Individual Histologic Lesions and Composite Scores in Implant Biopsies Affect Short-Term and Long-Term Kidney Allograft Function

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Abstract

Objectives: **Our aim was to evaluate which histologic lesions in a donor kidney were associated with graft function up to 5 years and with its dynamics.**

Materials and Methods: **We retrospectively investigated the association between acute and chronic individual histologic lesions and composite scores in preimplant and postreperfusion biopsies from deceased-donor (n = 101) and living-donor (n = 29) kidneys with initial graft function and function at discharge, at 6 months, and at 5 years and slopes of estimated glomerular filtration rate from discharge to 6 months and from 6 months to 5 years.**

Results: **A high frequency of chronic and acute histologic lesions in donor kidneys is characteristic of our population of donors with high cardiovascular risk. Glomerulitis in preimplant biopsies predicted delayed graft function. Arteriolar hyalinosis predicted impaired initial graft function. Arteriolar hyalinosis and arteriosclerosis both predicted lower estimated glomerular filtration rate at discharge and ≥ 25% drop in function after 6 months. Glomerulosclerosis affected the estimated glomerular filtration rate at discharge and at 6 months; percentage of changed glomeruli predicted lower function at discharge and at 5 years. Glomerular thrombi in preimplant and postreperfusion biopsies predicted negative slope in estimated glomerular filtration rate from discharge to 6 months and a ≥ 25% drop in function after 6 months, respectively. Fibrinoid necrosis in glomeruli in preimplant biopsies predicted decline in function of ≥ 5 mL/min/1.73 m² every year after 6 months. Chronic and total preimplant and posttransplant Banff scores predicted lower estimated glomerular filtration rate at discharge and at 6 months, with ≥ 25% drop in function after 6 months.**

Conclusions: **Intraoperative biopsies are important in identifying patients at risk for worse graft function, especially concerning absence of gain of function early after transplant and loss of function late after transplant.**

Key words: *Donor kidney, Histopathology, Prognosis*

Introduction

Kidney transplant is the most effective treatment method for patients with end-stage renal disease,[1] although the rates of late kidney allograft failure remain substantial,[1] making prediction of late graft loss an important issue.[2] However, studies with an endpoint of graft failure have disregarded different clinical courses toward complete loss of kidney function. Impairment of initial graft function, such as delayed graft function (DGF) and slow graft function (SGF),[3] and low graft function at discharge from hospital[4] and at 6 months or at 1 year[2,5] are well-recognized indicators of suboptimal long-term results. Some authors have considered that measuring changes in kidney function over time is even more predictive of graft loss.[2,6]

The relationship between donor-related factors and initiation of chronic renal allograft dysfunction has been extensively studied, and the baseline histology of the transplanted kidney has been demonstrated to be of critical importance, especially given the expanding pools of donors.[1,7] Glomerulosclerosis,[8-10] vascular narrowing,[9,10,11-16] acute and chronic tubulointerstitial lesions,[9,10,12,14-16] and several composite scoring systems, which integrate histopathologic findings in different kidney compartments,[7,8,17-22] have been assessed as predictive variables for immediate-term,

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short-term, and long-term graft function. However, studies have yielded inconsistent results, as reviewed by Wang and coauthors.[23]

Many questions remain unanswered. In particular, most existing studies have reported on baseline biopsy findings in predicting early and late kidney graft outcomes in recipients of deceased-donor grafts, whereas there have been few studies in the setting of living donors.[24,25] Moreover, it is unclear whether baseline biopsies are necessary for all categories and types of donors. It remains to be established what constitutes an adequate baseline biopsy in terms of number of cores, timing, and reported lesions.[26,27] There is still no consensus on the prognostic significance of the pathologic findings in individual compartments of donor kidney biopsy compared with integrative assessment.[23] One of the possible explanations for inconsistent results is nonuniformity in defining graft outcomes.[7,17] Moreover, the impact of baseline histology on changes in kidney graft function is understudied. It remains unclear whether acute biopsy features can provide prognostic information in addition to the chronic lesions.[14,15,24] Not all results have been corrected for covariates,[23] and histologic lesions were scored nonuniformly.[17,22,27,28] Furthermore, a scoring system that is designed to assess abnormalities in preimplant biopsies has only been recently published,[27] and its predictive significance has not yet been examined in detail.

In this retrospective single-center study of unselected donor and recipient cohorts, we aimed to evaluate which acute and chronic histologic lesions and composite histologic scores in donor kidney preimplant and postreperfusion intraoperative biopsies were best associated with initial graft function, function at discharge, and function at 6 months and at 5 years, as well as with slopes of GFR from discharge to 6 months and from 6 months to 5 years.

Materials and Methods

Study population

In April 2005, the practice to obtain intraoperative preimplant and 30-minute postreperfusion biopsies to study the effects of ischemic-reperfusion injury (IRI) on transplant outcomes and to serve as reference for subsequent biopsies was introduced at the Zaporizhzhia, Ukraine transplant center. Up to December 2010, our center had conducted 165 consecutive deceased-donor and living-donor kidney transplant procedures with 156 kidney biopsied (no biopsies were conducted on children under 13 years old). After exclusion of 9 grafts that failed within the first 2 weeks posttransplant, 7 patients without follow-up data, and 10 inadequate biopsies, the remaining 130 patients were included in the study (Table 1). Among the study group, 102 patients had both preimplant and postreperfusion biopsies, and, at the discretion of the transplant surgeon, 17 patients and 11 patients had only preimplant or postreperfusion biopsies, respectively. The donor population included living donors (32.6%), ideal deceased donors (50%), expanded criteria donors (7.9%), and donors after cardiac death (9.0%). Donors were subjected to an evaluation protocol in accordance with local guidelines,

Table 1. Demographics for Donors and Recipients

Characteristic	Transplant From Deceased Donor	Transplant From Living Donor	*P*
	Recipients		
Number of recipients (N = 130)	101	29	
Age, years	40 ± 11	26 ± 11	< .001
Male recipient, No. (%)	65 (64.4)	16 (55.2)	.368
Cause of ESRD, No. (%)			
Glomerulonephritis	80 (79.21)	18 (62.07)	.059
Congenital urological anomaly	5 (4.95)	4 (13.79)	.098
Polycystic kidney disease	7 (6.93)	2 (6.90)	.995
Metabolic/diabetic nephropathy	5 (4.95)	1 (3.45)	.734
Pyelonephritis/interstitial nephritis	2 (1.98)	3 (10.34)	.039
Hereditary	1 (0.99)	1 (3.45)	.343
Vascular	1 (0.99)	0 (0)	.591
Treated hypertension, No. (%)	69 (68.3)	20 (70.0)	.947
Body mass index, kg/m^2	24.2 ± 4.3	21.9 ± 3.8	.020
Dialysis duration (range), mo	30 (12-48)	10 (5-20)	< .001
HD vs PD, No. (%)	96 (95.0)/5 (5.0)	26 (89.7)/3 (10.2)	.287
Second warm ischemia time, min	22.8 ± 9.1	22.4 ± 4.9	.819
Previous transplant	4 (3.1)	0	.276
	Donors		
Number of donors (N = 89)	Deceased (n = 60)	Living (n = 29)	
Male donor, No. (%)	48 (80)	9 (31)	< .001
Age, years	39 ± 11	46 ± 10	< .001
Cause of death, No. (%)			
Stroke	29 (48.3)		
Cranial trauma	24 (40.0)		
Polytrauma	3 (5.0)		
Brain tumor	3 (5.0)		
Anoxia	1 (1.7)		
DCD, No. (%)	8 (13.3)		
ECD, No. (%)	7 (11.7)		
Cold ischemia time, h	15.1 ± 4.1	1.22 ± 0.44	< .001

Abbreviations: DCD, donor after cardiac death; ECD, expanded-criteria donor; ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis
Results are shown as mean ± standard deviation (*t* test used for comparison), numbers and percentages (chi-square tests used for comparison), or median and interquartile range (Mann-Whitney *U* test used for comparison).

including standard clinical, instrumental, and laboratory examinations. All recipients and donors were white.

Histologic scoring

Needle (14- to 18-gauge) biopsies were obtained, and tissue was fixed in 10% buffered formalin and embedded in paraffin. A 3- to 4-μm section of preimplant and postreperfusion biopsy tissue was stained for light microscopy with hematoxylin and eosin (3 slides), periodic acid Schiff (3 slides), and Masson trichrome (1 slide). Pathologic examination of sections was carried by 2 renal pathologists (TNN and AVT) according to Banff criteria,[28] as the biopsies arrived. Afterward, all biopsies were rescored by 1 pathologist (AVT) who remained blinded to demographic data and posttransplant course.

The following semiquantitative criteria were applied: (1) Banff criteria for posttransplant biopsies,[28] (2) Banff criteria for preimplant biopsies,[27] (3) Remuzzi criteria,[22] and (4) Cosyns criteria.[17] Individual acute lesions were scored separately for preimplant and postreperfusion biopsies to dissect importance of donor-derived and transplant-derived pathology. For calculation of composite scores, cases in which both preimplant and postreperfusion biopsies were available were classified according to the biopsy with the higher individual scores for acute lesions. For scoring of chronic lesions, we combined findings of both preimplant and postreperfusion biopsies.

Details of grading approach and related scores

For the Banff grading approach, individual acute and chronic lesions in all kidney compartments were evaluated with posttransplant Banff score.[28] Interstitial inflammation (I), tubulitis (T), glomerulitis (G), peritubular capillary capillaritis (PTC), arteritis (V), interstitial fibrosis (IF), tubular atrophy (TA), arteriolar hyalinosis (AH), arteriosclerosis (AS), glomerular basement membrane thickening (BM), and mesangial matrix increase (MM) were scored on a 0 to 3 scale. Glomerulosclerosis (GS) was assessed as a percentage of glomeruli with global sclerosis. Based on the estimation of individual variables, we calculated the chronic posttransplant Banff score as a sum of scores for BM, MM, TA, IF, AS, AH, and GS percentage × 3.[7] We derived acute posttransplant Banff score by adding scores for G, I, T, V, and PTC, and eventually we computed the total posttransplant Banff score.

For Banff criteria for preimplant biopsies, a 4-point scale (0, 1, 2, 3) was used, with evaluation of I score, glomerular thrombi (GT), and acute tubular injury (ATI) among acute lesions and TA, IF, AS, AH, and GS among chronic lesions. The sum of scores for individual variables yielded the composite scores, including the chronic preimplant Banff score (TA, IF, AS, AH, GS percentage × 3), acute preimplant Banff score (I, ATI, GT), and total preimplant Banff score. When scoring GT, true fibrin-containing thrombi, as well as erythrocyte and thrombocyte aggregates, occluding glomeruli capillary lumen were considered. In addition, biopsy specimens were coded for the percentage of changed glomeruli (ie, the sum of globally and segmentally sclerotic glomeruli and those with chronic ischemic glomerulopathy). We also assessed fibrinoid necrosis in glomeruli (FN) using Banff grading for MM. Furthermore, we calculated previously published composite histologic scores, such as donor damage score (DDS),[19] interstitial fibrosis and fibrous thickening score (CIV),[7] chronic allograft damage index (CADI),[18] and chronic damage score (CDS).[20] These scores grade the lesions semiquantitatively based on Banff criteria,[28] although GS is treated as a categorical variable, as described in the original studies.

The criteria of Remuzzi and associates[22] included evaluation of the percentage of global GS, TA, IF, and vascular narrowing, each scored from 0 to 3. The Remuzzi score was calculated by adding GS, TA, IF, and vascular narrowing scores.

For the Cosyns grading approach and scores, acute and chronic changes in all kidney compartments were graded from 1 to 3, using definitions suggested by Cosyns and colleagues.[17] Acute lesions included GT, tubular epithelial cell degeneration, tubular epithelial cell vacuolization (TEV), and edema (E). Chronic lesions included global GS, TA, AS, AH, IF, and I scores. Based on the estimation of individual variables, we calculated acute lesion index as a sum of GT, tubular epithelial cell degeneration, TEV, and E scores and chronic lesion index by adding GS, TA, I, IF, AH, and AS scores. The total score was the sum of acute lesion index and chronic lesion index.

Clinical risk factors and outcomes

Our analysis was performed 60 months after the last transplant in the study population. Donor, graft, and

recipient characteristics (Table 1) and transplant outcomes were extracted from archival patient and outpatient records. Posttransplant data on graft function were limited to type of initial graft function and serum creatinine at discharge, at months 3 and 6, and annually for 5 years until December 2015 or until graft failure/death. These creatinine levels were used to estimate the glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration equation. As intercepts, we used eGFR at discharge from hospital[4] and also eGFR at 6 months, since the highest mean eGFR (59.7 ± 19.4 mL/min/1.73 m^2) was achieved at that point. Slopes in eGFR over periods of discharge to 6 months (mL/min/1.73 m^2/month) and from 6 months to 5 years (mL/min/1.73m^2/year) were calculated by the linear mixed-effects model. Slopes were derived for each patient, having at least 3 eGFR values for each period. We noted patients having a negative eGFR slope from discharge to 6 months. Patients with an eGFR slope from 6 months to 5 years of ≥ -5 mL/min/1.73m^2/year and patients having an eGFR drop of ≥ 25% after 6 months, which indicated progressive loss of kidney function, were also selected.[29] During the follow-up period, 9 deaths with functioning graft occurred and 16 grafts failed. For patients who returned to dialysis, we imputed a GFR of 10 mL/min/1.73 m^2.

We classified initial allograft function as follows: immediate function and impaired function, with SGF representing serum creatinine on day 7 of ≥ 300 μmol/L and DGF showing requirement for dialysis in the first week posttransplant. For linear regression analysis, the initial allograft function was classified as immediate function (0 points), SGF (1 point), or DGF (2 points). Acute rejection (AR) was defined as the need for treatment, with or without biopsy confirmation. Acute rejection was classified as early (0-6 mo) or late (> 6 mo). For linear regression analysis, AR was classified as follows: absence of AR (0 points), AR successfully treated by steroid therapy (1 point), and steroid-resistant AR (2 points).

All recipients received triple maintenance immunosuppressive therapy consisting of calcineurin inhibitor, mycophenolate mofetil, and steroid. Recipients older than 16 years gave informed written consent; for participants under 16 years, parental consent was obtained. This research was approved by the local ethics committee and carried out in accordance with the ethical standards outlined in the Declaration of Helsinki (2013 version) and the Declaration of Istanbul.

Statistical analyses

Normally distributed data are presented as means ± SD, and results were compared with *t* tests. Continuous nonparametric data are expressed as median (interquartile range); for comparison, we used the Mann-Whitney U test and Wilcoxon test where appropriate, and calculated the Spearman correlation coefficient (ρ). Proportions are expressed as percentages, with comparisons made with chi-square test. Predictors of SGF and DGF were assessed with multinomial logistic regression. Binomial logistic regression was applied to show predictors of impaired initial graft function, negative slope from discharge to 6 months, and certain and rapid declines in eGFR after 6 months. The predictors of eGFR at discharge, at 6 months, and at 5 years and predictors of eGFR slopes were evaluated with linear regression. As measures of agreement for histologic lesions between preimplant and postreperfusion biopsies of a single kidney and between histologic lesions in paired kidneys from a single deceased donor, a kappa-statistics and intraclass correlation coefficient were used, where appropriate. All univariate analyses were followed by multivariate ones. All analyses were performed with SPSS (version 19.0; SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P < .05$.

Results

The demographics and clinical characteristics of recipients and donors are shown in Table 1.

Biopsy data (acute lesions)

Table 2 shows the extent and severity of the acute histopathologic lesions in preimplant and postreperfusion biopsies. All acute lesions, except for vasculitis and tubulitis, were present in both deceased-donor and living-donor biopsies. With the exception of interstitial inflammation and FN in living-donor biopsies postreperfusion, all acute lesions were found in both biopsy cores. Acute tubular injury of grades 1 and 2 according to Banff qualifiers were ubiquitous for deceased- and living-donor biopsies. The severity of ATI was significantly higher in deceased-donor kidneys preimplant than in living-donor kidneys ($P = .026$), whereas the difference

was not significant after reperfusion (P = .121). The severity of ATI in postreperfusion biopsies increased compared with preimplant (Table 2), but significance was only shown in deceased donors.

Table 2. Acute Lesions in Kidney Allograft Implant Biopsies

Histologic Lesion	Donor Type	Preimplant Biopsy Mean ± SD	Range	Postreperfusion Biopsy Mean ± SD	Range	*P**
		Banff qualifier				
ATI	L	1.54 ± 0.51	1-2	1.72 ± 0.46	1-2	.225
	D	1.84 ± 0.37	1-2	1.96 ± 0.21	1-2	.012
I	L	0.04 ± 0.20	0-1	0		NA
	D	0.02 ± 0.15	0-1	0.03 ± 0.18	0-1	NA
G	L	0.13 ± 0.45	0-2	0.21 ± 0.54	0-2	NA
	D	0.12 ± 0.42	0-2	0.16 ± 0.43	0-2	.093
GT	L	0.13 ± 0.34	0-1	0.37 ± 0.76	0-3	.109
	D	0.24 ± 0.56	0-3	0.80 ± 0.99	0-3	< .001
PTC	L	0.08 ± 0.28	0-1	0.11 ± 0.32	0-1	NA
	D	0.08 ± 0.27	0-1	0.14 ± 0.35	0-1	.091
FN	L	0.10 ± 0.31	0-1	0		NA
	D	0.05 ± 0.22	0-1	0.04 ± 0.20	0-1	NA
		Cosyns qualifier				
Edema	L	1.21 ± 0.41	1-2	1.33 ± 0.49	1-2	.043
	D	1.14 ± 0.35	1-2	1.26 ± 0.44	1-2	.019
I	L	1.00 ± 0.00	1-1	1.00 ± 0.00	1-1	NA
	D	1.01 ± 0.10	1-2	1.02 ± 0.15	1-2	NA
TED	L	1.17 ± 0.56	1-3	1.33 ± 0.59	1-3	.273
	D	1.35 ± 0.58	1-3	1.56 ± 0.74	1-3	.010
TEV	L	1.04 ± 0.20	1-2	1.16 ± 0.38	1-2	NA
	D	1.05 ± 0.23	1-2	1.06 ± 0.23	1-2	.109
GT	L	1.00 ± 0.00	1-1	1.11 ± 0.46	1-3	NA
	D	1.04 ± 0.21	1-2	1.10 ± 0.33	1-3	.109

Abbreviations: ATI, acute tubular injury; D, deceased; FN, fibrinoid necrosis; G, glomerulitis, GT, glomerular thrombi; I, interstitial inflammation; L, living; NA, not applicable; PTC, peritubular capillary capillaritis; SD, standard deviation; TED, tubular epithelial cell degeneration; TEV, tubular epithelial cell vacuolization

*Wilcoxon test was used for comparison (P < .05 was significant).

Glomeruli thrombi, qualified with Banff criteria, were found in 3 living-donor (12.5%) and 17 deceased-donor (18.5%) biopsies preimplant (P = .490), as well as in 5 (26.3%) and 42 (47.2%) after reperfusion (P = .096). However, when the 2 cores were combined for evaluation, living-donor kidneys were more likely to be free from GT versus deceased-donor kidneys (75.8% vs 56.0%; P = .039). Glomeruli thrombi Banff score increased in postreperfusion biopsies; however, significance was only shown in deceased-donor kidney biopsies.

Tubular epithelial cell degeneration by Cosyns was not significantly higher in deceased donors preimplant but increased significantly in post-reperfusion biopsies in deceased donors. Edema was present in 5 living-donor kidneys (20.8%) and 13 deceased-donor kidneys (14.3%) preimplant. The extent of edema increased in postreperfusion biopsies from both types of kidney donors. For the other acute lesions, we observed no significant differences in frequency and severity between deceased-donor and living-donor kidneys or between preimplant and postreperfusion biopsies.

Fibrinoid necrosis in glomeruli was graded as 1 in 8 preimplant biopsies (6.7%), which included 3 living-donor and 5 deceased-donor kidneys, and in 4 postreperfusion biopsies (3.5%) from deceased-donor kidneys only (P = .274) as postreperfusion biopsy was not available in 4 other patients. Regarding composite score systems, only acute preimplant Banff score was significantly higher in deceased-donor than in living-donor kidneys: 2 ([2-4]; range, 1-5) versus 2 ([2-2]; range, 0-5) (P < .001).

Some acute histologic abnormalities in a single core, when they were graded with the Banff scoring system, correlated between each other. In preimplant biopsies, PTC score was correlated with the I score (ρ = 0.358; P < .01). In postreperfusion biopsies, GT score was correlated with the PTC score (ρ = 0.231; P = .017), PTC score was correlated with the I score (ρ = 0.421; P < .001), and I score was correlated with the G score (ρ = 0.237; P = .014). Acute histologic abnormalities assessed by Cosyns criteria in any core were not correlated between each other.

Deceased-donor status was correlated (P < .01) with ATI preimplant (ρ = 0.287) and postreperfusion (ρ = 0.352). Stroke as a cause of death was correlated with I Banff score (ρ = 0.220; P = .023), whereas status as a donor after cardiac death was correlated with G score in preimplant biopsies (ρ=0.337; P < .001). Donor age was correlated with TEV postreperfusion (ρ = 0.222; P = .021). The agreement between preimplant and postreperfusion biopsies was significant (P < .001) for most of the individual acute lesions graded with Banff approach (presented here as kappa ± SE), including FN (1.000 ± 0.000), I (1.000 ± 0.000), PTC (0.593 ± 0.128), G (0.430 ± 0.125), and GT (0.203 ± 0.059) but not ATI (0.099 ± 0.066; P = .071). The agreement between paired kidneys from a single deceased donor was also significant (P < .01) for most individual acute lesions classified by Banff criteria, including I (0.656 ± 0.319), G (0.538 ± 0.154), ATI (0.537 ± 0.182), PTC (0.417 ± 0.197), and GT (0.370 ± 0.105) but not FN (0.000 ± 0.000; P > .05). The agreement between preimplant and postreperfusion biopsies, as well as between paired kidneys from a single deceased donor, was also significant (P < .001) for all individual acute lesions, as graded by Cosyns approach (data not shown).

Biopsy data (chronic lesions)

Table 3 provides the extent and severity of the chronic histopathologic lesions in kidneys from deceased and living donors. Twenty-two patients (16.9%) had global GS of 1% to 10%, 9 patients (6.9%) had GS of 11% to 19%, and 6 patients (4.6%) had GS of ≥ 20%. A GS of > 10% was more frequent in deceased-donor biopsies (31.0% vs 20.7%; $P = .040$). The vast majority of sclerotic glomeruli showed an obsolescence pattern (data not shown). Glomeruli with segmental sclerosis were found in 13 biopsies (10%), including 2.3% having globally sclerotic glomeruli also present. Chronic ischemic glomerulopathy was observed in 41 biopsies (31.5%), including 15.4% having both globally and segmentally sclerotic glomeruli present. Nine patients (6.9%) had MM increase of grade 1, and 2 patients (1.5%) had grade 2. Thickening of BM was graded as 1 in 7 patients (5.4%). Arteriosclerosis of Banff grade 1 was found in 47 biopsies (36.2%), of grade 2 in 20 biopsies (15.4%), and of grade 3 in 9 biopsies (6.9%). Arteriosclerosis Banff score was significantly higher in deceased-donor kidneys (Table 3). Frequencies of AS > 0 were observed in 12 living-donor biopsies (41.4%) and in 64 deceased-donor biopsies (63.4%; $P = .034$). Arteriolar hyalinosis of Banff grade 1 was shown in 23 biopsies (17.7%), of grade 2 in 20 biopsies (15.4%), and of grade 3 in 10 biopsies (7.7%). Vascular score by Remuzzi was significantly higher in deceased-donor kidneys.

We found IF of Banff grade 1 in 74 biopsies (56.9%) and of grade 2 in 6 biopsies (4.6%), although severity of IF was significantly higher in deceased-donor kidneys (Table 3). Interstitial fibrosis was absent in 58.6% of living-donor versus 32.6% of deceased-donor biopsies ($P = .010$). We observed TA of Banff grade 1 in 103 biopsies (79.2%) and grade 2 in 7 biopsies (5.4%). Among chronic composite scores, CIV, Remuzzi, CADI, DDS, and CDS were significantly higher in deceased-donor kidneys (data not shown).

Chronic lesions in a single kidney were correlated among each other. Arteriosclerosis was correlated ($P < .01$) with AH ($\rho = 0.408$), IF ($\rho = 0.414$), TA ($\rho = 0.462$), percentage of global GS ($\rho = 0.283$), and changed glomeruli ($\rho = 0.335$). Arteriolar hyalinosis was correlated ($P < .01$) with IF ($\rho = 0.323$), TA ($\rho = 0.278$), percentage of global GS ($\rho = 0.304$), and changed glomeruli ($\rho = 0.422$). Interstitial fibrosis and TA were correlated ($P < .01$) with percentage of global GS ($\rho = 0.250$ and $\rho = 0.312$) and changed glomeruli ($\rho = 0.271$ and $\rho = 0.312$). All chronic lesions by Remuzzi and by Cosyns were correlated with each other (data not shown). We found associations between chronic and acute lesions evaluated by Banff criteria in the same kidney: AS was correlated with I score ($\rho = 0.227$; $P < .01$) and GT score ($\rho = 0.199$; $P = .023$). Arteriolar hyalinosis was correlated ($P < .05$) with I score ($\rho = 0.184$) and GT score ($\rho = 0.209$). Percentage of changed glomeruli was correlated only with GT ($\rho = 0.313$; $P < .001$). Interstitial fibrosis was correlated ($P < .05$) with ATI ($\rho = 0.215$) and GT ($\rho = 0.174$). Tubular atrophy and

Table 3. Chronic Lesions in Kidney Allograft Implant Biopsies

	Deceased-Donor Kidney (n = 101)			Living-Donor Kidney (n = 29)			
Histologic Lesion	Score > 0, No. (%)	Mean ± SD	Range	Score > 0, No. (%)	Mean ± SD	Range	*P**
		Banff qualifier					
Global GS, %	31 (30.7)	3.78 ± 7.19	0-38.5	6 (20.7)	1.37 ± 2.90	0-10	.267
Changed glomeruli, %	56 (55.4)	9.58 ± 12.46	0-61.5	11 (37.9)	4.92 ± 7.34	0-25	.091
BM	6 (5.9)	0.06 ± 0.24	0-1	1 (3.4)	0.03 ± 0.19	0-1	.841
MM	8 (7.9)	0.10 ± 0.36	0-2	3 (10.3)	0.10 ± 0.31	0-1	.859
AS	64 (63.4)	0.97 ± 0.94	0-3	12 (41.4)	0.55 ± 0.74	0-2	.042
AH	42 (41.6)	0.76 ± 1.02	0-3	11 (37.9)	0.59 ± 0.91	0-3	.546
IF	70 (69.3)	0.72 ± 0.55	0-2	10 (34.5)	0.45 ± 0.57	0-2	.035
TA	86 (85.1)	0.92 ± 0.44	0-2	24 (82.8)	0.83 ± 0.47	0-2	.487
		Remuzzi qualifier					
GS	31 (30.7)	0.37 ± 0.60	0-2	6 (20.1)	0.21 ± 0.41	0-1	.361
Vascular score	76 (75.2)	1.34 ± 1.04	0-3	17 (58.6)	0.83 ± 0.89	0-3	.021
IF	87 (81.1)	1.00 ± 0.53	0-2	26 (89.7)	0.90 ± 0.49	0-2	.469
TA	88 (87.1)	1.01 ± 0.52	0-2	24 (82.8)	0.90 ± 0.49	0-2	.423
		Cosyns qualifier					
GS	2 (2.0)	1.02 ± 0.14	1-2	0	1.00 ± 0.00	1-1	.872
AH	18 (17.8)	1.26 ± 0.60	1-3	2 (6.9)	1.10 ± 0.41	1-3	.370
AS	32 (31.7)	1.45 ± 0.71	1-3	4 (13.8)	1.17 ± 0.47	1-3	.148
IF	3 (3.0)	1.03 ± 0.17	1-2	0	1.00 ± 0.00	1-1	.811
TA	3 (3.0)	1.03 ± 0.17	1-2	0	1.00 ± 0.00	1-1	.811

Abbreviations: AH, arteriolar hyalinosis; AS, arteriosclerosis; BM, glomerular basement membrane thickening; GS, glomerulosclerosis; IF, interstitial fibrosis; MM, mesangial matrix increase; SD, standard deviation; TA, tubular atrophy

*Mann-Whitney *U* test was used for comparison (significant if $P < .05$).

MM were correlated ($P < .05$) with GT ($\rho = 0.206$ and $\rho = 0.217$). Among donor clinical variables, age was correlated with AH Banff score ($\rho = 0.276$; $P = .001$), percentage of changed glomeruli ($\rho = 0.209$; $P = .017$), and vascular score by Remuzzi criteria ($\rho = 0.291$; $P = .001$). Deceased-donor status correlated ($P < .05$) with AS Banff ($\rho = 0.190$), IF Banff ($\rho = 0.213$), and vascular score by Remuzzi criteria ($\rho = 0.212$; $P = .016$).

The agreement (kappa ± SE) between paired kidneys from the same deceased donor was significant ($P < .001$) for all chronic lesions assessed with Banff criteria, including AH (0.557 ± 0.109), AS (0.518 ± 0.105), IF (0.545 ± 0.124), TA (0.600 ± 0.146), BM (1.000 ± 0.000), and MM (0.380 ± 0.271). The intraclass correlation coefficient was significant for percentage of global GS at 0.459 (95% confidence interval [CI], 0.029-0.703; $P = .020$) and changed glomeruli at 0.638 (95% CI, 0.334-0.804; $P < .001$). The kappa-statistic was significant ($P < .001$) for all chronic lesions graded by Remuzzi and Cosyns approaches between paired kidneys from a single deceased donor (data not shown).

Posttransplant course, graft function, and predictive variables

Acute rejection during follow-up

Acute rejection during follow-up was diagnosed in 20 recipients (19.8%) with deceased-donor grafts and in 2 recipients (6.90%) with living-donor grafts ($P = .102$). Of these, early AR and late AR were diagnosed in 17 and 5 patients, respectively. Occurrence of early AR was independently predicted ($P < .05$) by higher vascular Remuzzi score (odds ratio [OR] = 1.75; 95% CI, 1.05-2.92), Banff AH > 0 (OR = 3.10, 95% CI, 1.07-9.00), and GT Banff in preimplant biopsies (OR = 2.40; 95% CI, 1.07-5.35). Late AR was independently predicted ($P < .05$) by severe AS Banff score (OR = 11.24, 95% CI, 1.61-78.59), IF Banff (OR = 6.34; 95%CI, 1.14-35.23), and I Banff score preimplant (OR = 18.33; 95% CI, 1.28-262.20) and postreperfusion (OR = 67.33; 95% CI, 4.71-963.54).

Graft function at the immediate posttransplant period

Eighteen recipients of deceased-donor grafts (17.8%) and 1 recipient of a living-donor graft (3.45%) experienced DGF ($P = .053$). Twelve recipients of deceased-donor grafts (11.9%) and 1 recipient of a living-donor graft (3.45%) experienced SGF ($P = .182$). In multivariate multinomial logistic regression, longer cold ischemia time (CIT) and higher G score in preimplant biopsies only predicted DGF but not SGF (OR = 1.29; 95% CI, 1.06-1.56; $P = .011$ and OR = 5.57; 95% CI, 1.55-20.10; $P = .009$). Given such inconclusive results and because SGF may represent a continuum with DGF,[3,8] we combined patients with SGF and DGF into 1 group. Among clinical variables, every increase in the category of body mass index and every 6 hours of CIT increased the risk of impaired initial graft function (OR = 1.92; 95% CI, 1.07-3.48; $P = .030$ and OR = 1.77; 95% CI, 1.11-2.83; $P = .017$). Moderate to severe AH assessed by Banff criteria (OR = 3.08; 95% CI, 1.10-8.66; $P = .033$) and every grade of AH by Cosyns grading (OR = 2.34; 95% CI, 1.13-4.85; $P = .022$) predicted impaired initial graft function in multivariate binary logistic regression, whereas effects of any of the composite histologic lesions were not significant.

Graft function at discharge from hospital

Estimated glomerular filtration rate at discharge from hospital varied from 10 to 106 mL/min/1.73 m^2, with rates being significantly ($P = .002$) lower in recipients of deceased-donor kidney than in recipients of living-donor kidney transplants (38.9±16.2 vs 49.7±15.0 mL/min/1.73 m^2). Table 4 presents predictors of eGFR at discharge. Higher recipient age and longer CIT among clinical variables predicted lower eGFR at discharge in multivariate linear analysis. The AS and AH by Banff and by Cosyns criteria, the vascular score by Remuzzi, the percentage of global GS, and the percentage of changed glomeruli were predictive of lower eGFR at discharge after adjustment for clinical variables. Lower eGFR at discharge was independently predicted by such composite histologic scales as chronic and total preimplant and posttransplant Banff, DDS, CDS, chronic lesion index, CADI, Remuzzi, and CIV scores.

Slope in estimated glomerular filtration rate from discharge to 6 months.

Mean monthly slope of eGFR from discharge to month 6 was +3.24 ± 3.58 mL/min/1.73 m^2/month. Only clinical variables, namely, regraft status ($\beta = -0.223$, $t = -2.655$), longer warm ischemia time ($\beta = -0.223$, $t = -2.647$), and serum creatinine at discharge ($\beta = 0.314$, $t = 3.737$) predicted monthly slope of eGFR in multivariate liner regression

($P < .01$). We found that 23 patients (17.7%) exhibited negative slope in eGFR from discharge to month 6. Regraft status (OR = 29.72; 95% CI, 2.18-405.26), serum creatinine at discharge (OR = 0.99; 95% CI, 0.98-1.00), and GT Banff score in preimplant biopsies (OR = 3.30, 95% CI, 1.24-8.82) predicted negative monthly slope in multivariate binary logistic regression ($P < .05$). Composite histologic scores were not predictive of slope in eGFR from discharge to 6 months and did not predict negative slope.

Table 4. Significant Clinical and Histological Predictors of Estimated Glomerular Filtration Rate at Discharge From Hospital

	Linear Regression					
Predictive		Univariate			Multivariate	
Variable	beta	*t*	*P*	beta	*t*	*P*
Recipient age	-0.420	-5.242	< .001	-0.356	-4.021	< .001
Recipient BMI	-0.225	-2.497	.014			
CIT	-0.325	-3.883	< .001	-0.184	-2.082	.040
DCD	-0.213	-2.466	.015			
Cause of donor death	-0.229	-2.667	.009			
Global GS, %	-0.230	-2.669	.009	-0.256	-3.161	.002
Changed glomeruli, %	-0.187	-2.154	.033	-0.188	-2.282	.024
ATI preimplant	-0.199	-2.169	.032			
AH Banff	-0.209	-2.424	.017	-0.207	-2.563	.012
AS Banff	-0.242	-2.824	.006	-0.220	-2.686	.008
Chronic preimplant Banff score	-0.245	-2.855	.005	-0.269	-3.343	.001
Total preimplant Banff score	-0.240	-2.801	.006	-0.266	-3.308	.001
Chronic posttransplant Banff score	-0.241	-2.808	.006	-0.266	-3.299	.001
Total posttransplant Banff score	-0.244	-2.850	.005	-0.266	-3.307	.001
CDS	-0.275	-3.241	.002	-0.263	-3.268	.001
CADI	-0.196	-2.256	.026	-0.207	-2.525	.013
DDS	-0.281	-3.308	.001	-0.287	-3.592	< .001
CIV	-0.235	-2.730	.007	-0.228	-2.795	.006
Vascular score Remuzzi	-0.258	-3.006	.003	-0.252	-3.105	.002
Remuzzi score	-0.215	-2.487	.014	-0.246	-3.062	.003
AH Cosyns	-0.186	-2.137	.034	-0.202	-2.456	.016
AS Cosyns	-0.284	-3.356	.001	-0.246	-3.007	.003
CLI	-0.288	-3.401	.001	-0.262	-3.234	.002

Abbreviations: AH, arteriolar hyalinosis; AS, arteriosclerosis; ATI, acute tubular injury; beta, standardized regression coefficient; BMI, body mass index; CADI, chronic allograft damage index; CDS, chronic damage score; CIT, cold ischemia time; CIV, interstitial fibrosis and fibrous thickening score; CLI, chronic lesion index; DCD, donor after cardiac death; DDS, donor damage score; GS, glomerulosclerosis; *t*, t statistics

Graft function at 6 months

Individual eGFRs at 6 months varied from complete loss of function to hyperfiltration at 124 mL/min/1.73 m^2. Five patients lost their grafts by 6 months, and 2 patients died. Mean eGFR at 6 months was not significantly lower in recipients of deceased-donor grafts versus those with living-donor grafts (57.6 ± 19.9 vs 64.5 ± 19.9 mL/min/1.73 m^2; $P = .111$). Table 5 summarizes predictors of eGFR at 6 months. Higher recipient age, longer warm ischemia time, DGF, and AR within the first 6 months were independent clinical predictors of lower eGFR. Lower eGFR at 6 months was independently predicted by percentage of global GS and chronic and total preimplant and posttransplant Banff scores.

Table 5. Significant Clinical and Histological Predictors of Estimated Glomerular Filtration Rate at 6 Months

	Linear Regression					
Predictive		Univariate			Multivariate	
Variable	beta	*t*	*P*	beta	*t*	*P*
Recipient age	-0.268	-3.063	.003	-0.317	-3.989	< .001
Regraft status	-0.186	-2.088	.003			
CIT	-0.179	-2.003	.047			
WIT	-0.220	-2.482	.014	-0.178	-2.239	.027
DGF	-0.238	-2.691	.008	-0.199	-2.491	.014
Serum creatinine at discharge	-0.240	-2.724	.007			
Early AR	-0.247	-2.803	.006	-0.225	-2.897	.005
Global GS, %	-0.232	-2.622	.010	-0.207	-2.676	.009
ATI preimplant	-0.199	-2.097	.038			
Chronic preimplant Banff score	-0.235	-2.656	.009	-0.202	-2.612	.010
Total preimplant Banff score	-0.233	-2.632	.010	-0.202	-2.609	.010
Chronic posttransplant Banff score	-0.225	-2.539	.012	-0.197	-2.541	.012
Total posttransplant Banff score	-0.227	-2.559	.012	-0.192	-2.474	.015
CDS	-0.181	-2.020	.046			
DDS	-0.198	-2.217	.028			
AS Cosyns	-0.204	-2.290	.024			
CLI	-0.208	-2.334	.021			

Abbreviations: AR, acute rejection; AS, arteriosclerosis; ATI, acute tubular injury; beta, standardized regression coefficient; CDS, chronic damage score; CIT, cold ischemia time; CLI, chronic lesion index; DDS, donor damage score; DGF, delayed graft function; GS, glomerulosclerosis; t, t-statistics; WIT, second warm ischemia time

Slope in estimated glomerular filtration rate (6 months to 5 years)

Mean slope of eGFR from 6 months to 5 years was -1.89 ± 3.84 mL/min/1.73 m^2/year. We found that 23 patients (18.9%) demonstrated improved eGFR, 62 patients (50.8%) exhibited declined eGFR, and 37 patients (30.3%) displayed stable function. Slope was not different between recipients of deceased-donor versus living-donor grafts (-1.90 ± 3.71 vs -1.86 ± 4.33 mL/min/1.73 m^2/year; $P = .960$). Only higher eGFR at 6 months ($\beta = -0.462$, $t = -5.753$) significantly predicted a more negative slope of eGFR in multivariate linear regression ($P < .001$). The individual and composite scores were not predictive of slope of eGFR from 6 months to 5 years. Table 6 provides predictors of certain declines in eGFR from 6 months to 5 years. In our patient group, 44 patients (35.8%) exhibited a decline in eGFR of more than 25%. This 25% loss of

eGFR was predicted by older donor age and longer CIT in multivariate analysis. Severe AS, any AH, and GT in posttransplant biopsies (all scored by Banff approach), chronic and total posttransplant Banff score, and chronic and acute preimplant Banff score significantly predicted 25% loss of eGFR after adjustment for clinical variables. We also found that 19 patients (15.4%) showed decline in eGFR from 6 months to 5 years of more than 5 mL/min/year. Only higher eGFR at 6 months (OR = 1.07; 95% CI, 1.04-1.11; $P < .001$) and FN in glomeruli in preimplant biopsies (OR = 6.38; 95% CI, 1.18-34.37; $P = .031$) predicted rapid decline in eGFR in multivariate analysis. The composite scores were not predictive of rapid decline in eGFR.

Graft function at 5 years

At 5 years, 11 patients had lost their grafts (16 in total) and 11 more patients died (13 in total). Mean eGFR at 5 years was significantly lower in recipients of deceased-donor versus living-donor grafts (47.5 ± 19.8 vs 56.0 ± 19.0 mL/min/1.73 m^2; $P = .042$). Predictors of eGFR at 5 years are outlined in Table 7. Longer CIT, late AR, and lower eGFR at 6 months among clinical variables significantly independently predicted lower eGFR at 5 years. Only higher percentage of changed glomeruli was predictive of lower eGFR at 5 years in multivariate analysis.

Table 6. Significant Clinical and Histological Predictors of Estimated Glomerular Filtration Rate Decline by ≥ 25% After 6 Months

	Logistic Regression					
Predictive		Univariate			Multivariate	
Variable	OR	95% CI	*P*	OR	95% CI	*P*
CIT, every 6 hours	1.45	1.01-2.09	.045	1.63	1.11-2.40	.013
Early AR	2.27	1.04-4.97	.040			
Donor age	1.04	1.00-1.08	.032	1.05	1.01-1.09	.009
GT Banff score postreperfusion	1.84	1.21-2.82	.005	1.74	1.12-2.70	.014
Acute preimplant Banff score	2.15	1.24-3.74	.006	2.12	1.21-3.73	.009
Changed glomeruli, %	1.04	1.00-1.07	.032			
Banff AS, severe	6.55	1.26-33.97	.025	7.10	1.35-37.30	.021
Banff AH, any	2.83	1.33-6.02	.007	2.68	1.27-5.66	.010
Chronic posttransplant Banff score	1.67	1.09-2.55	.018	1.67	1.09-2.55	.018
Total posttransplant Banff score	1.67	1.10-2.54	.017	1.67	1.10-2.54	.017
Chronic preimplant Banff score	1.69	1.08-2.64	.021	1.69	1.08-2.64	.021
Total preimplant Banff score	1.55	1.03-2.33	.035			
DDS	1.82	1.03-3.22	.040			

Abbreviations: AH, arteriolar hyalinosis; AR, acute rejection; AS, arteriosclerosis; CI, confidence interval; CIT, cold ischemia time; DDS, donor damage score; GT, glomeruli thrombi; OR, odds ratio

Table 7. Significant Clinical and Histologic Predictors of Estimated Glomerular Filtration Rate at 5 Years

	Linear Regression					
Predictive		Univariate			Multivariate	
Variable	beta	*t*	*P*	beta	*t*	*P*
Deceased donor	-0.178	-2.051	.042			
Cause of death	-0.188	-2.160	.033			
Recipient age	-0.219	-2.544	.012			
Regraft status	-0.274	-3.218	.002			
CIT	-0.272	-3.204	.002	-0.177	-2.308	.023
DGF	-0.173	-1.993	.048			
Early AR	-0.300	-3.555	.001			
Late AR	-0.259	-3.029	.003	-0.214	-2.837	.005
eGFR at discharge	0.236	2.745	.007			
eGFR at 6 months	0.499	6.326	<.001	0.464	6.068	<.001
Global GS, %	-0.246	-2.872	.005			
Changed glomeruli, %	-0.275	-3.241	.002	-0.218	-2.879	.005
I Banff score	-0.235	-2.740	.007			
AS Banff	-0.230	-2.672	.009			
AH Banff	-0.239	-2.785	.006			
Vascular Remuzzi score	-0.197	-2.268	.025			
I Cosyns score	-0.252	-2.945	.004			

Abbreviations: AH, arteriolar hyalinosis; AR, acute rejection; AS, arteriosclerosis; beta, standardized regression coefficient; CIT, cold ischemia time; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; GS, glomerulosclerosis; I, interstitial inflammation; t, t-statistics

Discussion

There is a strong medical rationale to assist clinicians with the prognostic significance of histopathologic findings in implant biopsies regarding kidney allograft function, which is an important surrogate for allograft survival.[2-5] We evaluated associations between 8 previously published composite histopathologic scoring algorithms and their acute and chronic components and individual lesions and allograft function and changes in graft function early and late posttransplant. We found a variety of acute lesions in both living- and deceased-donor kidneys, including severe ones like FN and GT. Because different acute lesions were often found together and their severity correlated between each other, we suggest that these represent significant pathologies related to death in deceased donors[15-17] and are associated with IRI and with diseases in both type of donors.[15,17,24,30-32] Deceased donations were associated with higher ATI and GT Banff scores and higher acute preimplant Banff score. In addition, ATI, GT, and E scores were significantly increased in postreperfusion biopsies, underscoring the importance of IRI, as described previously.[32]

Glomerular thrombi have been found in pretransplant kidney biopsies from deceased donors in case studies[30,31,33] and in several cohort studies,[17,34,35] although the reported frequency was not more than 9.9%. However, we observed unexpectedly high

frequency of GT in deceased-donor kidneys (18.5% preimplant) as well as their presence in living-donor kidneys. This can be due to several reasons. First, most of the donors in our cohort were brain dead, and activation of coagulation during brain death often results in microthrombi formation within the renal vasculature, as reported in the literature.[30,35] Furthermore, 40% of our deceased donors died from cranial trauma, a condition that often provokes disseminated intravascular coagulation.[30] Second, GTs were scored as a percentage of capillaries occluded in the most severely affected glomerulus, whereas earlier studies[34,35] evaluated percentage of glomeruli with GT, which cannot adequately capture the extent of pathology (as suggested by Sood and associates[36]). Third, we considered GT as not only fibrin-containing thrombi but also erythrocyte and thrombocyte aggregates, occluding capillary lumen, which more probably represented glomerular congestion, associated with endothelial damage during perfusion.[16]

Fibrinoid necrosis in glomeruli was a rare finding in deceased and living donors from our cohort. Fibrinoid necrosis in glomeruli is not often reported for baseline biopsies; however, some authors have previously found FN[16] and fibrin deposits[17] in glomeruli and extraglomerular vessels[13] in deceased-donor kidneys. One study described glomerular capillary loop necrosis in 2.5% of postreperfusion biopsies from living-donor kidney grafts.[37] Reported frequencies of immunoglobulin A nephropathy, which can present with GT and FN[38] among asymptomatic kidney donors, fluctuate from 3.1% to 10%.[15,17,24] Apart from immunoglobulin A nephropathy, a wide spectrum of preexisting glomerular diseases has been reported in donor kidneys,[39] which can present in baseline biopsies with acute lesions. Chronic vascular pathology can also promote development of acute lesions in donor kidneys, which was shown previously for FN.[13]

Regarding predictive performance of acute lesions, we report here for the first time the significant negative impact of GT on the dynamics of kidney graft function early and late after transplant. Every point increase of GT Banff score in preimplant biopsies increased the risk of a negative monthly slope from discharge to 6 months by 3.3 times. Only one previous study[5] has examined predictive variables for eGFR slope early posttransplant, although only the effects of chronic lesions were shown. Every point increase of GT Banff score in postreperfusion biopsies increased the risk of a certain drop in eGFR from 6 months to 5 years by 1.7 times. Acute preimplant Banff score also predicted certain declines in eGFR from 6 months to 5 years, which was most likely due to presence of a GT component. Fibrinoid necrosis in glomeruli in preimplant biopsies was the only acute lesion associated with a 6-fold risk of rapid decline in graft function from 6 months to 5 years. These findings are of importance because both certain and rapid declines in GFR indicate a risk of end-stage renal disease.[29] Our data also imply that GT and FN in glomeruli of donor kidneys have no direct effects on graft function because their impact begins to be visible only from discharge. Absence of immediate effects might be attributed to low grades of GT and FN in most patients or their resolution.[31,34,36] On the other hand, GT and FN in some patients can trigger rejection, which was shown earlier by Takeda and associates,[33] or other long-lasting pathological processes.

Indeed, because GT preimplant predicted early AR in our cohort, this can explain the impact of GT on eGFR slopes early and late posttransplant. The higher risk of a negative slope after retransplant, which implies sensitization, also highlights the importance of AR. In addition, GT itself can evolve with time into chronic glomerular lesions,[40] or their effects can combine with other deleterious factors, eventually leading to chronic glomerular injury and graft dysfunction. In this context, it would be appropriate to remind that, in our study, GT correlated with glomerular, vascular, and tubulointerstitial lesions already at the time of transplant, some of which (AS and AH) exhibited independent associations with decline in eGFR late posttransplant. Several authors have shown declines in GFR late posttransplant and reduced survival only when chronic lesions in biopsies (interstitial fibrosis) were associated with acute lesions (interstitial inflammation).[41]

Our findings can complete and widen the concept of Halloran and associates, applying to implant biopsies, in which progression of kidney transplant dysfunction can be explained only as a consequence of ongoing disease or injury and/or an inability to restore the damaged tissue.[42] In terms of the concept of Halloran and associates, GT and FN can represent ongoing disease and/or the elements of the injury-repair response to donation and implant stresses.

Our data confirm the importance of scoring GT[26,27] and FN, since these allowed predicting unfavorable patterns of evolution in graft function. Current results also imply that kidneys with GT or FN at procurement should be used with caution and that their recipients require closer monitoring. These findings indirectly indicate that suppression or elimination of factors that promote GT formation and enhancement of mechanisms that remove them might be important to protect kidney graft function. Glomerulitis in preimplant biopsies predicted DGF. A possible explanation for this is the ability of intragraft passenger leukocytes to predispose to AR,[43] which can manifest as DGF.[32] If this is the case, the presence of glomerulitis in preimplant biopsies may help to differentiate potential causes of DGF. Here, we show for the first time that glomerulitis in donor kidney can affect the immediate graft function. However, in earlier studies, authors used different definitions for glomerulitis.[44] Although G score is absent in Banff schemas for preimplant biopsies, some authors, including ourselves, have suggested that this factor should be included.[26]

Although over 80% of donors in our cohort were standard-criteria deceased and living donors, chronic lesions were absent in only 10.9% of deceased-donor kidney and in 10.3% of living-donor kidney biopsies. These numbers are significantly lower than those reported by other authors for deceased donors (37%[18]) and living donors (from 38.4% to 51.4%[24,25]). The frequencies of TA, IF, AS, and AH in our donors were also higher than reported for deceased[9,15,18,20] and living donors.[24,25] However, our donor cohort represented a population with high cardiovascular risk.[45] We found that 6.9% and 7.7% of biopsies of our donors displayed severe AS and AH, respectively. Moreover, we observed the strongest correlations between chronic vascular lesions and all other lesions. The importance of vascular lesions was supported by obsolescence pattern of GS and by high prevalence and extent of chronic ischemic glomerulopathy. Thus, we consider chronic intrarenal vascular lesions as a main determinant of chronic glomerular and tubulo-interstitial lesions in kidneys, which is supported by the literature.[46]

Although severity and frequencies of AS and IF, as well as most of the chronic composite scores, were significantly higher in deceased-donor biopsies, they were also frequently shown in living-donor biopsies, which is characteristic for populations with high cardiovascular risk.[13,25] In our study, AS and AH demonstrated significant effects on early graft function. In particular, AH by Banff and Cosyns predicted impaired initial graft function; AH and AS by Banff and Cosyns and vascular score by Remuzzi predicted lower function at discharge. We believe that reduction of kidney interstitial blood flow due to moderate to severe AH and AS can significantly disturb the resistance of tubular epithelium to IRI and its potential to regenerate, which is supported by the literature.[47] In agreement with our findings, other authors[48] also found that mild AH did not affect graft function. We did not find reports on the association of donor kidney histologic lesions, including chronic vasculopathy, with such surrogate endpoint as graft function at discharge. In our study, donor-derived AH and AS predicted certain decreases in graft function after 6 months. Among possible causes, we suggest the influence of injurious risk factors accumulating with time posttransplant, which became deleterious in kidneys with low functional reserve and donor-derived pathology. Woestenburg and associates[5] showed that moderate to severe allograft arteriopathy was associated with a declining eGFR during the first 15 months. In agreement with our results, several groups failed to show association of donor-derived vascular lesions and allograft function at different times during the late posttransplant period.[10,16,24] However, we did not find reports on association of donor chronic vasculopathy with GFR slope late posttransplant.

In our cohort, GS, which is a common pathway for the development of end-stage renal failure regardless of cause, independently affected eGFR at discharge and at 6 months. Our results confirm earlier published data on the association of donor GS with worse graft function in the early posttransplant period.[9,24,27] Similar to our results, other authors[10] did not observe independent associations of global GS with graft function late posttransplant. Although percentage of global GS did not affect eGFR after 1 year, percentage of changed glomeruli predicted lower eGFR at 5 years and was also not independently associated with certain decreases in eGFR after 6 months. The idea to score percentage of changed glomeruli was related to suspected vascular origin of glomerular lesions, as vascular sclerosis can induce a variety of chronic glomerular lesions, including ischemic lesions and focal and global

glomerulosclerosis.[46] The ability of a fraction of changed glomeruli versus global GS to predict graft function in the later posttransplant period seems logical since segmental sclerosis and chronic ischemic glomerulopathy can evolve during follow-up into global GS, eventually leading to declined renal function late posttransplant. A low functional kidney reserve with ischemic and segmental lesions in glomeruli can also make such kidneys more vulnerable to posttransplant insults. Therefore, it seems valuable to count, in addition to global GS, segmentally sclerotic glomeruli and glomeruli with chronic ischemic glomerulopathy, especially since this is in line with a recent proposal for standardized grading of chronic changes in native kidney biopsy specimens.[49]

None of the composite scores predicted DGF or SGF, in agreement with earlier studies regarding the predictive performance of Remuzzi,[8] CADI,[21] CDS,[20] and Maryland aggregate pathology index scores.[8] Associations between individual chronic glomerular and vascular lesions in our cohort and graft function at discharge translated to significant prediction of lower function at discharge by all higher chronic and total scores. Only CADI score in baseline biopsies was reported previously to correlate with higher creatinine at discharge.[21] Thus, our findings significantly expand views on predictors of GFR at discharge, which itself is a surrogate for late transplant outcomes.[4]

We observed that only chronic and total preimplant and posttransplant Banff scores were predictive of lower 6-month graft function. Previously, only a positive correlation between CADI in donor kidneys and higher creatinine at 6 months was reported.[21] We also established that only chronic and total posttransplant, as well as chronic and acute preimplant Banff scores, predicted certain declines in eGFR from 6 months to 5 year. The association between composite scores and dynamics of GFR is only shown in 1 previous study,[5] which showed that the global Banff score of chronicity was associated with a steeper decline in eGFR over time. None of composite scores in our study predicted a rapid decline in eGFR from 6 months to 5 years or in eGFR at 5 years. Other authors also failed to show the association between histologic scores and graft function late posttransplant.[17] Our results show that individual glomerular and vascular lesions are better than integral scores in predicting function because they allowed predicting more outcomes, although several groups disagree with this conclusion.[19,20]

Our results allowed us to make some considerations regarding practice of implant biopsies. First, because a deceased-donor status was not predictive of any outcome in our study and donor age was associated with only a certain drop in eGFR after 6 months, we believe that, in populations with high cardiovascular risk, implant biopsies are relevant for kidneys from both living donors and deceased donors and of all ages, as previously supported.[39] Second, because the agreement between paired kidneys from a single deceased donor was moderate for G score, fair for GT, and poor for FN in glomeruli, MM increase, and percentage of global GS, we suggest that both kidneys from deceased donors require evaluation, as previously suggested.[19] Third, when we take into account that agreements between preimplant and postreperfusion cores from the same kidney were moderate for glomerulitis (kappa = 0.41-0.60) and fair for GT (kappa = 0.21-0.40) and there was an unequal impact of glomerulitis and GT in preimplant and postreperfusion biopsies on outcomes, we believe that both cores from a single kidney should be taken.

We found discrepancies between our data and the literature regarding predictive performance of individual and composite lesions for early and late kidney allograft function. Contrary to our results, some authors reported association between GS,[20,27] AS,[7,20] AH,[9] IF,[7] and composite CADI score[18] and DGF. Glomerulosclerosis,[27] AS,[14] and IF[12] were also reported to predict SGF. Several earlier studies reported an association between ATI and impaired initial function[12,14] or worse function at 6 months.[12] Others have reported associations between GT and DGF[30,33,35] and suboptimal function late posttransplant.[30] Several groups reported associations between GS,[18,25] vascular lesions[9,11-13,18] and higher DDS,[19] Remuzzi score,[8] and CADI[18,21] and late graft function. Such discrepancies can be attributed to the different donor cohorts, use of wedge or needle biopsies, timing of biopsy, and different methodologies in assessing lesions. Finally, different definitions for DGF and SGF and different methodologies for assessment of graft function were applied, and some results were not corrected for covariates, together making comparisons of the reported results difficult.

Our finding has several other clinical implications. In addition to unfavorable baseline histology, our study highlighted clinical risk factors of worse posttransplant function such as obese recipients, older recipient age, longer CIT and warm ischemia time, and regraft status. When we consider the evidences for synergy between clinical risk factors and histologic lesions,[7] we suggest that, in the settings of older or obese recipients, retransplant, older deceased donors, and long CIT, implant biopsies could be of special use. Because AR represents an additional risk factor for lower function at 6 months and at 5 years, minimization of immunosuppression might not be recommended for recipients of kidneys with significant histologic lesions, which of course needs further investigation. Moreover, as far as the presence of AH predisposes to development of arteriolopathy associated with calcineurin inhibitors,[11,50] management of immunosuppression based on presence of AH in implant biopsy might be recommended. Recipients of grafts with moderate to severe vasculopathy may require aggressive blood pressure control to ensure an optimal preservation of graft function.

The present study has several weaknesses. It was a single-center retrospective study carried out on a small group of patients from a population with high cardiovascular risk. However, it should be mentioned that there was also a reported tendency for moderate and severe arteriosclerosis in those with low to moderate cardiovascular risk. The limited number of cases and rarity of some pathologies did not allow us to validate results internally. Hence, it would be desirable to evaluate their reproducibility on a larger-scale external cohort from populations with low to moderate cardiovascular risk. For many of the deceased donors, anamnestic and laboratory data were not available. Consequently, having complete data could have refined some results. In addition, low limits for biopsy adequacy chosen should be mentioned, which raised the question of sampling error.

Conclusions

A high frequency of chronic and acute histologic lesions in donor kidneys is characteristic of a donor population with high cardiovascular risk. In our study, the prognostic implication of specific chronic and acute histologic changes in intraoperative kidney transplant biopsies was expanded to the late post-transplant period and associated with unfavorable patterns of change in graft function. Because of the modest agreement in histologic scores between the 2 cores from a single kidney, as well as between paired kidneys from a single deceased donor, and because sometimes only lesions in 1 of 2 cores correlated with outcomes, we argue in favor of taking both preimplant and postreperfusion biopsies from every transplanted kidney. The Banff qualifier appeared superior to the Remuzzi and Cosyns criteria in assessment of lesions because it revealed more associations of individual lesions with each other and with clinical data and also allowed more outcomes to be predicted.

Vascular and glomerular lesions were the primary determinants of lower kidney graft function early and late posttransplant. Glomerulosclerosis, AS, and AH were the most important chronic lesions, whereas glomerular lesions (G, GT, and FN) were the most important acute lesions. Glomerulitis in preimplant biopsies predicted DGF. Arteriolar hyalinosis Banff score predicted impaired initial graft function, lower eGFR at discharge, and a certain drop in eGFR after 6 months. Arteriosclerosis Banff score predicted lower eGFR at discharge and a certain drop in eGFR after 6 months. Percentage of global glomerulosclerosis predicted lower eGFR at discharge and at 6 months, whereas percentage of changed glomeruli predicted lower eGFR at discharge and at 5 years. Acute severe glomerular lesions better predicted changes in graft function than function at fixed times. More precisely, GT predicted lower positive and even negative slope in eGFR from discharge to 6 months and a certain decline in eGFR after 6 months, whereas FN predicted rapid loss of function after 6 months. Predictive performance of composite scores appeared inferior compared with individual lesions since not all outcomes were associated with higher composite scores, although chronic and total preimplant and posttransplant Banff scores independently predicted lower eGFR at discharge and at 6 months and 25% loss of eGFR after 6 months.

We infer from the results that intraoperative biopsies are important in identifying patients at high risk for worse graft function, especially regarding absence of gain of function early posttransplant and loss of function late posttransplant; these patient might benefit from close monitoring and early therapeutic interventions.

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