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A Banff-based histologic chronicity index is associated with graft loss in patients with a kidney transplant and antibody-mediated rejection

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Abstract

Antibody-mediated rejection (AMR) is the major cause of graft loss in kidney transplant recipients. The Banff classification defines two classes of AMR, active and chronic active but over time this classification has become increasingly complex. To simplify the approach to AMR, we developed activity and chronicity indices based on kidney transplant biopsy findings and examined their association with graft survival in 147 patients with active or chronic active AMR, all of whom had donor-specific antibodies and were treated for AMR. The activity index was determined as the sum of Banff glomerulitis (g), peritubular capillaritis (ptc), arteritis (v) and C4d scores, with a maximum score of 12. The chronicity index was the sum of interstitial fibrosis (ci), tubular atrophy (ct), chronic vasculopathy (cv), and chronic glomerulopathy (cg) scores, the latter doubled, with a maximum score of 15. While the activity index was generally not associated with graft loss, the chronicity index was significantly associated with graft loss with an optimal threshold value of 4 or greater for predicting graft loss. The association of the chronicity index of 4 or greater with graft loss was independent of other parameters associated with graft loss, including the estimated glomerular filtration rate at the time of biopsy, chronic active (versus active) AMR, AMR with *de novo* (versus persistent/rebound) donor-specific antibodies, Banff (gDptc) scores, concurrent T cell–mediated rejection and donor-specific antibody reduction post-biopsy. The association of the chronicity index of 4 or greater with graft loss was confirmed in

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DISCLOSURE

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an independent cohort of 61 patients from Necker Hospital, Paris. Thus, our findings suggest that the chronicity index may be valuable as a simplified approach to decision-making in patients with AMR.

Keywords

antibody-mediated rejection; Banff classification; chronicity index; donor-specific antibodies; kidney transplant; transplant glomerulopathy

Antibody-mediated rejection (AMR) represents the major cause of graft loss in kidney transplant recipients.[1–4] If unrecognized or not successfully treated in a relatively early stage, AMR typically leads to chronic damage, including transplant glomerulopathy (TG), arterial intimal fibrosis, and interstitial fibrosis/tubular atrophy.[5–10] TG in particular is strongly associated with increased rates of graft loss.[11–13] Over the past 3 decades, the Banff classification has been the major internationally recognized system for diagnosing and grading rejection in kidney allograft biopsies,[14] with diagnostic criteria for AMR first introduced in a 2003 publication[15] and having undergone 2 major revisions since.[14] The most recent version, Banff 2019,[16] recognizes 2 major subtypes of AMR—active and chronic active (CA)—with a third, infrequently encountered subtype of purely chronic AMR. Within these subtypes, there are diagnostic criteria based on active lesions, including glomerulitis (g), peritubular capillaritis (ptc), arteritis (v; which may also be a manifestation of acute T cell–mediated rejection [TCMR]), and C4d deposition in peritubular capillaries, and chronic lesions including TG (cg), peritubular capillary basement membrane multilayering (ptcml), and chronic vasculopathy (cv; which, like arteritis, may be a manifestation of AMR, TCMR, or both). Many pathologists further divide AMR subtypes according to other factors shown to potentially influence graft survival, such as C4d-positive versus C4d-negative, early versus late post-transplantation, associated with *de novo* donor-specific antibodies (DSAs) versus persistent/rebound DSAs, and pure AMR versus mixed AMR and TCMR.[17–22]

These modifications, although aimed at improving the diagnostic and prognostic value of the classification and helping to guide therapy, have also come with a price: increased complexity. A 2019 survey, completed by 95 clinicians and 72 pathologists, found the classification to be complex and vulnerable to misinterpretation, leading to heterogeneity in whether patients, particularly those with CA AMR, received treatment directed at AMR.[23]

To address this, a major objective of the Banff 2019 meeting report[16] was clarification of definitions for individual histologic lesion scores and all diagnostic categories. Still, a more straightforward approach to guiding clinicians with respect to prognosis of and therapeutic approach to patients diagnosed with AMR would likely be helpful. In this study, we investigate the potential value of one such approach, scoring biopsies from DSA-positive patients meeting Banff 2019 criteria for AMR according to activity and chronicity indices (AI and CI) similar to those proposed for lupus nephritis[24] but incorporating the Banff histologic lesion scores. In 2 separate patient cohorts from Cedars-Sinai Medical Center and Necker Hospital with an initial diagnosis of active or CA AMR, we found that a CI composed of the sum of ci, ct, cv, and cg scores, the latter doubled because of the well-

documented impact of TG on graft outcomes, was strongly associated with graft survival with an optimal threshold value of <4 versus ≥4.

METHODS

Cedars-Sinai patients and biopsies

Computerized records of the Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, were searched to identify all renal transplant biopsies performed from January 2015 to December 2018 with a diagnosis of active or CA AMR (including mixed AMR/TCMR), according to Banff 2013 or 2017 criteria,[25,26] including documentation of the presence of anti–human leukocyte antigen (HLA) DSA within 10 days of the biopsy. DSA were assessed using Luminex (One Lambda, Canoga Park, CA) single antigen testing, and this was routinely performed at 1, 3, 6, and 12 months post-transplantation and then annually on all sensitized patients (calculated panel reactive antibodies ≥30% and/or prior transplant), annually on remaining patients, plus whenever a biopsy showed histologic changes of AMR. For each DSA present, a relative intensity score was assigned on the basis of the mean fluorescence intensity, and the relative intensity sum score was determined as the sum of the individual scores as previously described.[20] Biopsies of ABO-incompatible grafts and those showing recurrent or *de novo* glomerulonephritis were excluded, as were biopsies from patients with a diagnosis of AMR or suspicious for AMR before the study period. In addition, for patients with >1 biopsy showing AMR during the study period, only the first such biopsy was included, so that for any given patient only a single biopsy was included. A total of 68 such biopsies were identified, all performed for graft dysfunction or increased protein excretion rate. These were added to 79 biopsies meeting the same criteria that were performed from January 2010 through December 2014 and included in a previous study,[20] giving a total of 147 biopsies from 147 different patients.

Processing of biopsies and diagnosis of AMR

Each biopsy was studied by routine light microscopy (hematoxylineosin, periodic acid–Schiff, Masson's trichrome, and Jones silver methenamine stains); direct immunofluorescence for IgG, IgA, IgM, C3, C1q, albumin, fibrin, and kappa and lambda light chains; and indirect immunfluorescence for C4d, performed using a monoclonal anti-C4d antibody as previously described.[27] Electron microscopy was performed in all but 12 cases. The latter included recording the maximum number of basement membrane layers in the most severely involved peritubular capillaries.

For each biopsy, histologic slides were reviewed by a renal pathologist (MH) and the following lesion scores (0–3) were graded according to Banff 2019 criteria[16]: interstitial inflammation in nonscarred cortex (i), tubulitis (t), arteritis (v), glomerulitis (g), peritubular capillaritis (ptc), chronic glomerulopathy (cg), interstitial fibrosis (ci), tubular atrophy (ct), arterial intimal fibrosis (cv), total inflammation (ti), and interstitial inflammation in scarred cortex (i-interstitial fibrosis/tubular atrophy) with the modification that cg scores were based solely on light microscopy (i.e., cg1a was considered as cg = 0). Four biopsies were classified as showing CA AMR with a cg score of 0 by light microscopy; 2 had severe ptcml and 2 had new-onset arterial intimal fibrosis with no prior TCMR or documented

hypertension; 3 of these biopsies and 5 others showed cg1a lesions by electron microscopy. C4d staining results were taken from the biopsy reports and scored as 0 to 3 according to Banff criteria.

Finally, computerized patient records were searched, blinded to biopsy findings, and the following information recorded: days post-transplantation of the biopsy, estimated glomerular filtration rate (eGFR) at the time of biopsy (determined using the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation), whether graft loss occurred and the interval between biopsy and time of graft loss (return to dialysis), interval between the biopsy and last follow-up for patients not developing graft loss and serum creatinine level at last follow-up, and treatment given after the biopsy. For patients included in the previous study,[20] an updated records search was performed. Follow-up was available for all 147 patients, including 4 who died with a functioning graft, although eGFR at the time of biopsy was available only for 143. A total of 61 patients developed graft loss at a median postbiopsy interval of 28 months (interquartile range 8–46 months; total range 1–109 months); for patients not developing graft loss, the median time from biopsy to last follow-up was 37 months (interquartile range 18–64 months; total range 4–147 months). All patients were treated for AMR directly after the biopsy results were reported, with all but 2 receiving i.v. Ig, 117 rituximab, and varying numbers plasmapheresis, tocilizumab, eculizumab, bortezomib, alemtuzumab, and obinutuzumab. Patients with acute or CA TCMR (Banff 1A grade or higher) also received corticosteroids, with or without thymoglobulin. All study procedures were approved by the Institutional Review Board of Cedars-Sinai Medical Center.

Necker Hospital cohort

A total of 61 biopsies (from 61 patients) from Necker Hospital, Paris, with a diagnosis of active or CA AMR, with or without concurrent TCMR, performed from 2010 through 2016, were identified in which the following criteria were met: (i) there were no previous biopsies showing AMR; (ii) anti-HLA DSA were present at the approximate time of biopsy; and (iii) the patient was treated specifically for AMR. Banff 2019 indices from these biopsies were scored by a renal pathologist from that center (MR), and clinical and serologic data were recorded as described above.

Statistical analysis of data

Morphologic and clinical parameters are expressed as mean ± SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Differences in the development of graft loss between patient groups were analyzed using the Kaplan-Meier method with the log-rank test to determine significance as well as Cox proportional hazards models to determine hazard ratios (HRs) and their 95% confidence intervals. All tests were 2-tailed, and significance was defined as $P < 0.05$. SAS version 9.4 (SAS Institute) was used for calculations.

Thresholds for each discrete numerical variable (AI, CI, and AI + CI) were based on the model fit statistics Akaike information criterion (AIC) and Bayesian information criterion (BIC) obtained from the Cox regression models, with smaller AIC and BIC indicating a

better fitting model. AIC and BIC are estimators of the prediction error. Given a collection of models for the data, AIC and BIC estimate the quality of each model, relative to each of the other models, and thus provide a means for model selection. For example, AI had discrete values from 2 to 11 (2, 3, 4, …, 11), thus creating potential thresholds of 3 (AI ≥ 3), 4, 5, …, 10 (AI ≥ 10). Individual Cox regression models were estimated for each AI threshold, and the AIC and BIC were obtained for each model. The AI threshold with the smallest AIC and BIC was selected as the "best fitting" model. Initial multivariable Cox models were based on stepwise selection. Addition of a predictor to the resulting stepwise Cox model was based on the −2LogLikelihood fit statistic using the change (Δ) in −2LogLikelihood as the test statistic. Δ(−2LogLikelihood) is approximately chi-square distributed with degrees of freedom equal to the number of additional predictors in the larger model.

RESULTS

Cedars-Sinai cohort

Features of the 147 patients and biopsies are listed in Table 1. The majority had DSAs directed against HLA class II, with or without antibodies against class I. Slightly more than half of the patients had >1 DSA, and 91 of 147 had *de novo* DSAs (type 2 AMR). Fifty-three percent had active AMR compared with 47% with CA AMR; 98 of 147 biopsies (67%) were C4d-positive, and 45 of 147 (31%) showed TCMR (acute or CA, Banff grade 1A or higher), mainly acute. Only 9 of 147 (6%) biopsies showed changes of thrombotic microangiopathy in glomeruli and/or arterioles. The median AI (g + ptc + v + C4d; maximum score 12) was 5, and the median CI (ci + ct + cv + cg[x2]; maximum score 15) was 3 (Table 1). Not surprisingly, the CI increased with time post-transplantation of the biopsy (slope of the linear regression plot of CI vs. months post-transplantation 0.0406 ± 0.005; intercept 2.35 ± 0.33; $r^2 = 0.31$; $P < 0.0001$).

Our previous studies of AMR[20] showed that several parameters were significant predictors of graft loss postbiopsy by univariate analysis, including *de novo* DSA versus persistent/rebound DSA (type 2 AMR vs. type 1 AMR), interval between transplantation and biopsy (per month increase), interval from transplantation to biopsy of ≥84 (vs. <84) months, concurrent TCMR grade 1A or higher, and failure of DSA relative intensity sum score to decrease by >2 (or to 0 if this score at the time of biopsy was 2). Table 2 presents the results of the univariate analysis of the impact of these factors as well as eGFR at the time of biopsy, active versus CA AMR, AI (per 1-unit increase), CI (per 1-unit increase), the sum of AI and CI, and Banff chronic lesion scores (cg, [ci + ct], and cv) on death-censored graft survival. Of these factors, all but AI were significantly associated with graft loss. Both CI and (AI + CI) were significantly associated with graft loss, with optimal predictive cutoff values being CI ≥4 versus CI <4 (Table 3 and Figure 1) and (AI + CI) ≥13 versus (AI + CI) <13 (Table 3). Similar analysis for AI alone showed that AI ≥9 (but no other AI threshold) was associated with graft loss by univariate analysis (HR 2.78; 95% confidence interval 1.10–7.02; $P = 0.030$); however, only 7 of the 147 biopsies had AI ≥9 and this variable is therefore not appropriate for a multivariable model. When only biopsies with active AMR, CA AMR, pure AMR (no acute or CATCMR with Banff grade ≥1A), and mixed AMR +

TCMR were considered separately, in each case CI per 1-unit increase and CI ≥4 remained significantly associated with graft loss whereas AI was not. Table 2 also presents that Banff chronic lesion scores were significantly associated with graft loss; however as shown in Table 3, the association of CI ≥4 versus CI <4 with graft loss was stronger than cg ≥1 (vs. 0) or cg ≥2 (vs. <2). Thus, adding additional chronic elements to TG to formulate the CI, even with the double weighting of the cg score in the CI, appears to improve the value of TG alone as a predictor of graft outcome.

In a multivariable model including each of the morphologic and serologic variables in Table 2 that were significantly associated with graft loss, only 3 remained significant: CI ≥4, TCMR (acute or CA) of grade 1A or higher, and failure of the HLA antibody relative intensity sum score to decline by >2 (Table 4). Adding the sum of Banff (g + ptc) scores (which per 1-unit increase were significantly associated with graft loss by univariate analysis: HR 1.23; 95% confidence interval 1.01–1.51; $P = 0.041$) to the multivariable analysis did not change these findings. In a separate multivariable analysis, CI ≥4 and eGFR at the time of biopsy were each significantly associated with graft loss after adjusting for the other (Table 5).

Necker Hospital cohort

To determine whether the above findings were applicable to an independent group of patients with DSA-positive AMR, biopsies from 61 patients from Necker Hospital, Paris, performed from 2010 through 2016, were scored by a pathologist from that center (MR), and the findings correlated with graft outcomes. As shown in Table 6, this cohort differed from the Cedars-Sinai cohort in that biopsies in the former were performed earlier post-transplantation with a higher fraction of patients having persistent/rebound DSA and active AMR. Biopsies from the Necker cohort also included 18 protocol biopsies (30%) performed at 3 or 12 months post-transplantation, whereas all the Cedars-Sinai biopsies were indication biopsies. A higher fraction of Necker patients also had a single DSA and a lower sum of DSA mean fluorescence intensity values, and there were fewer graft losses in this cohort. There were also notable differences in treatments given for AMR at the 2 centers. As shown in Tables 7 and 8, the association between CI and graft survival (per 1-unit increase) did not reach statistical significance, perhaps related to the relatively early timing of the biopsies. However, as with the Cedars-Sinai cohort, there was a strong and significant association between CI ≥4 and graft loss (Figure 2); this was the optimal cutoff value for CI in predicting graft loss (Table 8). AI was not significantly associated with graft loss, but (AI + CI) was; the optimal cutoff value for (AI + CI) was 10 in the Necker cohort compared with 13 in the Cedars-Sinai cohort, perhaps reflecting the higher median value for (AI + CI) in the latter (Table 6). The only other parameter that was close to being significantly associated with graft loss was AMR type 2 versus AMR type 1 (*de novo* DSA vs. persistent/rebound DSA) (Tables 7 and 8). In multivariable analysis including the latter, CI ≥4 remained significantly associated with graft loss (HR 3.50; 95% confidence interval 1.34–9.18; $P = 0.011$) but (AI + CI) ≥10 did not (HR 2.20; 95% confidence interval 0.84–5.80; $P = 0.11$).

DISCUSSION

In the current era of immunosuppression, AMR has been identified as the leading cause of long-term kidney allograft failure.[1–4] TG, the most identifiable morphologic lesion of AMR progression,[7–9,11] is well established as a predictor of poor graft outcomes,[12,13,28] so much so that clinicians are often reluctant to aggressively treat patients with documented TG for AMR, although there are newer treatments that show promise for these patients.[29]

Pathologic features that help distinguish different archetypes of AMR and TG are contained in the most recent (2019) version of the Banff classification.[16] This classification, and particularly criteria dealing with AMR, has evolved considerably over the past 2 decades as knowledge has expanded through clinical and molecular studies, with subcategories that in some cases are specifically designated by Banff (e.g., active and CA) and others that, although not officially designated (e.g., C4d-positive vs. C4d-negative, *de novo* DSA vs. persistent/rebound DSA), may nonetheless be associated with differences in graft outcomes.[17–22] Although these subcategories may be valuable to some clinicians in making treatment decisions, the added complexity of the classification has proven difficult to others. In this regard, a 2019 survey completed by 95 clinicians and 72 pathologists found the Banff criteria for AMR to be vulnerable to misinterpretation, leading to heterogeneity in whether patients, particularly those with CA AMR, received treatment specifically directed at AMR.[23]

To try and help simplify this classification as a prognostic indicator (but not with respect to diagnostic criteria), we examined the potential value of scoring biopsies from patients meeting Banff 2019 criteria for AMR according to AI and CI similar to those proposed for lupus nephritis[24] but incorporating the Banff histologic lesion scores (g, ptc, v, C4d, cg, ci, ct, and cv). Like Banff, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification for lupus nephritis is complex and includes lesions with a wide range of activity and chronicity within the same subcategory (e.g., class IV),[24,30] leading to heterogeneity in how the same biopsy findings are approached by different clinicians. For this reason, a recently proposed revision of the ISN/RPS classification recommended the use of AI and CI on the basis of specific pathologic findings rather than broader subcategories of active, active and chronic, and chronic.[24]

We initially determined AI and CI in 147 DSA-positive patients with an initial diagnosis of active or CA AMR on kidney allograft biopsy. All were treated for AMR postbiopsy, although treatment was not uniform. Although AI was not associated with graft loss except at an extremely high (≥9) and rarely seen level, CI was strongly and significantly associated with death-censored graft loss, with an optimal threshold value of ≥4, independent of factors previously shown[20] and confirmed here to also be associated with graft loss by univariate and in some cases multivariable analysis, including eGFR at the time of biopsy. Although the Banff cg score is heavily weighed within the CI because of the well-documented association of TG with poor graft outcomes,[12,13,19] our data analysis showed that the association of CI ≥4 with graft loss was stronger than that for cg scores of ≥1 or ≥2. The latter is noteworthy as it suggests that mild TG does not necessarily imply a poor graft outcome in patients treated for AMR, especially if there are little or no other chronic

changes on the biopsy. Furthermore, in the Necker Hospital cohort where only 3 of 61 patients had a cg score of ≥1, CI ≥4 was still predictive of graft loss. Thus, the presence of more than mild chronic changes in grafts showing active inflammation, whether it be microvascular[13,22] or tubulointerstitial,[31–33] is associated with worse graft outcomes. Consistent with this, unit increases in (AI + CI) were significantly associated with graft loss in both the Cedars-Sinai and Necker cohorts.

The confirmation of the association of CI ≥4 with a significantly higher risk of graft loss in the Necker cohort is also noteworthy in that the latter differed from the Cedars-Sinai cohort with respect to a number of parameters including time from transplantation to biopsy, fraction of patients having persistent/rebound (as opposed to *de novo*) DSA and active (as opposed to CA) AMR, inclusion of protocol biopsies, DSA sum scores, and frequency of graft losses. Thus, the predictive value of CI <4 versus CI ≥4 appears to remain valid for a wide range of patients diagnosed with AMR.

The finding that CI is associated with graft loss is not surprising. In the initial studies of AI and CI in lupus nephritis, CI was strongly associated with kidney failure rates.[34] Chronicity sum scores based on interstitial fibrosis/tubular atrophy, glomerulosclerosis, and chronic vascular changes have also been shown to be predictive of loss of kidney function across a large spectrum of native kidney diseases.[35,36] In addition to TG, interstitial fibrosis/tubular atrophy has been shown to negatively affect renal graft survival[33] and arterial intimal fibrosis may be a manifestation of persistent exposure to DSA.[10] By contrast, the finding that AI was generally not predictive of graft survival is somewhat surprising, noting that previous studies in *de novo* DSA-positive patients found (g + ptc) ≥3 (but not 1–2) to be predictive of graft loss compared with (g + ptc) = 0.[37] In the Cedars-Sinai cohort of 147 DSA-positive patients, 1-unit increases in (g + ptc) were significantly associated with graft loss by univariate but not multivariable analysis, although there was not a statistically significant cutoff value for (g + ptc) for predicting graft loss. Perhaps the impact of (g + ptc) is weakened by its inclusion in the AI with other parameters (C4d and v scores), although arteritis (v > 0) in patients with other diagnostic changes of AMR was shown to be predictive of graft loss,[38] and some, but not all, studies have shown an impact of diffuse C4d staining on graft survival, albeit usually by univariate analysis only and often not statistically significant.[17,37,39,40] Still, molecular studies in cases of AMR without concurrent TCMR showed that transcripts associated with fibrosis and tissue injury, but not those associated with active inflammation, were most strongly associated with graft survival.[41]

This study does have significant limitations. It is retrospective, albeit with similar findings in 2 independent patient cohorts from different centers. A detailed statistical analysis of the weighting of the different parameters comprising AI and CI was not conducted, and it should be emphasized that these indices are not meant to represent a statistically based prediction tool similar to the iBox[42] or the IgA nephropathy prediction tool.[43] All patients were treated for AMR, although this was not uniform. Still, inclusion of only treated patients may have contributed to the lack of association of AI with graft loss. Furthermore, the time of initial biopsy showing AMR spanned a rather long interval (2010–2018 for Cedars-Sinai, 2010–2016 for Necker), during which new treatments for AMR, such as tocilizumab,[29] were introduced into practice at Cedars-Sinai. The size of the Necker cohort was also

relatively small with rather few cases showing CA AMR and mixed AMR/TCMR, limiting multivariable analyses that could be performed. Finally, we limited our study to DSA-positive patients with biopsies fully diagnostic of AMR according to Banff criteria,[16,26] excluding DSA-negative patients with microvascular inflammation termed “suspicious for AMR” in Banff 2013,[25] as reports of the clinical significance of the latter lesions are quite variable.[44–46] Notably, 1 study of such lesions diagnosed early post-transplantation found that these patients had excellent graft outcomes, far better than those in patients with DSA-positive AMR, despite lack of treatment for AMR.[45] Indeed, microvascular inflammation in the absence of DSA may represent a response to missing self or another factor related to HLA mismatches rather than undetected HLA DSA or non-HLA antibodies.[47,48]

In summary, we found that a CI (ci + ct + cv + cg[x2]) of ≥4 on a renal allograft biopsy with an initial AMR diagnosis was strongly associated with graft loss in 2 separate cohorts of 147 and 61 DSA-positive patients, respectively. The 2 cohorts differed with respect to a number of features, although each consisted of patients and biopsies with features that have been shown in different studies to be predictors of graft outcomes in AMR. For clinicians making treatment decisions for patients diagnosed with AMR, particularly CA AMR, a relatively simple pathologic score that is highly associated with graft survival in patients treated for AMR after the biopsy would appear to be useful in this process.

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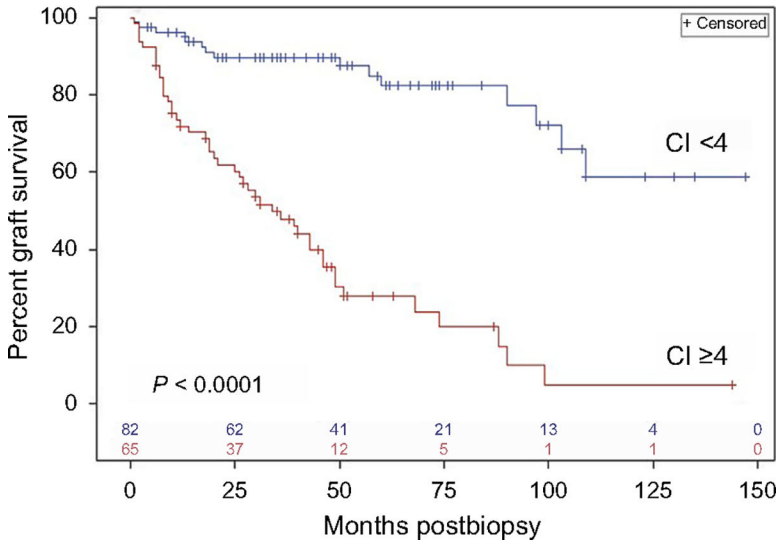

Figure 1 |. Kaplan-Meier analysis of death-censored graft survival in patients with chronicity index (CI) <4 (n = 82) versus CI ≥4 (n = 65) in the Cedars-Sinai cohort.

Vertical ticks on each curve indicate censored values (time post-transplantation of last follow-up without graft loss), and the numbers of remaining uncensored cases are indicated just above the x-axis. The 2 curves are significantly different ($P = 0.0001$) by log-rank analysis.

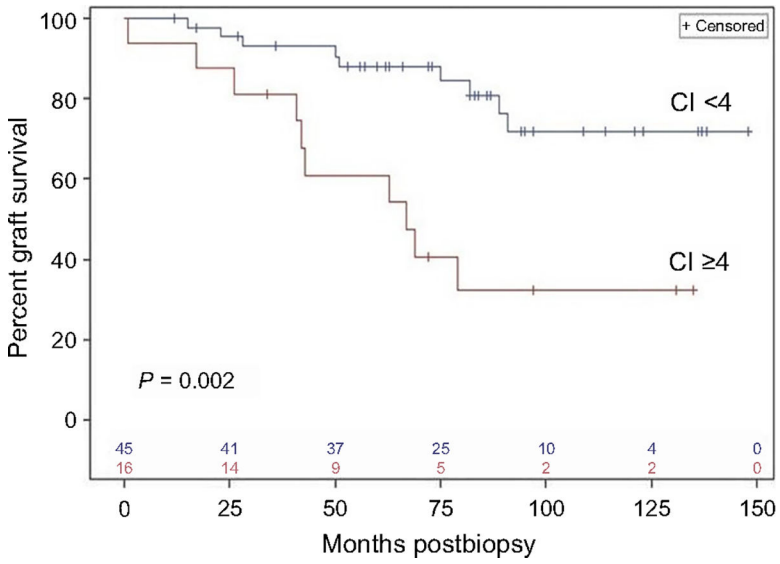

Figure 2|. Kaplan-Meier analysis of death-censored graft survival in patients with chronicity index (CI) <4 (n = 45) versus CI ≥4 (n = 16) in the Necker Hospital cohort.

Vertical ticks on each curve indicate censored values (time post-transplantation of last follow-up without graft loss), and the numbers of remaining uncensored cases are indicated just above the x-axis. The 2 curves are significantly different ($P = 0.0024$) by log-rank analysis.

Table 1 |

Demographic, serologic, and pathologic features

Variable	Value
Age at the time of biopsy, yr	42.4 ± 16.9
Patient sex (M/F)	85/62
Donor type	
Deceased	93 (63)
Living related	24 (16)
Living unrelated	30 (20)
Months, transplant to biopsy	30.0 (6.0–72.0)
eGFR at the time of biopsy, ml/min[a]	47.5 ± 25.0
Graft loss (yes/no)	61/86
Nonadherence (reported, yes/no)	12/135
HLA DSA class	
I only	27
II only	84
I and II	36
Number of DSAs	
1	72
2	47
3	13
>3	15
Immunodominant DSA strength	
Weak (MFI <5000)	39
Moderate (MFI 5000–10,000)	60
Strong (MFI >10,000)	48
DSA sum strength	
Weak (MFI <5000)	38
Moderate (MFI 5000–10,000)	50
Strong (MFI >10,000)	59
DSA type	
De novo	91
Persistent/rebound	56
AMR type	
Active	78
Chronic active	69
TCMR grade	
None/borderline	102
1A acute	13
1B acute	10
1A chronic active	3
1B chronic active	3

Variable	Value
2A acute	13
2B acute	3
C4d in peritubular capillaries	
Negative (C4d 0–1)	49
Positive (C4d 2–3)	98
Thrombotic microangiopathy (yes/no)	9/138
g score	
0	26
1	67
2	33
3	21
ptc score	
0	6
1	31
2	79
3	31
(ci + ct) score	
0–1	68
2	44
3–4	26
5–6	9
cg score	
0[b]	86
1	27
2	13
3	21
cv score	
0	72
1	44
2	26
3	5
AI	5 (4–7)
CI	3 (1–7)
(AI + CI)	9 (6–13)

AI, activity index; AMR, antibody-mediated rejection; cg, Banff chronic glomerulopathy score, ci, Banff interstitial fibrosis score; CI, chronicity index; ct, Banff tubular atrophy score; cv, Banff chronic arteriopathy score; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; F, female; g, Banff glomerulitis score; HLA, human leukocyte antigen; M, male; MFI, mean fluorescence intensity; ptc, Banff peritubular capillaritis score; TCMR, T cell-mediated rejection.

[a]Based on 143 cases; other parameters based on 147.

[b]Includes 8 biopsies with cg1a.

All Banff scores are graded as 0–3 according to criteria detailed in Banff 2019,[16] and C4d was determined by immunofluorescence on frozen sections with Banff C4d scores assigned accordingly. Data are expressed as mean ± SD, median (interquartile range), or n (%).

Table 2 |

Variables associated with death-censored graft loss by univariate analysis

Variable	Hazard ratio	95% confidence interval	*P*
CI per 1-unit increase	1.28	1.19–1.37	<0.0001
CI ≥4 vs. CI <4	6.93	3.79–12.65	<0.0001
AI per 1-unit increase	1.09	0.96–1.24	0.19
AI ≥9 vs. AI <9	2.78	1.10–7.02	0.030
(AI + CI) per 1-unit increase	1.26	1.18–1.35	<0.0001
(AI + CI) ≥13 vs. (AI + CI) <13	4.99	2.97–8.38	<0.0001
cg score per 1-unit increase	1.54	1.26–1.88	<0.0001
(ci + ct) per 1-unit increase	1.48	1.29–1.71	<0.0001
cv score per 1-unit increase	2.34	1.74–3.15	<0.0001
TCMR grade 1A or higher	2.32	1.41–3.85	<0.0001
Active AMR vs. chronic active AMR	0.30	0.17–0.52	<0.0001
AMR type 2 vs. AMR type 1	2.21	1.23–3.96	0.008
Biopsy ≥84 mo vs. biopsy <84 mo	2.51	1.47–4.30	0.0008
Biopsy post-transplant time (per month)	1.009	1.005–1.014	0.0002
eGFR (per ml/min)[a]	0.958	0.943–0.972	<0.0001
eGFR (per 10 ml/min)[a]	0.649	0.557–0.756	<0.0001
ΔRIS >−2	4.00	2.33–7.14	<0.0001

AI, activity index; AMR, antibody-mediated rejection; cg, Banff chronic glomerulopathy score; ci, Banff interstitial fibrosis score; CI, chronicity index; ct, Banff tubular atrophy score; cv, Banff chronic vasculopathy score; eGFR, estimated glomerular filtration rate; ΔRIS, change in donor-specific antibody relative intensity sum score; TCMR, T cell–mediated rejection.

Type 1 AMR indicates persistent/rebound donor-specific antibody, whereas type 2 AMR indicates *de novo* donor-specific antibody.

Development of graft loss in patient groups was analyzed using the Kaplan-Meier method with the log-rank test to determine significance, and Cox proportional hazards models were used to determine hazard ratios and their 95% confidence intervals.

[a]Based on 143 cases; other determinations based on 147.

Table 3 |

Determination of optimal CI and (AI + CI) thresholds for predicting death-censored graft loss

Threshold value	Hazard ratio	95% confidence interval	*P*	AIC	BIC
CI ≥3	6.92	3.37–14.19	<0.0001	493.34	495.45
CI ≥4	6.93	3.79–12.65	<0.0001	484.91	487.02
CI ≥5	5.70	3.27–9.95	<0.0001	491.75	493.86
(AI + CI) ≥11	4.18	2.49–7.03	<0.0001	503.63	505.74
(AI + CI) ≥12	4.61	2.74–7.74	<0.0001	500.84	502.95
(AI + CI) ≥13	4.99	2.97–8.38	<0.0001	499.03	501.14
(AI + CI) ≥14	4.27	2.53–7.23	<0.0001	508.24	510.35
cg ≥1	1.17	1.91–5.48	<0.0001	512.78	514.89
cg ≥2	2.75	1.64–4.63	<0.0001	519.85	521.96

AI, activity index; AIC, Akaike information criterion; BIC, Bayesian information criterion; cg, Banff chronic glomerulopathy score; CI, chronicity index.

Differences in the development of graft loss between different patient groups was analyzed using the Kaplan-Meier method with the log-rank test to determine significance; Cox proportional hazards models were used to determine hazard ratios and their 95% confidence intervals. Thresholds for CI and (AI + CI) were based on the model fit statistics AIC and BIC obtained from the Cox regression models, with smaller AIC and BIC indicating a better fitting model.

Table 4 |

Predictors of death-censored graft loss by multivariable analysis

Variable	Hazard ratio	95% confidence interval	*P*
CI ≥4 vs. CI <4	6.30	3.36–11.84	<0.0001
TCMR grade 1A or higher	2.68	1.58–4.55	0.0002
ΔRIS ≥−2	3.72	2.08–6.67	<0.0001

AI, activity index; CI, chronicity index; g, Banff glomerulitis score; ptc, Banff peritubular capillaritis score; ΔRIS, change in donor-specific antibody relative intensity sum score; TCMR, T cell–mediated rejection.

The multivariable Cox model included the following variables in addition to those listed above that were the only variables found to be significant ($P < 0.05$): active AMR vs. chronic active AMR, AMR type 1 vs. AMR type 2, biopsy ≥84 mo vs. biopsy <84 mo post-transplantation, and AI per 1-unit increase. Similar results were obtained with the sum of Banff (g + ptc) scores substituting for AI. When time post-transplantation of biopsy per month was substituted for biopsy ≥84 mo vs. biopsy <84 mo post-transplantation, the former was also not significantly associated with graft loss in this model, while CI ≥4 remained significant. Analysis is based on 147 cases.

Table 5 |

Predictors of death-censored graft loss by multivariable analysis

Variable	Hazard ratio	95% confidence interval	*P*
CI ≥4 vs. CI <4	5.23	2.65–10.32	<0.0001
eGFR (per 1 ml/min increase)	0.958	0.941–0.976	<0.0001
CI ≥4 vs. CI <4	5.23	2.65–10.32	<0.0001
eGFR (per 10 ml/min increase)	0.652	0.542–0.784	<0.0001

CI, chronicity index; eGFR, estimated glomerular filtration rate.

eGFR is at the time of biopsy. Analysis is based on 143 cases.

Table 6 |

Comparison of Cedars-Sinai and Necker cohorts

Variable	Cedars-Sinai	Necker
Number of cases	147	61
Age at the time of biopsy, yr	42.4 ± 16.9	51.4 ± 14.8
Months, transplant to biopsy	30.0 (6.0–72.0)	3.0 (1.0–6.0)
Graft loss (yes/no)	61/86 (41/59)	16/45 (26/74)
HLA DSA class		
I only	27 (18)	14 (23)
II only	84 (57)	34 (56)
I and II	36 (24)	13 (21)
Number of DSAs		
1	72 (49)	37 (61)
>1	75 (51)	24 (39)
DSA sum strength (sum of MFIs)		
<5000	38 (26)	40 (66)
5000–10,000	50 (34)	10 (16)
>10,000	59 (40)	11 (18)
DSA type		
De novo	91 (62)	15 (25)
Persistent/rebound	56 (38)	46 (75)
AMR type		
Active	78 (53)	58 (95)
Chronic active	69 (47)	3 (5)
TCMR (acute or chronic active)		
None/borderline	102 (69)	48 (79)
≥1A	45 (31)[a]	13 (21)[a]
C4d in peritubular capillaries		
Positive/negative	98/49	35/23[b]
% positive	67	60
Thrombotic microangiopathy		
Present/absent	9/138	3/58
% present	6	5
Biopsy indication		
For cause	147 (100)	43 (70)
Protocol	0 (0)	18 (30)
Postbiopsy treatments		
IVIG	145 (99)	48 (79)
Rituximab	117 (80)	35 (57)
Corticosteroids	69 (47)	57 (93)
PP/PE	36 (24)	50 (82)

Variable	Cedars-Sinai	Necker
Eculizumab	6 (4)	0 (0)
Tocilizumab	11 (7)	0 (0)
Others[c]	24 (16)	2 (3)
AI	5 (4–7)	5 (4–6)
CI	3 (1–7)	2 (0–4)
(AI + CI)	9 (6–13)	7 (5–10)

AI, activity index; AMR, antibody-mediated rejection; CI, chronicity index; DSA, donor-specific antibody; HLA, human leukocyte antigen; IVIG, i.v. immunoglobulin; MFI, mean fluorescence intensity; PE, plasma exchange; PP, plasmapheresis; TCMR,T cell-mediated rejection.

[a]Five biopsies from each cohort listed as showing TCMR ≥ Banff grade 1A had isolated intimal arteritis, defined as Banff v (arteritis) score of 1 or 2 with i (interstitial inflammation score) = 0, t (tubulitis score) = 0, or both. C4d was determined by immunofluorescence on frozen sections with Banff C4d scores assigned accordingly as negative (C4d 0–1) or positive (C4d 2–3).

[b]C4d staining was not performed for 3 of the Necker cases.

[c]Other treatments for AMR included bortezomib, alemtuzumab, and obinutuzumab.

Data are expressed as mean ± SD, median (interquartile range), or n (%).

Table 7 |

Predictors of death-censored graft loss in the Necker cohort

Variable	Hazard ratio	95% confidence interval	*P*
CI per 1-unit increase	1.18	0.98–1.41	0.073
CI ≥4 vs. CI <4	4.06	1.65–10.06	0.002
AI per 1-unit increase	1.09	0.86–1.37	0.48
AI ≥7 vs. AI <7	1.65	0.59–4.62	0.34
(AI + CI) per 1-unit increase	1.26	1.03–1.39	0.022
(AI + CI) ≥10 vs. (AI + CI) <10	3.21	1.28–8.06	0.013
AMR type 2 vs. AMR type 1	2.52	0.99–6.44	0.053
TCMR grade 1A or higher	0.64	0.20–1.82	0.37

AI, activity index; AMR, antibody-mediated rejection; CI, chronicity index; TCMR, T cell–mediated rejection.

Development of graft loss in patient groups was analyzed by univariate analysis using the Kaplan-Meier method with the log-rank test to determine significance, and Cox proportional hazards models were used to determine hazard ratios and their 95% confidence intervals.

Table 8 |

Predictors of death-censored graft loss in the Necker cohort

Threshold value	Hazard ratio	95% confidence interval	*P*	AIC	BIC
CI ≥3	2.39	0.96–5.97	0.061	139.48	140.42
CI ≥4	4.07	1.65–10.06	0.002	134.28	135.22
CI ≥5	1.37	0.40–4.69	0.62	142.81	143.76
(AI + CI) ≥9	2.69	1.08–6.65	0.033	138.71	139.66
(AI + CI) ≥10	3.21	1.28–8.06	0.013	137.46	138.40
(AI + CI) ≥11	2.44	0.88–6.79	0.087	140.54	141.48

AI, activity index; AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, chronicity index.

Thresholds for CI and (AI + CI) were based on the model fit statistics AIC and BIC obtained from the Cox regression models, with smaller AIC and BIC indicating a better fitting model.