–mediated rejection; v, vascular.

isolated graft loss were assigned a serum creatinine value of 8.0 mg/dL from the date of graft loss.[14] Impending graft loss was defined as those with persistent GFR <20 mL/min.[14] Renal function was assessed by the proportion of patients with decline in renal function with a delta-creatinine >0.3 mg/dL from 3 to 12 mo and last follow-up.

Data Collection and Study Variables

Using electronic medical records, data were collected on donor-recipient demographics and transplant variables (donor source: living versus deceased, donor-recipient cytomegalovirus [CMV]/Epstein-Barr virus [EBV] serostatus, pretransplant levels of class I/II PRA, cPRA, PRA/cPRA >20%, mean Kidney Donor Profile Index [KDPI] [%] scores, and warm ischemia time [WIT]/cold ischemia time [CIT] in min).

Outcome Measures

Outcome measures were evaluated for 5 groups for (1) renal function, (2) chronic allograft histology, and (3) patient and graft loss.

1. Renal function: changes in renal function were evaluated using (a) proportion of patients with delta-creatinine >0.3 mg/dL from 3 to 12 mo and last follow-up and (b) eGFR values overtime using linear mixed model.
2. Chronic allograft changes: changes in cumulative chronic allograft histology scores were evaluated (a) from 3 to 12 mo and (b) proportion of patients with IFTA ≥2 at 12 mo.
3. Patient and graft loss: Kaplan-Meier survival estimates were evaluated for patient loss, death-censored graft loss, and composite of graft loss and impending graft loss (persistent eGFR <20 mL/min).

Statistical Methods

Data are presented as mean ± SD for normally distributed data and median (interquartile range) for nonparametric data. Demographics and transplant characteristics across the groups were tested using ANOVA and chi-square test. Savage multisample tests were used for nonparametric data when appropriate. The McNemar test was used to examine changes in the biopsies from 3 to 12 mo within each group. The

differences in eGFR over time between groups were examined using linear mixed models after adjusting for donor type, delayed graft function (DGF), recipient age, recipient race (Black versus other), and pretransplant dialysis duration. We tested for differences in the slope of eGFR over time by group using an interaction term. All statistical significance tests were 2-tailed tests, Bonferroni adjusted *P* values are reported, and alpha <0.05 was considered significant.

Attributable risk percent for graft loss was calculated for AMR/MR, C-TCMR, and TCMR groups. Kaplan-Meier survival estimates were compared between the 5 groups. Odds ratio (OR) for the occurrence of IFTA ≥2 at 12 mo was estimated using NI as the baseline group. Cox proportional hazard modeling was performed to assess the risk of graft loss and impending graft loss using NI as the reference. We used SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.6.0 for analyses.

Ethical Guidelines and Privacy Protection

Data were obtained through the transplant center registry regulated by the University of Pittsburgh's institutional review board (IRB number PRO-13060220).

RESULTS

Study Populations

A total of 552 study recipients (Figure 1) were divided based on pathological findings: NI (n = 95), SCI (n = 244), SC-TCMR (n = 110), C-TCMR (n = 83), and AMR/MR (N = 20). Among patients with AMR/MR, 18 of 20 (90%) had combination of TCMR + AMR and 2 had isolated AMR. The overall incidence of NI was 17.2% and the corresponding values for SCI, SC-TCMR, C-TCMR, and AMR/MR were 44.2%, 19.9%, 15%, and 3.6%, respectively (Figure 2). The overall combined incidence of C-TCMR and SC-TCMR (34.9%) was higher than the incidence of AMR/MR (3.6%). SCI was the most prevalent histological finding (44.2%).

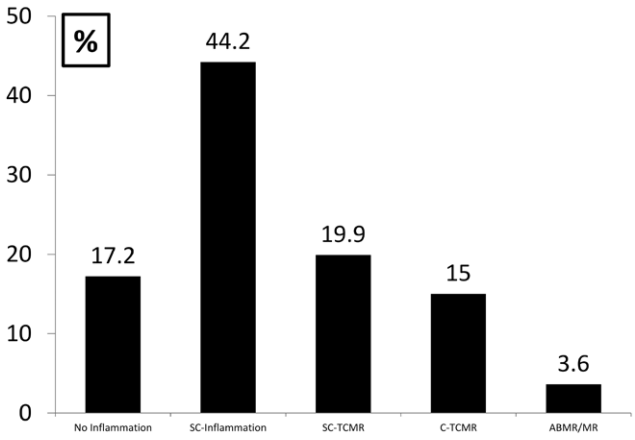

FIGURE 2. The overall incidences of NI, SCI, SC-TCMR, C-TCMR, and AMR/MR within 1 y posttransplantation among 552 transplant recipients are shown as % on "y" axis. SCI was the most common diagnosis observed in 44.2% of recipients and AMR/MR was the least common observed in 3.6% of recipients. The incidence of TCMR including both clinical and subclinical was 34.9%. ABMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; MR, mixed rejection; NI, no inflammation; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection.

Demographics

The differences in demographics, transplant, and posttransplant variables for all the groups are shown in Table 1. The baseline demographics were similar except that the SC-TCMR and AMR/MR groups contained more younger recipients ($P < 0.05$). Pretransplant dialysis duration was longer among recipients with C-TCMR ($P < 0.05$) and the proportion of recipients with class II PRA >20% was higher in the AMR/MR group ($P < 0.05$) (Table 1).

Follow-up

Recipients were followed for a mean of 57.0 (±15.6) mo posttransplant. Follow-up time for recipients with NI, SCI, SC-TCMR, C-TCMR, and ABMR/MR were 58.3 ± 15.4, 55.5 ± 16.0, 55.9 ± 14.8, 54.5 ± 15.9, and 58.1 ± 15.5 mo, respectively ($P = 0.50$).

Allograft Biopsy

A total of 552 recipients underwent 946 biopsies within 1 y posttransplant.

Renal Function

The proportion of recipients with delta-creatinine increase of >0.3 mg/dL from 3 to 12 mo for NI was 4.2%, and the proportion increased to 14.3%, 20.9%, 31.3%, and 30% for SCI, SC-TCMR, C-TCMR, and AMR/MR, respectively ($P < 0.001$) (Table 2). Changes in delta-creatinine from 3 mo to last follow-up was also significant ($P < 0.0001$) and is shown in Table 2. Thus, there was an increase in proportion of patients with delta-creatinine >0.3 mg/dL from 3 to 12 mo according to the type of allograft inflammation.

eGFR Over Time

Figure 3 shows the differences in the mean and trajectory of eGFR posttransplant. Significant differences between the mean eGFR was noted between the groups over time ($P < 0.0001$). The mean eGFR over time was lower for the C-TCMR and AMR/MR groups compared with NI group (−19.1 mL/min [95% confidence interval (CI), −25.9 to −12.3] and −11.1 mL/min [95% CI, −21.8 to −0.4], respectively; $P < 0.05$). There were no significant differences in mean eGFR between SCI and SC-TCMR compared with the NI group (mean difference −0.9 mL/min [95% CI, −6.5 to 4.6] and −4.5 mL/min [95% CI, −10.9 to 1.9], respectively). Compared with the NI group, only AMR and C-TCMR had significantly different negative slopes (−0.3 [95% CI, −0.4 to −0.1] and −0.15 [95% CI, −0.2 to −0.05], respectively; $P < 0.05$). Thus, C-TCMR and AMR/MR were associated with lower eGFR and decline in eGFR over time using a linear mixed model.

Histology Scores

The mean acute cumulative inflammatory scores at 3 mo posttransplant for NI, SCI, SC-TCMR, C-TCMR, and AMR/MR were 0.01 ± 0.06, 1.16 ± 0.95, 2.75 ± 1.85, 3.57 ± 2.07, and 3.29 ± 2.09, respectively ($P < 0.0001$). The mean cumulative chronic allograft scores at 3 mo posttransplant for NI, SCI, SC-TCMR, C-TCMR, and AMR/MR group of recipients were 0.55 ± 0.73, 1.01 ± 0.86, 1.38 ± 1.01, 1.79 ± 1.11, and 1.34 ± 1.11, respectively ($P < 0.0001$). The mean chronic scores increased at 12 mo posttransplant to 0.94 ± 0.82, 1.54 ± 0.94, 2.27 ± 1.00, 2.57 ± 1.06, and 2.33 ± 1.09, respectively ($P < 0.0001$). Among those with 2 biopsies, we

TABLE 1.

Differences in donor and recipient demographics, various pretransplant and posttransplant variables (n = 552) according to type of allograft inflammation within 1 y posttransplant

	All (n = 552)	No inflammation (n = 95)	Subclinical inflammation (n = 244)	SC-TCMR (n = 110)	C-TCMR (n = 83)	AMR/MR (n = 20)	*P* trend
Recipient variables							
Age (y), mean ± SD	51.4 ± 4.9	54.9 ± 14.3	52.5 ± 13.8	**48.6 ± 16.4**	50.1 ± 15.7	**43.50 ± 14.2**	**0.002**
Male, n (%)	330 (59)	64 (67.4)	146 (59.8)	66 (60)	43 (51.8)	11 (55)	0.32
Race, n (%)							0.74
White	415 (75.2)	74 (77.9)	187 (76.6)	81 (73.6)	60 (72.3)	13 (65)	
African American	119 (21.6)	19 (20)	47 (19.3)	25 (22.7)	22 (26.5)	6 (30)	
Other	18 (3.3)	2 (2.1)	10 (4.1)	4 (3.6)	1 (1.2)	1 (5)	
ESRD cause, n (%)							
HTN	111 (20.1)	18 (19)	48 (19.7)	23 (20.9)	18 (21.7)	4 (20)	**0.11**
Diabetes	92 (16.7)	22 (23.2)	42 (17.2)	15 (13.6)	12 (14.5)	3 (15)	0.24
Cystic kidney	68 (12.3)	9 (9.5)	34 (13.9)	11 (10)	10 (12.1)	2 (10.)	0.29
GN	27 (4.9)	3 (3.2)	11 (4.5)	7 (6.4)	5 (6)	1 (5)	0.68
Other	254 (46)	43 (45.3)	109 (44.7)	54 (49.1)	38 (45.8)	10 (50)	0.42
BSA, mean ± SD	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.3	0.77
BMI, mean ± SD	28.4 ± 5.7	28.7 ± 5.5	28.5 ± 5.5	28.1 ± 6.2	27.8 ± 5.6	28.7 ± 5.5	0.78
Dialysis duration (d), mean ± SD	1130 ± 1215	917 ± 956	1162 ± 1309	908 ± 894	**1486 ± 1398**	1500 ± 1459	**0.003**
Dialysis duration (d), median (IQR)	786 (116–1803)	643 (5–1532)	780 (96–1777)	584 (117–1630)	1066 (199–2487)	1077 (401–2592)	**0.002**
Donor variables							
Age (y), mean ± SD	41.8 ± 12.8	40.59 ± 13.1	41.3 ± 12.3	43.2 ± 13.1	43.6 ± 13.0	37.5 ± 13.2	0.16
Male, n (%)	293 (53.1)	46 (48.4)	132 (54.1)	61 (55.5)	46 (55.4)	8 (40)	0.60
Race, n (%)							0.50
White	502 (91)	87 (91.6)	222 (91)	103 (93.6)	73 (88)	17 (85)	
African American	34 (6.2)	4 (4.2)	14 (5.7)	5 (4.6)	8 (9.6)	3 (15)	
Other	16 (2.9)	4 (4.2)	8 (3.3)	2 (1.8)	2 (2.4)	0 (0)	
Deceased, n (%)	327 (59.2)	47 (49.5)	146 (59.9)	67 (60.9)	55 (66.3)	12 (60)	0.23
KDPI, mean ± SD	45.5 ± 24.6	41.6 ± 26.3	42.9 ± 23.6	47.5 ± 25.3	53.7 ± 23.8	45.7 ± 24	**0.05**
Transplant variables							
Thymoglobulin induction, n (%)	529 (95.9)	92 (96.8)	237 (97.1)	101 (91.8)	80 (96.4)	19 (95)	0.21
CMV risk, n (%)							0.45
Low	141 (25.5)	28 (29.5)	68 (27.9)	21 (19.1)	19 (22.9)	5 (25)	
Med	296 (53.6)	48 (50.5)	129 (52.9)	61 (55.5)	47 (56.6)	11 (55)	
High	102 (18.5)	18 (19.0)	43 (17.6)	25 (22.7)	12 (14.5)	4 (20)	
EBV risk, n (%)							**0.002**
Low	2 (0.4)	0 (0.00)	0 (0.00%)	1 (0.91%)	0 (0.00%)	1 (5.00%)	
Med	514 (93.1)	92 (96.8)	232 (95.1)	93 (84.6)	79 (95.2)	18 (90)	
High	28 (5.1)	3 (3.2)	8 (3.3)	13 (11.8)	3 (3.6)	1 (5)	
WIT (min), mean ± SD	37.8 ±10.9	38.5 ±14.8	37.5 ± 9.8	38.0 ± 9.8	37.4 ± 10.4	38.7 ± 10.4	0.94
CIT (DD), mean ± SD	703.4 ± 318.1	720.6 ± 289.7	695.4 ±340	679.0 ± 285.4	679.0 ± 285.4	662.8 ± 325.7	0.75
PRA I ≥20, n (%)	96 (17.4)	15 (15.8)	39 (16.0)	18 (16.4)	18 (21.7)	6 (30)	0.42
PRA II ≥20, n (%)	105 (19.0)	17 (17.9)	49 (20.1)	16 (14.6)	14 (16.9)	**9 (45)**	**0.03**
cPRA ≥20, n (%)	252 (45.7)	42 (44.2)	110 (45.1)	45 (40.9)	42 (50.6)	13 (65)	0.19
DGF, n (%)	80 (14.5)	14 (14.8)	29 (11.9)	13 (11.8)	20 (24.1)	4 (20)	0.07

For CMV risk: low risk = (D^-R^-), medium risk = (D^+R^+, D^-R^+), high risk = D^+R^-. For EBV: high risk = D^+R. Each percent calculation includes % missing.

Recipients with NI, SCI, SC-TCMR, C-TCMR, and MR were followed for 58.3±15.4, 55.5±16.0, 55.9±14.8, 54.5±15.9, and 58.1±15.5 mo, respectively ($P = 0.50$). Statistically significant values are bolded.

The group without inflammation (NI) was considered the reference group.

AMR, antibody-mediated rejection; BMI, body mass index; BSA, body surface area; CIT, cold ischemia time; CMV, cytomegalovirus; cPRA, calculated panel reactive antibody; C-TCMR, clinical T cell–mediated rejection; DD, deceased donor; DGF, delayed graft function; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GL, graft loss; GN, glomerulonephritis; HTN, hypertension; IQR, interquartile range; KDPI, Kidney Donor Profile Index; MR, mixed rejection; NI, no inflammation; PL, patient loss; PRA, panel reactive antibody; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection; WIT, warm ischemia time.

examined the changes in acute and chronic scores within each group. The proportion of each group with cumulative acute and chronic inflammatory scores at 3 and 12 mo are shown in Figure 4A and B. We found an increase in chronic cumulative allograft histology scores at 12 mo across the groups ($P = 0.004$). We also observed a significant elevation in the chronic scores from 3 to 12 mo within the SCI, SC-TCMR, and TCMR groups ($P < 0.05$), but not in the NI and AMR/MR groups (Figure 4B). Relatively, more recipients with C-TCMR had elevated chronic scores at 12 mo followed by SC-TCMR, AMR/MR, SCI, and NI groups.

Odds of IFTA ≥2 at 12 mo after correcting for variables (age, race, and dialysis duration) for recipients with SCI, SC-TCMR, C-TCMR, and AMR/MR groups as compared to

TABLE 2.

Illustrates the kidney transplant outcome with *P* for the unpaired analysis for all 5 groups (n = 552)

Groups	All (n = 552)	No inflammation (n = 95)	Subclinical inflammation (n = 244)	SC-TCMR (n = 110)	C-TCMR (n = 83)	AMR/MR (n = 20)	*P* trend
Kidney function							
Delta creatinine >0.3 from 3 to 12 mo, n (%)	094 (17)	004 (4.2)	**35 (14.3)**	**23 (20.9)**	**26 (31.3)**	**6 (30.0)**	**<0.001**
Delta creatinine >0.3 from 3 last follow-up months, n (%)	174 (31.5)	28 (29.5)	60 (24.6)	31 (28.2)	**43 (51.8)**	**12(60.0)**	**<0.001**
Delta eGFR >10 mL/min from 3 to 12 mo, n (%)	126 (22.8)	16 (16.8)	49 (20.1)	27 (24.5)	**27 (32.5)**	**7 (35.0)**	**0.05**
Delta eGFR >10 mL/min from 3 last follow-up, n (%)	199 (36.1)	35 (36.8)	74 (30.3)	37 (33.6)	**41 (49.4)**	**12 (60.0)**	**0.004**
GL/PL							
GL, n (%)	88 (15.9)	14 (14.7)	32 (13.1)	13(11.8)	**24 (28.9)**	**5 (25.0)**	**0.006**
Death-censored GL, n (%)	44 (8.0)	7 (7.4)	11 (4.5)	7 (6.4)	16 (19.3)	3 (15.0)	**<0.001**
Impending GL (GFR <20 last follow-up), n (%)	29 (5.3)	5 (5.3)	8 (3.3)	2 (1.8)	**12 (14.5)**	**2 (10.0)**	**0.001**
GL and impending GL, n (%)	093 (16.8)	17 (17.9)	26 (10.7)	12 (10.9)	**032 (38.6)**	006 (30.0)	**<0.001**
PL, n (%)	051 (09.2)	9 (9.5)	23 (9.4)	8 (7.3)	9 (10.8)	002 (10.0)	0.94
Death with a functioning kidney, n (%)	044 (86.3)	007 (77.8)	021 (91.3)	006 (75.0)	008 (88.9)	002 (100.0)	0.65
GL, impending GL and PL, n (%)	111 (20.1)	019 (20.0)	036 (14.8)	015 (13.6)	**034 (41.0)**	007 (035.0)	**<0.001**

The outcome measures shown are: (i) changes in mean delta-serum creatinine, (ii) changes in mean eGFR, (iii) proportion of recipients with serum creatinine (>0.3 mg/dL), and decline in eGFR (>10 mL/min) from mo 3 to 12 and last follow-up, and (iv) the overall incidence of PL, GL, impending GL (eGFR <20 mL/min), combination of GL, and impending GL as well as composite of PL, graft loss, and impending GL.

Recipients with NI, SCI, SC-TCMR, C-TCMR, and MR were followed for 58.3±15.4, 55.5±16.0, 55.9±14.8, 54.5±15.9, and 58.1±15.5 mo, respectively ($P = 0.50$). Statistically significant values are bolded.

The group without inflammation (NI) was considered the reference group.

AMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; eGFR, estimated glomerular filtration rate; GL, graft loss; MR, mixed rejection; NI, no inflammation; PL, patient loss; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection.

NI at baseline were 1.9 (95% CI, 0.7-5.2; $P = 0.5$), 3.7 (95% CI, 1.3-10.4; $P = 0.04$), 3.1 (95% CI, 1.0-9.4; $P = 0.3$), and 2.5 (95% CI, 0.5-12.8; $P = 0.8$), respectively. SC-TCMR had a statistically higher risk of IFTA ≥2 at 12 mo posttransplant compared with NI, whereas SCI, C-TCMR, and AMR/MR also showed higher OR, without statistical significance.

Graft Loss, Impending Graft Loss, and Patient Death

There were 64 of 552 (11.6%) graft losses, 44 of 552 (7.9%) isolated graft losses (death-censored graft loss), and 29 of 502 (5.3%) impeding graft losses. Thus, 93 patients had either graft loss or impending graft loss. There was a significant difference in the proportion of isolated graft loss across the groups ($P < 0.001$) with higher losses among C-TCMR (19.3%) and AMR/MR (15.0%) groups as opposed to NI, SCI, and SC-TCMR groups (Table 2). The incidence of impending graft loss (persistent low GFR <20 mL/min) was also higher in the AMR/MR and C-TCMR group, and lowest in the SC-TCMR group ($P = 0.001$). The risk of composite of graft loss and impending graft loss was highest among the C-TCMR (38.6%) followed by the AMR/MR (30.0%), NI (17.9%), SC-TCMR (10.9%), and SCI (10.7%) ($P < 0.001$). Patient loss and death with a functioning kidney were not different between groups.

Population Attributable Risk

The contributions of C-TCMR and AMR/MR to the overall burden of death-censored graft loss were examined by calculating population attributable risk. We found that C-TCMR and SC-TCMR attributed to 25.1% (95% CI, 7.4%-39.4%) of the risk of all graft losses, whereas only 3.3% (95% CI, –4.2% to 10.3%) of graft losses could be attributed to AMR/MR.

Kaplan-Meier Survival Estimates

Kaplan-Meier survival estimates for patient loss were not statistically different between groups (Figure 5A) ($P > 0.05$). However, death-censored graft loss and composite of graft loss and impending graft loss for the C-TCMR group were significantly higher than the NI group ($P = 0.02$, 0.006, respectively) (Figure 5B and C).

Cox Proportional Hazard Model

Figure 6 shows the adjusted hazard model estimates for the groups in comparison with the NI group. We found that C-TCMR had 3.2 times (95% CI, 1.12-9.1; $P = 0.03$) the risk of graft loss and 2.4 times (95% CI, 1.26-4.6; $P = 0.008$) the risk for combination of graft loss and impending graft loss (Figure 6A and B). None of the other groups reached statistical significance ($P > 0.05$).

Immunosuppression

The mean MMF and MPA doses at 3 and 12 mo differed significantly across the groups, with C-TCMR having the lowest value and AMR having the highest value ($P = 0.003$) (Table 3). In a mixed model, we found that the mean trough TAC levels within 1 y were not statistically different between the groups ($P = 0.15$) (Figure 7).

Posttransplant DSA

Posttransplant DSA was detected in 111 of 552 (20.1%) cases and 33 of 111 (26.4%) had transient DSA (Table 4). The incidence rates of class I and II DSA were 10.6% and 13.9%, respectively. The proportion of recipients with DSA increased across the groups from NI to ABMR (ANOVA, $P < 0.001$) suggesting a strong correlation between DSA formation and the type of allograft inflammation.

Allograft Histology Findings for All For-cause Biopsies Beyond 1 Year Posttransplantation

There were 197 of 552 (35.6%) patients who underwent 278 for-cause biopsies beyond 1 y posttransplantation. The details including the timing and distribution of all allograft

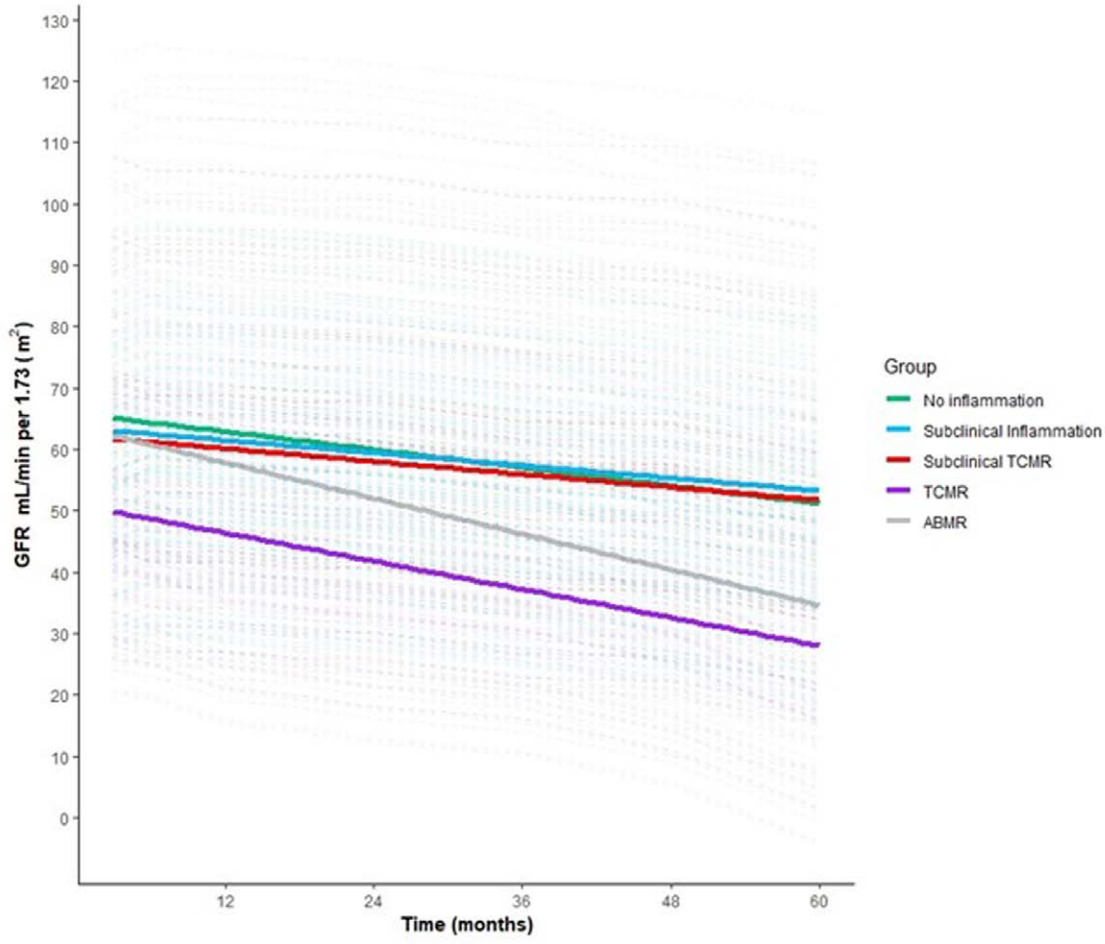

FIGURE 3. Linear mixed model showing the correlation between the histological group and the trajectory of eGFR posttransplant from 3 mo posttransplant. Significant differences between the adjusted mean cumulative eGFR of the groups were noted over time ($P<0.0001$). The mean eGFR over time was lower for the C-TCMR and AMR/MR groups compared with the NI group, −19.1 mL/min (95% CI, −25.9 to −12.3) and −11.1 mL/min (95% CI, −21.8 to −0.4), respectively (all $P<0.05$). There were no significant differences detected between the mean eGFR for SCI or SC-TCMR compared with the NI group (mean difference −0.9 mL/min [95% CI, −6.5 to 4.6] and −4.5 mL/min [95% CI, −10.9 to 1.9], respectively). The overall adjusted slope of eGFR was significantly different between 5 groups ($P<0.0001$). Compared with the NI group, only AMR/MR and C-TCMR had significantly different slopes (−0.3 [95% CI, −0.4 to −0.1] and −0.15 [95% CI, −0.2 to −0.05], respectively; all $P<0.05$). ABMR, antibody-mediated rejection; CI, confidence interval; C-TCMR, clinical T cell–mediated rejection; eGFR, estimated glomerular filtration rate; MR, mixed rejection; NI, no inflammation; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection; TCMR, T cell–mediated rejection.

biopsies for all 5 groups are shown in Table 5. There were more biopsies performed beyond 1 y among patients who had SC-TCMR, C-TCMR, and AMR compared with SCI and NI groups ($P=0.014$). The incidence of AMR/MR beyond 1 y posttransplant was 13.3% and was not statistically different between groups ($P>0.05$). Thus, patients who had alloimmune injury within 1 y continue to have subsequent immune injury to the kidney.

Sensitivity Analysis

In the subset of patients who had 2 biopsies (n = 394), the donor and recipient demographics, transplant variables, and Kaplan-Meier survival estimates for patient loss, death-censored graft loss, composite of graft loss, and impending graft loss across 5 groups were similar (data not shown).

DISCUSSION

Kidney transplantation remains the treatment of choice for patients with end-stage renal failure.[1,15] Rates of early clinical rejection post–kidney transplantation were as high as 50% in the mid-1980s when given azathioprine and cyclosporine A therapy, which decreased to 15% in late 1990s with the introduction of MMF and TAC as combination therapy.[16–20] Despite the marked reduction in the incidence of clinical acute rejection, there has been minimal improvement in long-term survival over the last 2 decades.[21–23] BPAR and renal function within 1 y are accepted surrogate markers of long-term kidney transplant outcome,[24,25] and it is known that posttransplant acute rejection influences long-term survival.[2,15,26] A UNOS survey revealed that only 38% of US transplant centers practice surveillance kidney biopsies in the management of patients.[27] Surveillance biopsies can detect SCR, which may be a precursor of clinical rejection or by itself can cause progressive allograft scarring.[28] Even lesser degrees of inflammation have the potential for altering the course of posttransplant events, namely subsequent rejection, scarring, and development of DSA.[29,30] This current study explored the incidence and the type of allograft inflammation through surveillance and for-cause biopsies within 1 y posttransplant and

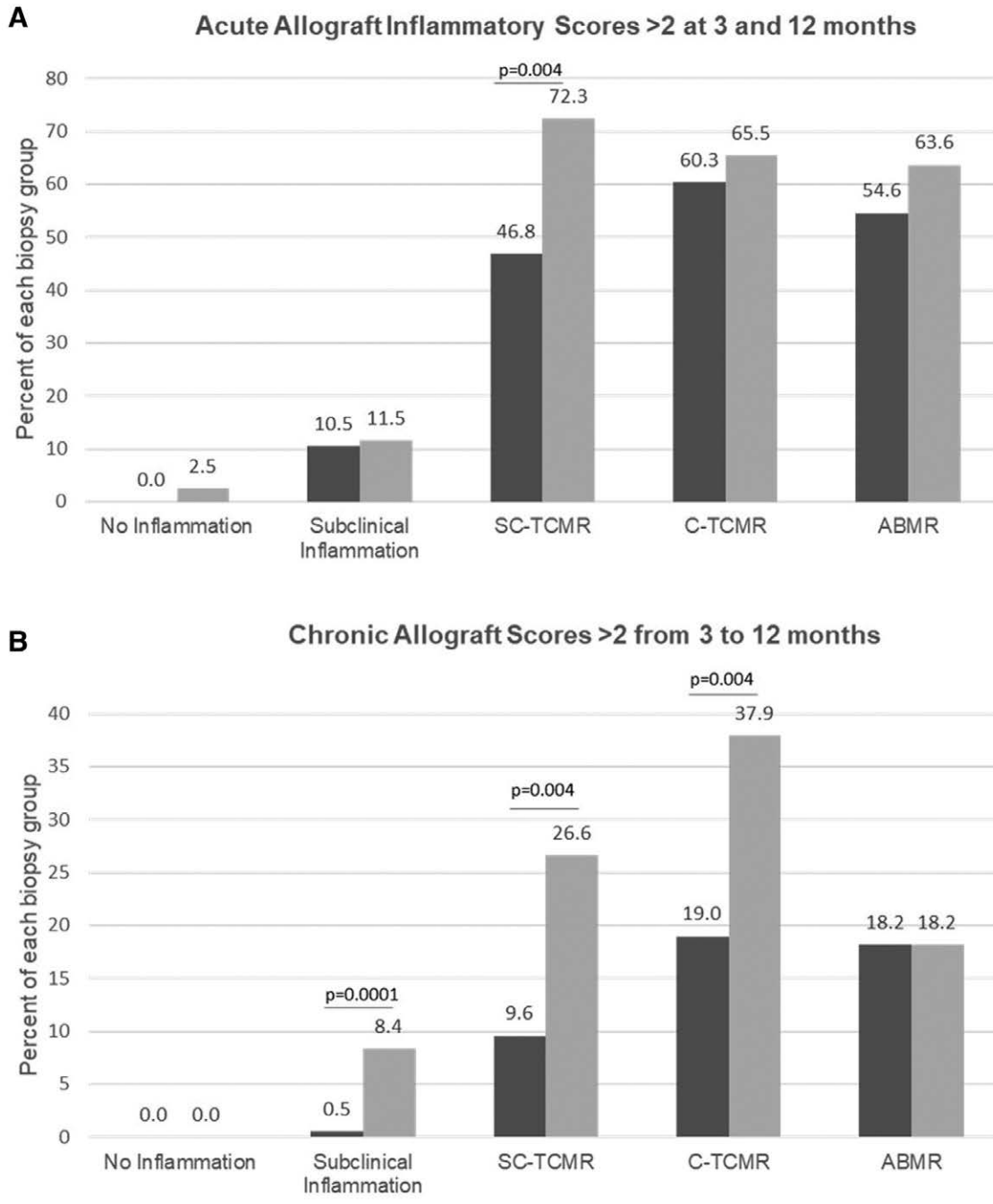

FIGURE 4. Representation of the proportion recipients who had 2 biopsies within the first y at 3 and 12 mo posttransplant with a cumulative acute allograft scores (t + i + v + g) >2 at 3 (black) and 12 (shaded) mo posttransplant (A) and cumulative chronic allograft score (ct + ci + cg + cv) ≥2 at 3 (black) and 12 (shaded) mo posttransplant (B) are shown. ABMR, antibody-mediated rejection; CI, confidence interval; C-TCMR, clinical T cell–mediated rejection; g, glomerular; i, interstitial; MR, mixed rejection; NI, no inflammation; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection; t, tubular; v, vascular.

its impact on outcome. The study evaluated posttransplant renal function, cumulative chronic allograft histology scores and IFTA ≥2 at 1 y, posttransplant DSA, late rejection, and long-term outcome.

Our study provides a comprehensive analysis using granular details of temporal changes in renal function and histological scores in a cohort of patients who underwent at least 1 biopsy within 1 y posttransplant. The overall demographic characteristics between the 5 groups were similar. Our study uncovered several important findings. First, an absence of any inflammation was seen in only 17% of patients, whereas the remaining 83% demonstrated different types of allograft inflammation that ranged from SCI, SC-TCMR to C-TCMR and AMR/MR. Second, we found a low incidence of pure AMR and nearly all AMRs (18 of 20, 90%) were MR and higher incidence of TCMR (clinical and subclinical combined). Third, kidney outcomes were inferior with C-TCMR, and the higher prevalence of TCMR in combination with poor outcomes resulted in a

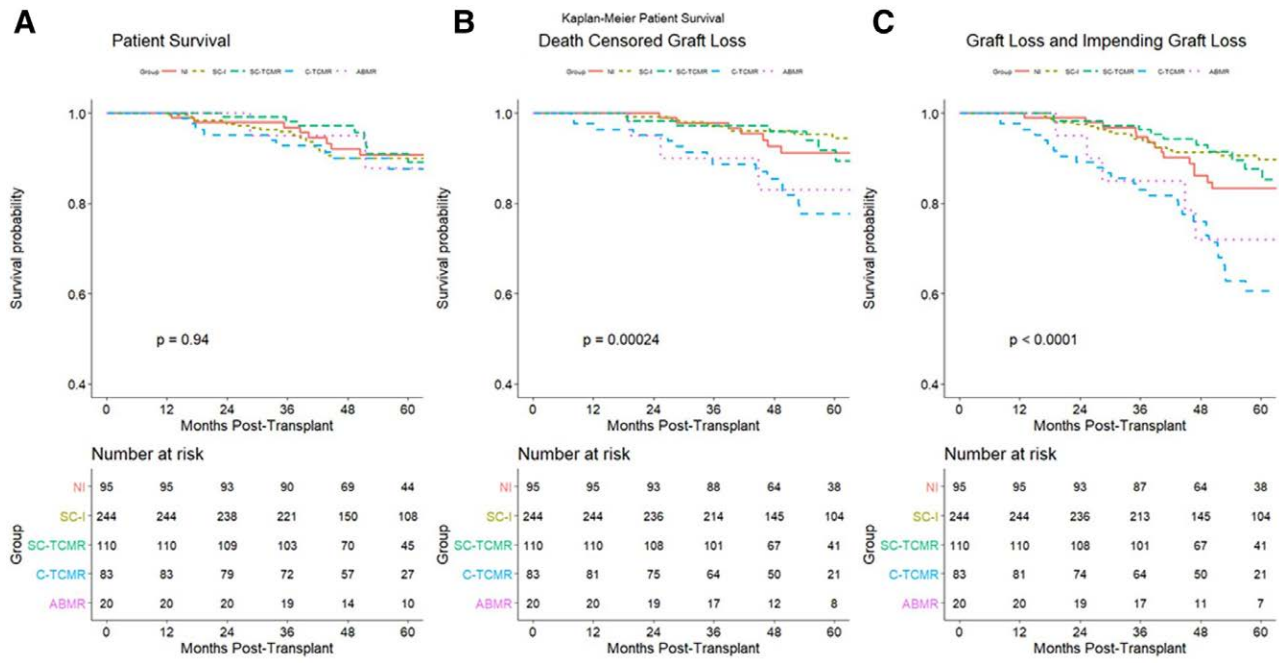

FIGURE 5. Kaplan-Meier survival estimates for 5 different study groups: no significant differences were noted for patient loss between groups (A). Death-censored graft loss was significantly higher in the C-TCMR group compared with the NI group (B), ($P = 0.02$). Combination of graft loss + impending graft loss (C) was also higher among patients with C-TCMR ($P = 0.001$). ABMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; NI, no inflammation; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection.

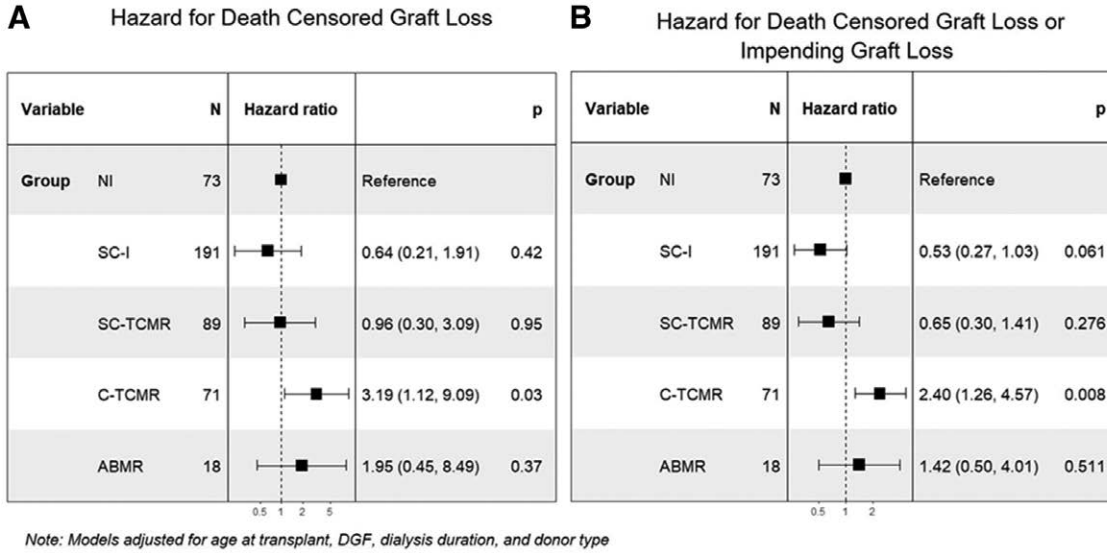

FIGURE 6. Cox proportional hazard model results for (A) DCGL and (B) DCGL or impending graft loss. Models were adjusted for DGF, dialysis duration, age at transplant, and donor type. The group without inflammation (NI) was considered the reference group. After adjustment, only C-TCMR had a significantly higher hazard for DCGL ($P = 0.03$) and DCGL/impending graft loss ($P = 0.008$). ABMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; DCGL, death-censored graft loss; DGF, delayed graft function; NI, no inflammation; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection.

higher attributable risk of graft loss for TCMR compared with AMR/MR. Fourth, the cumulative chronic allograft scores and IFTA ≥2, decline in kidney function, and mean eGFR over time were associated with all types of allograft inflammation. The role of early intervention, although not evaluated in this study, is relevant because scarring can be irreversible.[31] Fifth, we found a slightly higher incidence of DSA in all groups in comparison with the NI group (Table 4), which strengthens the link between inflammation and DSA formation.[4, 13, 29, 30] Finally, we found types of allograft inflammation within 1 y also correlated with late rejection (Table 5).

The differential contribution of TCMR versus AMR/MR to long-term kidney allograft survival remains debatable. The incidence of AMR/MR varies among transplant centers depending on a center's recipients immunological risk profile and proportion of ABO and antibody incompatible donor-recipient pairs. The incidence of AMR/MR within 1 y in our study was low at 3.6%. In contrast, the combined incidence of

TABLE 3.

Mean and median doses of MMF and MPA at 3 and 12 mo posttransplant for the entire study cohort and for each of the 5 study groups

		Study groups					
	Total (N = 552)	NI (N = 95)	SCI (N = 244)	SC-TCMR (N = 110)	C-TCMR (N = 83)	AMR/MR N = 20)	*P* for trend
MMF dose at 3 mo posttransplant							
MMF, n (%)	392 (71.0)	067 (70.5)	173 (70.9)	084 (76.4)	051 (61.4)	017 (85.0)	0.13
Mean (SD)	1589.29 (585.96)	1630.60 (552.81)	1651.73 (555.52)	1541.67 (617.07)	1323.53 (646.71)	1823.53 (430.88)	**0.003****
Median (IQR)	2000.0 (1000.0–2000.0)	2000.0 1000.0–2000.0)	2000.0 (1500.0–2000.0)	2000.0 (1000.0–2000.0)	**1500.0 (500.0–2000.0)**	2000.0 (2000.0–2000.0)	**0.0024***
MMF dose at 12 mo posttransplant							
MMF, n (%)	348 (63.0)	067 (70.5)	153 (62.7)	068 (61.8)	046 (55.4)	014 (70.0)	0.3
Mean (SD)	1566.09 (527.64)	1597.01 (531.14)	1544.12 (539.64)	1555.15 (497.84)	1619.57 (539.39)	1535.71 (535.81)	0.9
Median (IQR)	2000.0 (1000.0–2000.0)	2000.0 (1000.0–2000.0)	2000.0 (1000.0–2000.0)	1750.0 (1000.0–2000.0)	2000.0 (1000.0–2000.0)	1750.0 1000.0–2000.0)	0.84
MPA dose at 3 mo posttransplant							
MPA, n (%)	063 (11.4)	012 (12.6)	031 (12.7)	010 (9.1)	010 (12.0)	000 (0.0)	0.44
Mean (SD)	1137.14 (435.93)	1260.00 (325.63)	1068.39 (388.67)	828.00 (488.92)	1512.00 (371.81)	NA (NA)	**<0.001**
Median (IQR)	1440.0 (720.0–1440.0)	1440.0 (1080.0–1440.0)	1080.0 (720.0–1440.0)	720.0 (360.0–1440.0)	1440.0 (1440.0–1440.0)	NA (NA–NA)	**0.003**
MPA dose at 12 mo posttransplant							
MPA, n (%)	077 (13.9)	011 (11.6)	035 (14.3)	017 (15.5)	010 (12.0)	004 (20.0)	0.82
Mean (SD)	1051.95 (507.49)	883.64 (406.13)	1069.71 (375.40)	1122.35 (811.32)	1188.00 (381.37)	720.00 (293.94)	0.41
Median (IQR)	1080.0 (720.0–1440.0)	720.0 (720.0–1440.0)	1080.0 (720.0–1440.0)	1080.0 (360.0–1440.0)	1440.0 (1080.0–1440.0)	720.0 (540.0–900.0)	0.25

*Significantly different for C-TCMR.
**Significantly different for C-TCMR and AMR.
Significant values are in bold.
AMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolate acid; MR, mixed rejection; NA, not applicable; NI, no inflammation; SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection.

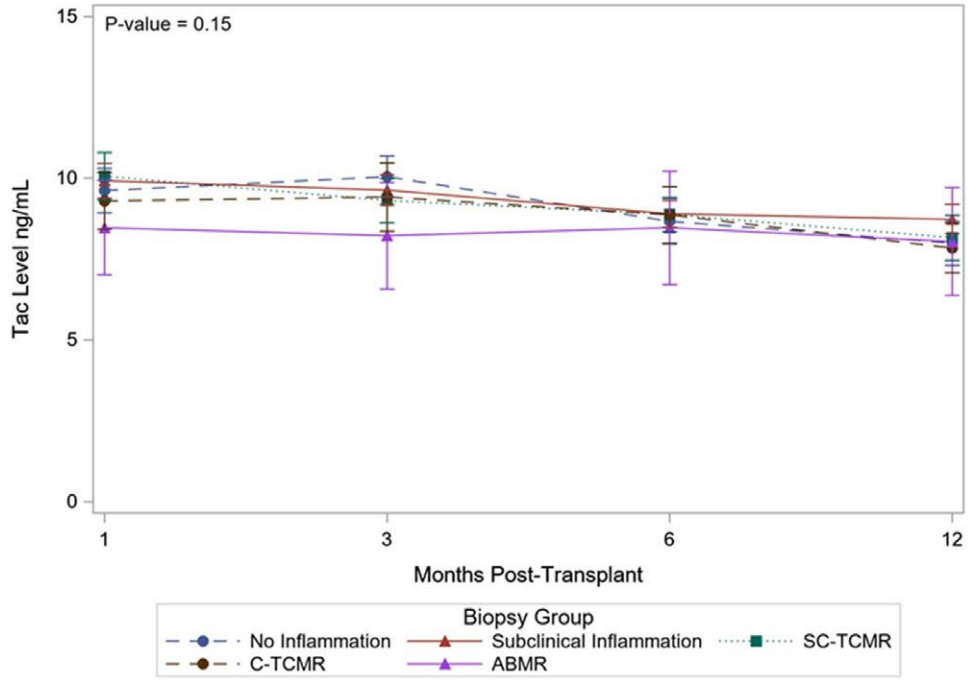

FIGURE 7. Figure provides the mean TAC level with 95% CI at 1, 3, 6, and 12 mo posttransplant for all 5 groups from the linear mixed model. No differences in TAC level were noted across the time points between the groups ($P = 0.15$). ABMR, antibody-mediated rejection; CI, confidence interval; C-TCMR, clinical T cell–mediated rejection; SC-TCMR, subclinical T cell–mediated rejection; TAC, tacrolimus.

TABLE 4.

Incidence of DSA posttransplant and characteristics of DSA among those who are DSA+: class I, class II, both class I/II, and persistent DSA

		Study groups					
	Total (N = 552)	NI (N = 95)	SCI (N = 244)	SC-TCMR (N = 110)	C-TCMR (N = 83)	AMR/MR (N = 20)	*P*
DSA+ posttransplant, n (%)	111 (20.1%)	009 (9.5%)	044 (18.0%)	020 (18.2%)	**022 (26.5%)**	**016 (80.0%)**	**<0.001**
Class I, n (%)	59 (53.2%)	05 (55.6%)	16 (36.4%)	**10 (50.0%)**	**15 (68.2%)**	**13 (81.3%)**	**0.015**
Class II, n (%)	77 (69.4%)	05 (55.6%)	30 (68.2%)	13 (65.0%)	15 (68.2%)	14 (87.5%)	0.45
Class I and II, n (%)	025 (04.5%)	001 (1.1%)	002 (0.8%)	003 (2.7%)	**008 (9.6%)**	**011 (55.0%)**	**<0.001**
Persistent, n (%)	78 (73.6%)	05 (62.5%)	25 (59.5%)	**15 (78.9%)**	**17 (81.0%)**	**16 (100.0%)**	**0.011***

*Significantly different for SC-TCMR, C-TCMR, and AMR.
Statistically significant values are bolded.
AMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; DSA, donor-specific antibody; MR, mixed rejection; NI, no inflammation (reference group); SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection.

TABLE 5.

The details on 278 for-cause biopsies from 197 patients beyond 1 y posttransplantation are shown below

		Study group					
	Total (N = 552)	NI (N = 95)	SCI (N = 244)	SC-TCMR (N = 110)	C-TCMR (N = 83)	AMR/MR (N = 20)	*P*
Biopsy after 1 y, n (%)	197 (35.7)	022 (23.2)	083 (34.0)	**046 (41.8)**	**036 (43.4)**	010 (50.0)	**0.014***
Groups, n (%)							0.043
No inflammation	19 (09.7)	05 (22.7)	09 (11.0)	04 (8.7)	01 (2.8)	00 (0.0)	0.11
Borderline changes	79 (40.3)	11 (50.0)	40 (48.8)	18 (39.1)	08 (22.2)	02 (20.0)	**0.047**
C-TCMR	72 (36.7)	03 (13.6)	**27 (32.9)**	**16 (34.8)**	**20 (55.6)**	**06 (60.0)**	**0.0087**
AMR/MR	26 (13.3)	03 (13.6)	06 (7.3)	08 (17.4)	07 (19.4)	02 (20.0)	0.30
Biopsy characteristics, median (IQR)							
Days to earliest biopsy after 1 y	545.0 (433.0–898.0)	789.0 (450.0–1451.0)	542.0 (449.0–877.0)	**461.5 (414.0–710.0)**	640.5 (461.5–1053.5)	496.5 (433.0–785.0)	**0.031***
Days to biopsy score	644.0 (450.0–1127.0)	828.5 (450.0–1451.0)	602.0 (449.0–972.0)	540.0 (420.0–987.0)	773.5 (552.5–1298.0)	584.0 (460.0–1289.0)	0.12
Days to most recent biopsy	672.0 (454.0–1276.0)	867.0 (523.0–1451.0)	607.0 (449.0–976.0)	**563.0 (435.0–1400.0)**	868.0 (582.5–1413.0)	850.5 (471.0–1346.0)	**0.046***
No. of biopsies	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–3.0)	**0.022**

*Significantly different for SC-TCMR.
Number and percent patients with no inflammation, borderline changes suspicious for rejection, C-TCMR, and MR for all 5 groups are shown. There were more biopsies performed among patients who had SC-TCMR, C-TCMR, and AMR/MR within 1 y ($P = 0.014$). The overall incidence of MR beyond 1 y posttransplant was 13.3% without any significant differences between groups. Statistically significant values are bolded.
One biopsy in the SCI group is missing from the groups as the results of the biopsy were cancer.
AMR, antibody-mediated rejection; C-TCMR, clinical T cell–mediated rejection; IQR, interquartile range; MR, mixed rejection; NI, no inflammation (reference group); SCI, subclinical inflammation; SC-TCMR, subclinical T cell–mediated rejection.

C-TCMR and SC-TCMR within 1 y was substantially higher at 35%, largely detected through 2 surveillance biopsies during the first year posttransplant, again highlighting the importance of surveillance biopsy in detecting TCMR. We also detected SCI as the most common (44%) histological finding. Lack of significant graft loss among SC-TCMR patients may be due to treatment with steroids. The influence of treatment could not be ascertained as all patients with SC-TCMR received treatment. Allograft scarring was noted despite early diagnosis of SC-TCMR with prompt treatment, and this ability to prevent progression remains speculative. In addition, fewer AMR/MR patients and limited follow-up may have influenced the lack of differences in graft loss in this group.

A higher prevalence of TCMR in comparison with AMR/MR meant that TCMR contributed to a greater amount of graft losses in the population. For example, if we were able to prevent TCMR, it could reduce graft losses by roughly 25%. This contrasts with AMR/MR, which attributed to 3.6% of all graft losses. Thus, TCMR within 1 y contributes to more graft losses and should be targeted for future studies. The incidence of graft failure among patients who had AMR within the first year is low. However, subsequent kidney rejection type, including AMR, may be causing later graft failure. Thus, acute rejection is a dynamic event, and it is prudent to consider evolution from one type of rejection to another leading to graft loss.

Renal function after kidney transplant has been correlated to kidney transplant outcome, and our analysis shows a stepwise increase in the proportion of patients with delta-creatinine >0.3 mg/dL from 3 to 12 mo and last follow-up by the type of allograft inflammation detected within 1 year posttransplant (Table 2). Recipients with NI had the lowest probability (4.2%), whereas C-TCMR (30.1%) and AMR/MR (30%) had the highest probability of decline in renal function. Intermediate outcomes were seen with SCI (14.3%) and SC-TCMR (20.9%) (Table 2). Renal function at last follow-up, measured by eGFR, was best in the NI group and worst in the C-TCMR and AMR groups ($P < 0.0001$) (Figure 3). Thus,

the types of allograft inflammation detected within 1 y posttransplant correlate with kidney function over time.

Renal allograft biopsy has remained the gold standard for diagnosing acute rejection. Histological findings of acute rejection have been subclassified into TCMR, AMR, and MR. Histological findings are also graded according to severity of rejection through the Banff classification.[12,32,33] Allograft chronicity is a common finding on biopsy and is perhaps a sequela of prior acute rejection. Our study finds that the total cumulative acute allograft score and IFTA ≥2 at 12 mo posttransplant correlates with the type of allograft inflammation, suggesting that allograft inflammation is the precursor for IFTA (Figure 4). Thus, cumulative chronic allograft score and IFTA ≥2 reflect prior injury and a potential surrogate marker in addition to BPAR for long-term outcomes.

Limitations of this study include it being a single-center study design and inclusion of both surveillance and for-cause biopsies with limited follow-up. However, we have done sensitive analysis on 2 biopsies done during the first year posttransplantation. Results with 2 surveillance biopsies are similar to the entire cohort. In addition, treatment decisions were made based on histological findings and may have altered the outcome. Thus, it was not possible to dissect the impact of treatment through our study cohort. The majority of recipients included in this study received Thymoglobulin induction with rapid steroid withdrawal, and biopsy findings may be different under alternate immunosuppressive regimens. Thus, steroid withdrawal, which is a center-specific protocol, may have resulted in higher incidence of allograft inflammation. The donor KDPI score was higher in the C-TCMR group, which may have been associated with more renal dysfunction and a higher biopsy rate. Time 0 biopsy was not performed and could have provided information about baseline allograft chronicity. No other reversible factors were identified between patients with various types of inflammation. Low incidence of AMR/MR may reflect our practice of limiting transplant to donor-recipient pairs who are matched for blood group and antibody with negative T/B Flow crossmatch. This study did not address nonadherence to transplant outcomes and we did not have sufficient patients to subdivide patients into various Banff grades. SCR and SCI have been described with cyclosporine as well as TAC through surveillance biopsies.[6,8,34,35] Low incidence of allograft biopsies without any inflammation in our study may reflect low threshold for the diagnosis of allograft inflammation. Long-term kidney transplant outcome cannot be singularly determined by events occurring within the 1 y posttransplantation as acute rejection including AMR/MR can occur beyond 1 y and may have impacted survival. Our comprehensive study on a large cohort of LD and DD kidney transplants is different from other published series as it includes both DD and LD kidney transplant recipients from all races. Our study primarily did not aim to address the differential impact of race for various outcomes due to fewer number of African Americans (21%) in our study cohort. However, our analysis did not show any differential impact on race. We evaluated the impact of various types of inflammation on short- and long-term renal function, allograft histology at 1 y, late rejection, DSA formation, and graft loss.

Strategies to identify, treat, and reverse TCMR before the progression of allograft chronicity and dysfunction carry the potential to improve long-term graft survival. This has been eluded through a study that identified nonresponders to treatment for TCMR.[36] Other studies have also shown the impact including the outcome of allograft inflammation seen in surveillance biopsies.[37,38] The cause of high IFTA score at 12 mo despite treatment of SC-TCMR remains unclear. It is possible that the treatment of SC-TCMR with bolus steroids may be suboptimal. However, our study clearly illustrates the short-term impact on allograft chronicity for various types of allograft inflammation as well as the long-term impact on renal function and graft loss.

In conclusion, our study demonstrates allograft inflammation within the 1 y posttransplant was very common in this cohort of ABO compatible and crossmatch negative transplant recipients with steroid withdrawal protocol. Both C-TCMR and SC-TCMR were commonly seen, and AMR was diagnosed in only a small proportion, nearly always mixed with TCMR. C-TCMR as opposed to AMR within 1 y accounted for higher number of late graft loss and impending graft losses. However, events beyond 1 y including AMR and MR may have led to late graft loss. Thus, kidney allograft inflammation within 1 y is common and predicted posttransplant eGFR, allograft chronicity at 12 mo, and subsequent graft loss.

REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341:1725–1730.
2. Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med*. 2000;342:605–612.
3. Loupy A, Lefaucheur C, Vernerey D, et al. Complement-binding anti-HLA antibodies and kidney-allograft survival. *N Engl J Med*. 2013;369:1215–1226.
4. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant*. 2012;12:1157–1167.
5. Campos EF, Tedesco-Silva H, Machado PG, et al. Post-transplant anti-HLA class II antibodies as risk factor for late kidney allograft failure. *Am J Transplant*. 2006;6:2316–2320.
6. Nankivell BJ, Borrows RJ, Fung CL, et al. Natural history, risk factors, and impact of subclinical rejection in kidney transplantation. *Transplantation*. 2004;78:242–249.
7. Nankivell BJ, Chapman JR. The significance of subclinical rejection and the value of protocol biopsies. *Am J Transplant*. 2006;6:2006–2012.
8. Gloor JM, Cohen AJ, Lager DJ, et al. Subclinical rejection in tacrolimus-treated renal transplant recipients. *Transplantation*. 2002;73:1965–1968.
9. Clayton PA, McDonald SP, Russ GR, et al. Long-term outcomes after acute rejection in kidney transplant recipients: an ANZDATA analysis. *J Am Soc Nephrol*. 2019;30:1697–1707.
10. O'Connell PJ, Zhang W, Menon MC, et al. Biopsy transcriptome expression profiling to identify kidney transplants at risk of chronic injury: a multicentre, prospective study. *Lancet*. 2016;388:983–993.
11. Friedewald JJ, Kurian SM, Heilman RL, et al; Clinical Trials in Organ Transplantation 08 (CTOT-08). Development and clinical validity of a novel blood-based molecular biomarker for subclinical acute rejection following kidney transplant. *Am J Transplant*. 2019;19:98–109.
12. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 kidney meeting report: revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant*. 2018;18:293–307.
13. Cherukuri A, Mehta R, Sharma A, et al. Post-transplant donor specific antibody is associated with poor kidney transplant outcomes only when combined with both T-cell-mediated rejection and non-adherence. *Kidney Int*. 2019;96:202–213.
14. Hoffman W, Mehta R, Jorgensen DR, et al. The impact of early clinical and subclinical T cell-mediated rejection after kidney transplantation. *Transplantation*. 2019;103:1457–1467.
15. Hariharan S. Long-term kidney transplant survival. *Am J Kidney Dis*. 2001;38(suppl 6):S44–S50.
16. Ekberg H, Grinyó J, Nashan B, et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. *Am J Transplant*. 2007;7:560–570.

17. Johnson C, Ahsan N, Gonwa T, et al. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. *Transplantation*. 2000;69:834–841.
18. Halloran P, Mathew T, Tomlanovich S, et al. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. *Transplantation*. 1997;63:39–47.
19. Merion RM, White DJ, Thiru S, et al. Cyclosporine: five years' experience in cadaveric renal transplantation. *N Engl J Med*. 1984;310:148–154.
20. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation*. 1995;60:225–232.
21. Saran R, Robinson B, Abbott KC, et al. US renal data system 2016 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2017;69(3 suppl 1):A7–A8.
22. Meier-Kriesche H-U, Schold JD, Srinivas TR, et al. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant*. 2004;4:378–383.
23. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant*. 2011;11:450–462.
24. Hariharan S, McBride MA, Cohen EP. Evolution of endpoints for renal transplant outcome. *Am J Transplant*. 2003;3:933–941.
25. Hariharan S, Kasiske B, Matas A, et al. Surrogate markers for long-term renal allograft survival. *Am J Transplant*. 2004;4:1179–1183.
26. Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int*. 2002;62:311–318.
27. Mehta R, Cherikh W, Sood P, et al. Kidney allograft surveillance biopsy practices across US transplant centers: a UNOS survey. *Clin Transplant*. 2017;31:e12945.
28. Mehta R, Sood P, Hariharan S. Subclinical rejection in renal transplantation: reappraised. *Transplantation*. 2016;100:1610–1618.
29. Mehta R, Bhusal S, Randhawa P, et al. Short-term adverse effects of early subclinical allograft inflammation in kidney transplant recipients with a rapid steroid withdrawal protocol. *Am J Transplant*. 2018;18:1710–1717.
30. Nankivell BJ, P'Ng CH, Chapman JR. Does tubulitis without interstitial inflammation represent borderline acute T cell mediated rejection? *Am J Transplant*. 2019;19:132–144.
31. Rockey DC, Bell PD, Hill JA. Fibrosis—a common pathway to organ injury and failure. *N Engl J Med*. 2015;372:1138–1149.
32. Solez K, Axelsen RA, Benediktsson H, et al. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. *Kidney Int*. 1993;44:411–422.
33. Haas M, Sis B, Racusen LC, et al; Banff Meeting Report Writing Committee. Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant*. 2014;14:272–283.
34. Loupy A, Vernerey D, Tinel C, et al. Subclinical rejection phenotypes at 1 year post-transplant and outcome of kidney allografts. *J Am Soc Nephrol*. 2015;26:1721–1731.
35. Heilman RL, Devarapalli Y, Chakkera HA, et al. Impact of subclinical inflammation on the development of interstitial fibrosis and tubular atrophy in kidney transplant recipients. *Am J Transplant*. 2010;10:563–570.
36. Bouatou Y, Viglietti D, Pievani D, et al. Response to treatment and long-term outcomes in kidney transplant recipients with acute T cell-mediated rejection. *Am J Transplant*. 2019;19:1972–1988.
37. Mengel M, Gwinner W, Schwarz A, et al. Infiltrates in protocol biopsies from renal allografts. *Am J Transplant*. 2007;7:356–365.
38. Sellarés J, de Freitas DG, Mengel M, et al. Inflammation lesions in kidney transplant biopsies: association with survival is due to the underlying diseases. *Am J Transplant*. 2011;11:489–499.