Assessment of the Utility of Kidney Histology as a Basis for Discarding Organs in the United States: A Comparison of International Transplant Practices and Outcomes

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ABSTRACT

Background Many kidneys donated for transplant in the United States are discarded because of abnormal histology. Whether histology adds incremental value beyond usual donor attributes in assessing allograft quality is unknown.

Methods This population-based study included patients who received a deceased donor kidney that had been biopsied before implantation according to a prespecified protocol in France and Belgium, where preimplantation biopsy findings are generally not used for decision making in the allocation process. We also studied kidneys that had been acquired from deceased United States donors for transplantation that were biopsied during allocation and discarded because of low organ quality. Using donor and recipient characteristics, we fit multivariable Cox models for death-censored graft failure and examined whether predictive accuracy (C index) improved after adding donor histology. We matched the discarded United States kidneys to similar kidneys transplanted in Europe and calculated predicted allograft survival.

Results In the development cohort of 1629 kidney recipients at two French centers, adding donor histology to the model did not significantly improve prediction of long-term allograft failure. Analyses using an external validation cohort from two Belgian centers confirmed the lack of improved accuracy from adding histology. About 45% of 1103 United States kidneys discarded because of histologic findings could be accurately matched to very similar kidneys that had been transplanted in France; these discarded kidneys would be expected to have allograft survival of 93.1% at 1 year, 80.7% at 5 years, and 68.9% at 10 years.

Conclusions In this multicenter study, donor kidney histology assessment during allocation did not provide substantial incremental value in ascertaining organ quality. Many kidneys discarded on the basis of biopsy findings would likely benefit United States patients who are wait listed.

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Nearly 95,000 patients are waiting for a kidney transplant in the United States, but only 14,725 deceased donor transplants were performed in the year 2018.[1] Despite the scarcity of organs, thousands of deceased donor kidneys are discarded each year in the United States.[2–4] The White House introduced in 2019 the Advancing American Kidney Health initiative, and advocacy groups, such as the National Kidney Foundation, have invested major efforts in reducing organ discard and setting

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aggressive goals to improve access to kidney transplantation in the United States.[2,5] These initiatives treat the need to increase the number of kidneys for transplant as a major public health priority.

One of the leading reasons for kidney discard by United States centers is the use of biopsies in the decision-making process due to concern about renal pathology findings, such as glomerulosclerosis, fibrosis, and arteriosclerosis, often found in older donors or those with comorbidities.[6] In a study spanning the years 2000–2015, biopsy findings were cited for 38.2% of United States kidney discards.[4] However, growing evidence suggests that many discarded kidneys could instead be transplanted and provide substantial health benefits to patients with ESKD.[7,8]

Unfortunately, biopsies performed during allocation may not provide accurate guidance about how these kidneys would function after transplant because the biopsy tissue may be interpreted under time pressure by pathologists without specific expertise in renal pathology.[9] Yet, convincing transplant professionals to forego allocation biopsies may be difficult without showing that judgments about organ quality will not be improved by taking into account information about renal histology.

Prior studies suggest that the reproducibility of procurement biopsy findings is poor, there is wide geographic variation in the United States about which kidneys get a biopsy, and transplant centers collectively have no systematic approach to integrating the biopsy results into decision making.[9,10] Kasiske *et al.*[6] examined biopsy reports from discarded kidneys in which the contralateral kidney was transplanted and reported that glomerulosclerosis >20% was the main pathologic feature predictive of discard. When repeat biopsies were performed on the same kidneys, there were often substantial differences in the results.[6] In contrast, Cockfield *et al.*[11] examined 730 implantation biopsies and proposed that vascular abnormalities, including arteriolar hyalinosis but not glomerulosclerosis, were most predictive of graft failure outcomes. Other groups have developed prognostic scoring systems, such as the Maryland Aggregate Pathology Index, that rely on detailed measurements from multiple anatomic compartments of the kidney.[12,13] Taken together, these results and others reveal substantial debate about whether and what features of renal biopsy ought to influence allograft acceptance decisions.[14,15]

Our group recently demonstrated that United States transplant centers commonly discard kidneys that would have been transplanted in Europe, particularly kidneys from older donors and those with comorbidities.[7] In addition, that study showed that the kidneys discarded in France came from much older donors than those in the United States (61.58 versus 52.15 years) and had a higher kidney donor risk index (KDRI) than kidneys discarded in the United States (2.03 versus 1.83). One key difference in allocation between countries is that approximately half of United States deceased donor kidneys undergo allocation biopsy, and centers often cite those results as the rationale for refusing that kidney.[4] In contrast, kidneys are rarely biopsied in the process of allocating kidneys in France, Belgium, and other European transplant systems.[16] Some European centers routinely perform preimplantation allograft biopsies in kidneys after organ acceptance, so that biopsy results do not interfere with the decision-making process of organ acceptance. This standard practice of preimplantation kidney biopsy that is unrelated to organ acceptance decisions provides a robust and unprecedented opportunity to examine the range of pathologic abnormalities and the clinical relevance of histologic lesions to post-transplant outcomes.

The primary aim of this study was to determine whether pretransplant biopsy results improve the prediction of allograft survival over routinely collected donor characteristics. The second aim was to estimate post-transplant outcomes for United States kidneys that were biopsied and discarded by matching those kidneys to very similar allografts that were transplanted at centers in Europe.

Significance Statement

Many kidneys donated for transplantation are discarded because of abnormal histology, but it is unknown whether preimplantation kidney biopsies that are routinely performed in the United States add incremental value beyond usual donor attributes in predicting allograft survival. The investigators analyzed detailed data from transplant centers in France and Belgium, where pretransplant biopsies are prospectively performed as standard practice but do not guide decision making for organ allocation. They found that transplant histology did not improve the prediction of allograft failure beyond a robust baseline set of donor and recipient characteristics. They also studied donor kidneys from deceased United States donors—specifically, organs discarded because of abnormal histology—and matched them with similar kidneys transplanted in Europe. The matched kidneys had acceptable allograft survival, illustrating lost transplant opportunities in the United States.

METHODS

Study Population

European Cohorts

The derivation cohort consisted of 1629 patients over 18 years of age who were prospectively enrolled at the time of kidney transplantation from a deceased donor at Necker Hospital (n=920) and Saint-Louis Hospital (n=709) in France between January 1, 2004 and January 1, 2014.

We excluded patients receiving kidneys from living donors (n=494) as well as deceased donor kidneys with biopsy performed but inadequate for full pathologic interpretation according to the international Banff classification (n=214). All data were anonymized and prospectively entered at transplantation; at 3 months, 6 months, and 1 year post-transplant; and at each transplant anniversary using a standardized protocol to ensure harmonization across the two study centers. Data from the derivation cohort were submitted for an annual audit to ensure data quality. Data were retrieved from the database on

January 1, 2019. All patients provided written informed consent at the time of transplantation.

An external validation was conducted using a cohort of 1107 recipients of deceased donor kidney transplants at the University Hospitals of Leuven (n=951) and Liege (n=156), Belgium, between January 1, 2004 and December 31, 2013 with preimplantation biopsy evaluation. Datasets from the validation centers were collected as part of routine clinical practice, entered in the centers' databases in compliance with local and national regulatory requirements, and sent anonymized to the Paris Transplant Group. Data were retrieved from the database March 1, 2019.

In France, the transplantation allocation system followed the rules of the French National Agency for Organ Procurement (Agence de la Biomédecine; https://www.agence-biomedecine.fr). Centers from Belgium followed the rules of the Eurotransplant allocation system (https://www.eurotransplant.org/cms/).

Kidneys Discarded in the US on the Basis of Histology Results

This cohort consisted of deceased donor kidneys that were recovered for transplantation, biopsied as part of the kidney allocation process, and then discarded because of low organ quality due by "biopsy findings" between 2015 and 2016 (n=1103). Data were obtained from the Organ Procurement and Transplantation Network (OPTN).[17] The OPTN data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, as submitted by the members of OPTN. The Health Resources and Services Administration of the US Department of Health and Human Services oversees the activities of the OPTN contractor. Donor data are collected and entered into the dataset by organ procurement organizations and then reported to OPTN.

Outcomes

The primary outcome was the additional predictive value of kidney histology over routinely collected donor characteristics to predict allograft failure as measured by change in the Harrell concordance index (C index) in models with and without histologic characteristics. The secondary outcome was predicted post-transplant outcomes for United States kidneys that were biopsied and discarded by matching those kidneys to very similar allografts that were transplanted at centers in Europe.

Procedures and Clinical Protocols

The following parameters were collected in the derivation cohort: (*1*) donor characteristics, including age at donation, sex, body mass index, renal function, donor history of hypertension, donor history of diabetes, donor cause of death, donor serum creatinine at donation, donor hepatitis C virus (HCV) serostatus, donation after circulatory death status, and extended criteria donor status (defined conventionally as age ≥60 years or age 50–59 years plus two or more of the following: hypertension, death from stroke, or terminal creatinine >1.5 mg/dl); (*2*) recipient characteristics at the time of transplantation, including age, sex, and prior transplant; (*3*) HLA mismatch (A, B, DR); and (*4*) the presence of circulating anti-HLA donor-specific antibodies (DSAs) at the time of transplantation assessed for all patients at the Jean Dausset Histocompatibility Laboratory.

Kidney Allograft Biopsy Protocol Performed at the Time of Transplantation

All deceased donor kidneys underwent preimplantation biopsies (referred to as "day 0") according to a prespecified protocol in the derivation cohort. These biopsies were performed by surgeons using a 16-gauge device in the operating suite after a definitive decision was made to accept the kidney for transplantation. The tissue was immediately fixed in an alcohol-formalin-acetic acid solution and subsequently embedded in paraffin. The biopsy sections (4 μm) were stained with periodic acid–Schiff, Masson trichrome, and hematoxylin and eosin. Using the international Banff criteria, trained renal pathologists graded the graft biopsies using the following criteria: glomeruli number, number of sclerotic glomeruli, arteriosclerosis (vascular fibrous intimal thickening—cv Banff score), arterial hyalinosis (ah Banff score), and interstitial fibrosis and tubular atrophy (IFTA). For each criterion, single Banff scores (not ranges) were provided.[18]

KDRI Calculation

The KDRI score was calculated on the basis of the following donor parameters: age, height, weight, history of hypertension, history of diabetes, cause of death (cerebral stroke), serum creatinine at donation, HCV serostatus, and donation after circulatory death status.[19] Notably, race/ethnicity for organ donors is not recorded in accordance with national French bioethics regulations. As a result, we entered "non-Black" for all French donors when calculating KDRI. The KDRI score for any kidney allograft estimates the risk of failure compared with a kidney from a reference donor defined as 40 years old, non-Black, and 170-cm tall weighing 80 kg with a creatinine level of 1 mg/dl, as well as negative history of hypertension, diabetes, and hepatitis C.

Statistical Analyses

Continuous variables were described using means and SDs or median and the interquartile range. We compared means and proportions between groups using the t test, ANOVA, or the chi-squared test (or the Fisher exact test if appropriate).

Predictive Models for Allograft Survival at the Time of Transplantation

The goal of this analysis was to determine whether day 0 deceased donor biopsy findings improve the prediction of allograft survival among kidney transplant recipients at two French centers. The analysis was performed from the time of transplantation with kidney graft loss as the event of interest, defined as the patient's return to dialysis or

retransplantation. For patients who died with a functioning graft, graft survival was censored at death.[20] Cox proportional hazards models were applied to quantify the hazard ratios (HRs) and the 95% confidence intervals (95% CIs) for kidney graft loss. The associations of donor and recipient baseline characteristics, transplant parameters, and immunologic factors with graft loss were first assessed in univariate regression analyses. All variables identified in these analyses with a *P* value of 0.10 were then entered in the initial multivariable model. A process of backward selection was then used to select variables for the final multivariable model. Internal validation of the final multivariable model was confirmed using a bootstrap procedure, which involved generating 1000 datasets derived from resampling the original dataset and permitted the estimation of the biased corrected 95% CI and the accelerated bootstrap HR.[21]

The discrimination ability of the final multivariable model was compared with the model with the addition of the day 0 biopsy results using the C index. We performed complete case analyses.

External Validation

The same analysis was independently replicated among kidney transplant recipients at two Belgian centers in order to assess whether the results obtained in France manifested similarly in Belgium. In this external validation cohort, the same donor and recipient baseline characteristic, transplant parameters, immunologic factors, and day 0 histologic factors were investigated.

Procedures for Matching United States Discarded Kidneys to Kidneys Transplanted in Europe

Using OPTN/United Network for Organ Sharing data, we identified donor kidneys that were classified as discarded due to "biopsy findings" in the United States from the years 2015 to 2016. We used 1:1 optimal matching without replacement to generate highly similar matched pairs of kidneys discarded in the United States to kidneys transplanted in France.[22] We used an iterative approach to reduce the distance between matched pairs. First, a propensity score model was generated using KDRI and biopsy findings of glomerulosclerosis, arteriosclerosis, and IFTA. Next, a Mahalanobis distance matrix was constructed using both the propensity score and the covariates included in the propensity score model, and the caliper was set at 20% of standardized difference of the logit of propensity score.[23] We then applied penalties to the distance matrix to prioritize the algorithm for finding optimal matches in the following order: KDRI, glomerulosclerosis, IFTA, and arteriosclerosis. Finally, we used near-exact matching for glomerulosclerosis and near-fine balance for IFTA and arteriosclerosis.[24] A postmatch standardized difference <0.1 was considered satisfactory balance between covariates.[25,26] R package "designmatch" was used to perform optimal matching, and covariate balance was assessed using R package "cobalt."[27,28]

All analyses were performed using R (version 3.2.1; R Foundation for Statistical Computing, Vienna, Austria) and Stata (Version 14.0; College Station, TX). Values of $P<0.05$ were considered significant, and all tests were two tailed (Supplemental Material).

RESULTS

Donor and Recipient Characteristics in the Derivation Cohort

In the derivation cohort, the mean donor age was 52.60 ± 16.68 years. A total of 958 (58.81%) donors were men, and 911 (55.92%) had died of cerebrovascular causes. A total of 473 (29.80%) donors presented with hypertension, and 126 (8.02%) donors had diabetes mellitus. The mean KDRI was 1.54 ± 0.64. A total of 224 (13.75%) biopsies displayed >20% glomerulosclerosis, 92 (5.65%) presented with a score of IFTA (IFTA Banff score) greater than or equal to two, 546 (33.52%) had an arteriosclerosis score (cv Banff score) greater than or equal to two, and 322 (19.83%) had an arteriolar hyalinosis score (ah Banff score) greater than or equal to two. Among the 1629 kidney transplant recipients from the derivation cohort, the mean recipient age was 51.40 ± 13.21 years, and 966 (59.30%) were men. A total of 283 (17.37%) had received a prior kidney transplant. The median follow-up after transplantation was 6.79 years (interquartile range, 4.38–9.43). Table 1 presents the donor and recipient characteristics and the protocol day 0 biopsy results of the derivation cohort.

Value of Day 0 Allograft Histology in Predicting Kidney Allograft Loss in the Derivation Cohorts

The associations of donor and recipient characteristics, transplant characteristics, and immunologic parameters with graft loss were assessed in univariate Cox models (Table 2). From these parameters selected on the basis of univariate analysis, we identified after multivariable analysis the following significant independent predictors of graft loss (Table 2): KDRI (log transformation; HR, 2.56; 95% CI, 1.92 to 3.43; $P<0.001$) and the presence of day 0 circulating DSA (HR, 1.89; 95% CI, 1.48 to 2.43; $P<0.001$). We confirmed the validity and the robustness of the final multivariable model by performing bootstrapping resampling procedure with 1000 samples (bias-corrected 95% CIs and bias-corrected and -accelerated bootstrap HRs). After bias-correction through bootstrapping, the 95% CI of the HR was 1.98 to 3.30 for the KDRI, and 1.47 to 2.41 for the anti-HLA DSA on day 0.

The association of day 0 biopsy results was assessed in univariate analysis (Supplemental Table 1A). After adjustment, only IFTA remained independently associated with kidney allograft loss (HR, 1.51; 95% CI, 1.00 to 2.26; $P=0.048$) (Supplemental Table 1B).

The discrimination capacity of the final multivariable model and the model with the addition of the day 0 biopsy

Table 1. Baseline characteristics of derivation and validation cohorts

Characteristics	*n*	French Transplanted Kidneys (Derivation), *n*=1629	*n*	Belgian Transplanted Kidneys (Validation), *n*=1107	*P* Value
Donor characteristics					
Age, yr, mean (SD)	1629	52.60 (16.68)	1096	48.09 (14.28)	**<0.001**
Donor men, no. (%)	1629	958 (58.81)	1100	607 (55.18)	0.06
Height, cm, mean (SD)	1628	170.15 (10.31)	1090	172.46 (8.79)	**<0.001**
Weight, kg, mean (SD)	1628	73.81 (15.57)	1091	75.63 (13.35)	**0.002**
BMI, kg/m^2, mean (SD)	1628	25.42 (4.75)	1089	25.39 (4.16)	**0.88**
Hypertension, no. (%)	1587	473 (29.80)	1082	232 (21.44)	**<0.001**
Diabetes mellitus, no. (%)	1571	126 (8.02)	1107	4 (0.36)	**<0.001**
Donor serum creatinine ≥1.5 mg/dl, no. (%)	1613	212 (13.14)	932	144 (15.45)	0.96
Death from cerebrovascular disease, no. (%)	1629	911 (55.92)	1107	579 (52.30)	0.06
Expanded criteria donor, no. (%)	1626	687 (42.25)	1107	282 (25.47)	**<0.001**
KDRI,[a] mean (SD)	1540	1.54 (0.64)	888	1.32 (0.40)	**<0.001**
Histologic factors on day 0					
Percentage of glomerulosclerosis	1629		1107		
0–5		818 (50.21)		722 (65.22)	
6–10		278 (17.07)		172 (15.54)	
11–15		180 (11.05)		68 (6.14)	
16–20		129 (7.92)		51 (4.61)	
>20		224 (13.75)		94 (8.49)	**<0.001**
IFTA	1629		1107		
Low score: 0 or 1		1537 (94.35)		1082 (97.74)	
High score: ≥2		92 (5.65)		25 (2.26)	**<0.001**
Arteriosclerosis	1629		1107		
Low score: 0 or 1		1083 (66.48)		1082 (97.74)	
High score: ≥2		546 (33.52)		25 (2.26)	**<0.001**
Arteriolar hyalinosis	1624		1103		
Low score: 0 or 1		1302 (80.17)		1044 (94.65)	
High score: ≥2		322 (19.83)		59 (5.35)	**<0.001**
Recipient characteristics					
Recipient age, yr, mean (SD)	1629	51.40 (13.21)	1107	54.49 (12.79)	**<0.001**
Recipient men, no (%)	1629	966 (59.30)	1106	683 (61.75)	0.20
Prior kidney transplant, no. (%)	1629	283 (17.37)	1107	154 (13.91)	**0.02**
Immunologic factors					
No. of HLA A/B/DR mismatches	1628	4.01 (1.25)	1107	2.53 (1.27)	0.68
Anti-HLA DSA on day 0, no. (%)	1629	343 (21.06)	1107	0	**<0.001**

Bold indicates $P<0.05$. BMI, body mass index.
[a]The KDRI score was calculated on the basis of the following donor parameters: age, height, weight, history of hypertension, history of diabetes, cause of death (cerebral stroke), serum creatinine at donation, HCV serostatus, and donation after circulatory death status.

results (in which all of the histologic Banff scores for glomerulosclerosis, IFTA, arteriosclerosis, and arteriolar hyalinosis were added) were assessed using the C index. The C index for the model without histology was 0.635 (95% CI, 0.60 to 0.66) compared with 0.646 (95% CI, 0.62 to 0.68) for the model with the addition of the day 0 biopsy results ($P=0.10$).

Value of Day 0 Allograft Histology in Predicting Kidney Allograft Loss in the External Validation Cohorts

Table 1 shows recipient characteristics and allograft histology for the external validation cohort from Belgium. Supplemental Table 2 shows the univariate Cox model. Only KDRI (log transformation; HR, 3.23; 95% CI, 1.80 to 5.81; $P<0.001$) remained independently associated with allograft loss in the multivariable analysis. As in the primary analyses, the discrimination capacity of the final multivariable model and the model with the addition of the day 0 biopsy results (in which all of the histologic Banff scores for glomerulosclerosis, IFTA, arteriosclerosis, and arteriolar hyalinosis were added) were assessed using the C index. The C index for the model without histology was 0.610 (95% CI, 0.56 to 0.67) compared with 0.617 (95% CI, 0.56 to 0.67) for the model with the addition of the day 0 biopsy results ($P=0.62$).

Taken together, these results confirmed the primary analysis that showed no incremental value of day 0 biopsy in predicting long-term kidney allograft outcomes.

Table 2. Determinants of kidney allograft loss in the derivation cohort: Univariate and multivariable analyses

Characteristics	No. of Patients	No. of Events	HR	95% CI	*P* Value
Univariate analysis					
Baseline recipient characteristics					
Age, per 1-yr increment	1629	335	1.01	(1.00 to 1.02)	**0.009**
Sex					
Women	663	136	1		
Men	966	199	1.01	(0.81 to 1.26)	0.92
Prior kidney transplant					
No	1346	262	1		
Yes	283	73	1.36	(1.05 to 1.77)	**0.02**
Baseline donor characteristics					
Age, per 1-yr increment	1629	335	1.02	(1.01 to 1.03)	**<0.001**
Sex					
Women	671	148	1		
Men	958	187	0.86	(0.69 to 1.07)	0.18
Death of CV disease					
No	718	116	1		
Yes	911	219	1.61	(1.29 to 2.02)	**<0.001**
Hypertension					
No	1114	200	1		
Yes	473	124	1.71	(1.37 to 2.14)	**<0.001**
Diabetes mellitus					
No	1445	295	1		
Yes	126	26	1.16	(0.77 to 1.73)	0.48
Creatinine, mg/dl					
<1.5	1401	277	1		
≥1.5	212	53	1.41	(1.05 to 1.89)	**0.02**
ECD					
No	939	162	1		
Yes	687	171	1.72	(1.39 to 2.13)	**<0.001**
KDRI,[a] log transformation	1540	312	2.44	(1.83 to 3.25)	**<0.001**
Baseline immunologic factors					
No. of HLA A/B/DR mismatches	1628	335	1.02	(0.94 to 1.11)	0.67
Anti-HLA DSA on day 0					
No	1286	241	1		
Yes	343	94	1.79	(1.41 to 2.77)	**<0.001**
Multivariable analysis, $n=1540$ analyzed in the full model					
KDRI,[a] log transformation	1540	312	2.56	(1.92 to 3.43)	**<0.001**
Anti-HLA DSA on day 0					
No	1206	222	1		
Yes	334	90	1.89	(1.48 to 2.43)	**<0.001**

Bold indicates $P<0.05$. CV, cardiovascular; ECD, expanded criteria donor; HLA, human leukocyte antigen; DSA, donor specific antibody.
[a]The KDRI score was calculated on the basis of the following donor parameters: age, height, weight, history of hypertension, history of diabetes, cause of death (cerebral stroke), serum creatinine at donation, HCV serostatus, and donation after circulatory death status.

Matching Kidneys Discarded in the United States Due to Abnormal Histopathology to Similar Kidneys Transplanted in Europe

Table 3 shows the characteristics of 1103 donor kidneys that were discarded due to "biopsy findings" in the United States over 2 years. Prior to matching, the mean donor age for the discarded kidneys in the United States was slightly older than donors of French transplanted kidneys (55.43±10.96 versus 52.60±16.68 years; $P<0.001$). The donors of the United States discarded kidneys were more likely to have hypertension (73.78% versus 29.80%; $P<0.001$) and diabetes (29.62% versus 8.01%; $P<0.001$) than donors of French transplanted kidneys. Day 0 biopsies from kidneys discarded in the United States revealed more glomerulosclerosis, more IFTA (IFTA Banff score), and more arteriosclerosis (cv Banff score) compared with the French transplanted kidneys ($P<0.001$ for all comparisons).

Overall, a total of 493 (45%) United States kidneys discarded due to histology were matched to kidneys transplanted in France. Figure 1 and Supplemental Tables 3 and 4 show that the matched kidneys were highly similar in terms of KDRI and histology, including glomerulosclerosis, arteriosclerosis, and IFTA. After matching, the standardized differences were <0.1 for the four variables in the match. While the mean KDRI was

Table 3. Baseline characteristics of kidneys transplanted in the French derivation cohort and kidneys discarded in the United States due to biopsy findings

Characteristics	Kidneys Transplanted in the French Derivation Cohort, *n*=1629		Kidneys Discarded in the United States Cohort, *n*=1103		*P* Value
	n	Value	*n*	Value	
Donor's characteristics					
Donor age, yr, mean (SD)	1629	52.60 (16.68)	1103	55.43 (10.96)	**<0.001**
Donor men, no. (%)	1629	958 (58.81)	1103	577 (52.31)	**0.001**
Height, cm, mean (SD)	1628	170.15 (10.31)	1103	169.12 (10.54)	**0.003**
Weight, kg, mean (SD)	1628	73.81 (15.57)	1103	85.51 (22.37)	**<0.001**
BMI, kg/m^2, mean (SD)	1628	25.42 (4.75)	1103	29.88 (7.35)	**<0.001**
Hypertension, no. (%)	1587	473 (29.80)	1087	802 (73.78)	**<0.001**
Diabetes mellitus, no. (%)	1571	126 (8.02)	1087	322 (29.62)	**<0.001**
Donor serum creatinine ≥1.5 mg/dl, no. (%)	1613	212 (13.14)	1103	571 (51.77)	**<0.001**
Death from cerebrovascular disease, no. (%)	1629	911 (55.92)	1103	926 (83.95)	**<0.001**
Expanded criteria donor, no. (%)	1626	687 (42.25)	1103	659 (59.75)	**<0.001**
KDRI, mean (SD)	1540	1.54 (0.64)	1085	1.885 (0.471)	**<0.001**
Day 0 biopsy					
Percentage of glomerulosclerosis	1629		1103		
0–5		818 (50.21)		190 (17.23)	
6–10		278 (17.07)		161 (14.60)	
11–15		180 (11.05)		145 (13.15)	
16–20		129 (7.92)		124 (11.24)	
>20		224 (13.75)		483 (43.79)	**<0.001**
IFTA	1629		1103		
Low score: 0 or 1		1537 (94.35)		416 (37.72)	
High score: ≥2		92 (5.65)		687 (62.28)	**<0.001**
Arteriosclerosis	1629		1103		
Low score: 0 or 1		1083 (66.48)		433 (39.26)	
High score: ≥2		546 (33.52)		670 (60.74)	**<0.001**

Bold indicates $P<0.05$. BMI, body mass index.

1.88 in each group after matching, there were differences between groups in the distributions of individual KDRI componenents of donor age, height, weight, history of hypertension, history of diabetes, cause of death (cerebral stroke), serum creatinine at donation, HCV serostatus, and donation after circulatory death status.

Figure 2 depicts kidney allograft survival for the matched and unmatched kidneys. Overall, allograft survival rates for French kidneys matched to United States discarded kidneys were 93.1%, 80.7%, and 68.9% at 1, 5, and 10 years post-transplant, respectively (Figure 2A). We next compared the allograft survival of transplanted kidneys matched to United States discarded kidneys to overall expanded criteria donor French kidneys and found similar allograft survival rates of 93.4%, 80.9%, and 69.9% ($P=0.69$), respectively (Figure 2B).

Supplemental and Sensitivity Analyses

The associations of donor and recipient characteristics, transplant characteristics, and immunologic parameters with all-cause graft loss were assessed in univariate and multivariable Cox models (Supplemental Table 5). Following the same variable selection process as in the primary analysis, we identified the following significant independent predictors of nondeath-censored graft loss: recipient age (HR, 1.02; 95% CI, 1.01 to 1.03; $P<0.001$), KDRI (log transformation; HR, 2.62; 95% CI, 1.93 to 3.56; $P<0.001$), prior kidney transplant (HR, 1.49; 95% CI, 1.20 to 1.86; $P<0.001$), and the presence of day 0 circulating DSA (HR, 1.55; 95% CI, 1.26 to 1.89; $P<0.001$). The discrimination capacity of the final multivariable model and the model with the addition of the day 0 biopsy results (in which all of the histologic Banff scores for glomerulosclerosis, IFTA, arteriosclerosis, and arteriolar hyalinosis were added) were assessed using the C index. In this supplemental analysis, the addition of biopsy data again was not associated with a statistically significant improvement in predictive accuracy, with a C index for the model without histology of 0.659 (95% CI, 0.64 to 0.68) compared with a C index of 0.667 (95% CI, 0.64 to 0.69) for the model with the addition of the day 0 biopsy ($P=0.07$ for the comparison of C statistics between models).

To confirm the robustness of the primary results, we matched kidneys using biopsy findings and the donor's age instead of KDRI. Using 1:1 optimal matching, we matched 496 (45%) United States discarded kidneys to kidneys transplanted in France (Supplemental Table 6). The baseline characteristics of the matched and unmatched kidneys are summarized in Supplemental Table 7. There were no statistically significant differences in the histology between the two groups in terms of

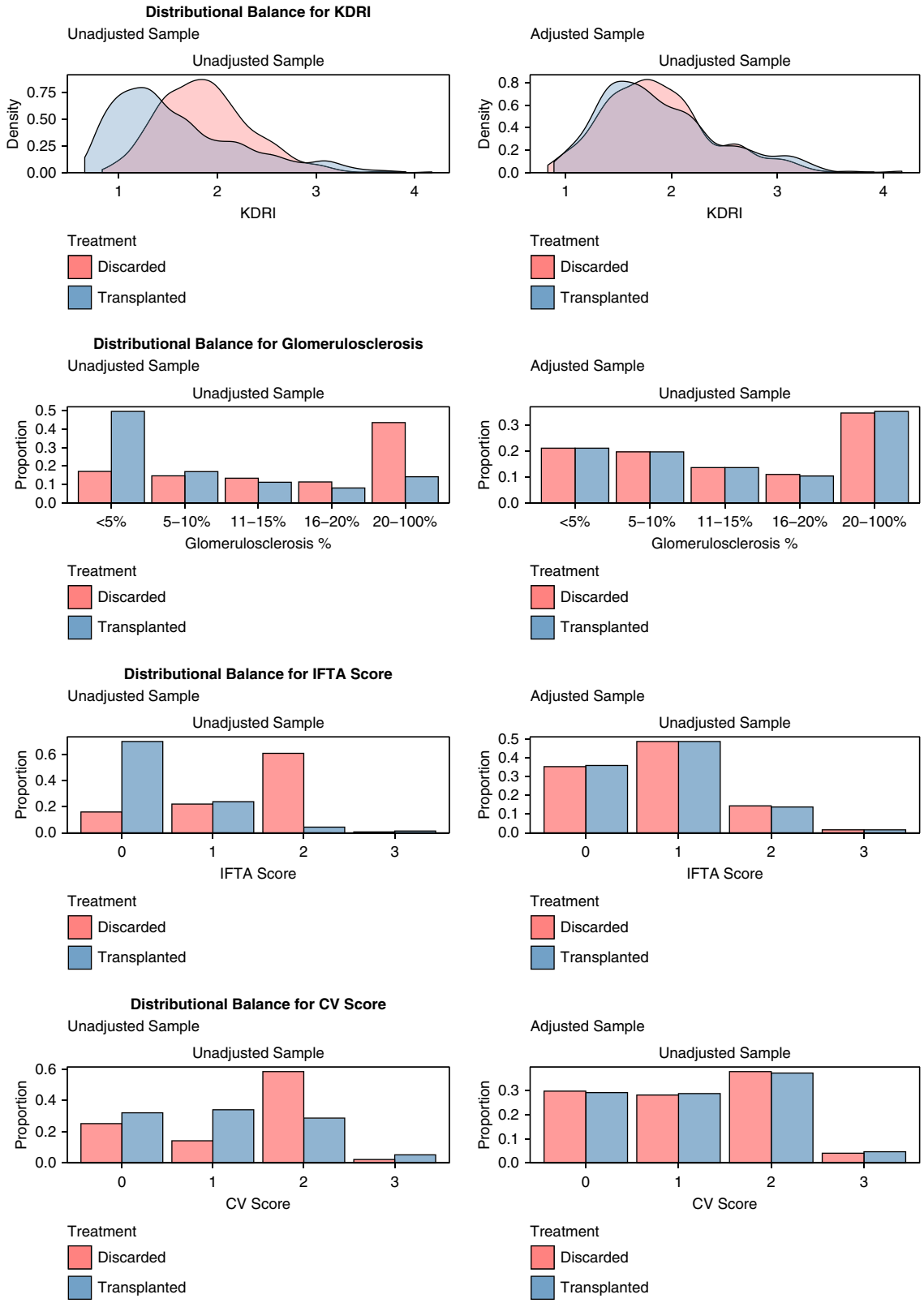

Figure 1. After matching, the kidneys were highly similar in terms of KDRI and histological features of glomerulosclerosis, interstitial fibrosis/tubular atrophy (IFTA), and arteriosclerosis (CV). The figure shows the distributional balance of the KDRI score and kidney histology before and after matching kidneys discarded in the United States to similar kidneys transplanted in the French derivation cohort. Overall, a total of 493 (45%) United States kidneys discarded due to histology were matched to kidneys transplanted in France.

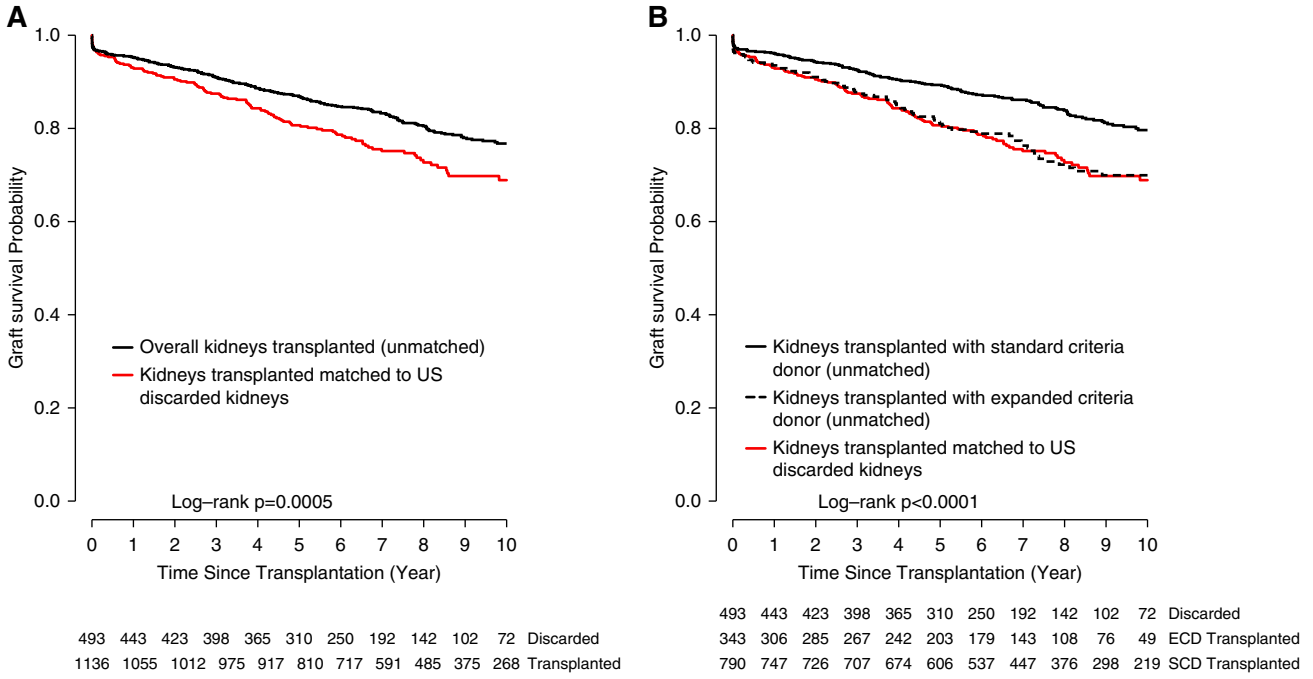

Figure 2. Kidneys transplanted in France matched to discarded US kidneys had survival similar to French expanded criteria donor kidneys. The figure shows Kaplan–Meier curves of allograft survival rates for kidneys transplanted in France matched and unmatched to United States discarded kidneys. (A) The allograft survival probability of the kidneys transplanted matched to United States discarded kidneys (red curve) to the rest of the population (unmatched kidneys; black curve). (B) The allograft survival probability of the matched kidneys (red curve) to the rest of the population according to the expanded criteria donor (ECD) status (kidneys transplanted with standard criteria donor [SCD], solid black curve; kidneys transplanted with ECD, dashed black curve). Among the recipients of the matched kidneys transplanted in France, 284 (57.61%) were men, 58 (11.76%) had diabetes, 39 (7.94%) were pre-emptive transplantations, 75 (15.21) had a prior kidney transplant, 107 (21.70%) had a DSA at the time of transplantation, the mean cold ischemia time was 18.99±7.64 hours, and 163 (33.75%) had delayed graft function.

glomerulosclerosis score, IFTA Banff score, ah Banff score, and cv Banff score (Supplemental Figure 1). Supplemental Figure 2 depicts kidney allograft survival for the matched kidneys and unmatched kidneys. Allograft survival rates for kidneys transplanted matched to United States discarded kidneys were 93.7%, 80.8%, and 71.2% at 1, 5, and 10 years post-transplant, respectively (Supplemental Figure 2A). We then compared the allograft survival of French transplanted kidneys matched to United States discarded kidneys to overall expanded criteria donor kidneys and found similar allograft survival ($P>0.99$) (Supplemental Figure 2B).

DISCUSSION

Kidneys donated for transplantation often provide tremendous benefit to patients with end organ disease by extending survival and improving quality of life compared with dialysis.[29] As many countries have expanded the pool of allografts by accepting donors who are older with more comorbidities, major questions have emerged about whether pathologic examination of donated kidneys helps to better characterize organ quality or instead, drives serious inefficiencies in organ allocation.[30] In this large multinational study, we demonstrate that kidney biopsies performed for decision making in the allocation process did not improve the prediction of allograft survival beyond routinely available clinical attributes of deceased donors and recipients. Next, we provide evidence that many kidneys discarded in the United States due to biopsy findings likely could have been transplanted and improved the lives of patients who are waitlisted. Specifically, we matched 45% of those discarded kidneys to kidneys with very similar pathologic findings transplanted in France and found that approximately 70% of these matched kidneys were functioning at 10 years. These analyses raise substantial doubts about the value of using procurement biopsies to guide kidney acceptance decisions and reveal a straightforward opportunity to utilize many kidneys currently being discarded in the United States.

These robust findings about the prognostic value of renal histology should challenge clinical practice at many transplant centers because approximately half of deceased donor kidneys in the United States undergo allocation biopsy. Our results are bolstered by long-standing concerns about the quality of the samples and the interpretation of biopsies obtained during allocation.[4] Allocation biopsies are often wedge biopsies,

prepared by frozen section, and/or interpreted by pathologists without specialized kidney histology training. Additionally, biopsies may be vulnerable to sampling "error" if not representative of the whole organ. Despite these concerns, the act of biopsy has a strong relationship with kidney discard. Marrero *et al.*[31] examined United States deceased donor kidneys from 2000 to 2012 and found that a biopsy—regardless of pathologic results—was independently associated with more than two times the odds of discard.

On the other hand, the pretransplant biopsies from European centers that were examined in our study are less susceptible to these quality concerns. The biopsies from the development and validation cohorts were obtained in a standardized fashion at academic transplant centers and then, processed and reviewed by the dedicated renal pathologists at those centers as part of usual care and without the time pressure of biopsies obtained and interpreted during organ allocation. Even in this setting of standardized kidney biopsies read by experts, however, day 0 donor biopsies added no predictive accuracy in the European derivation and validation cohorts. We also note that although some studies have asserted that wedge biopsies systematically overestimate the degree of kidney glomerulosclerosis, such overestimation would actually lead our study to underestimate the predicted graft survival of the matched European kidneys and reinforce our conclusions that viable kidneys are being discarded.[15,32]

Our results suggest a viable pathway to bring transplantation to more patients in the United States through better stewardship of the resource of donated kidneys. Using advanced matching methods, we found that 45% of United States kidneys discarded for abnormal histology in the United States were highly similar in terms of the KDRI quality score and histology to kidneys actually transplanted in France. The ability to find matches for 45% of the discarded kidneys supports our clinical intuition that not every procured kidney would provide acceptable transplant outcomes. Some kidneys—for a variety of reasons related to function or disease—warrant discard. Not surprisingly, the overall pool of kidneys discarded in the United States was more likely than French transplanted kidneys to have higher-risk features, such as advanced donor age and diabetes, in addition to higher histopathologic grades of chronic injury. Yet, the recipients of kidneys matched on KDRI and histology that were transplanted in France enjoyed allograft survival that would likely be acceptable to some of the 95,000 patients on the United States kidney waiting list. In particular, well-informed individuals who are older or have diabetes (a large percentage of United States patients who are wait listed) might derive substantial benefits from accepting kidneys with histologic abnormalities compared with enduring the elevated risks of death or health deterioration caused by chronic dialysis.[33–36] A reduction in allocation biopsies may benefit transplant systems in other ways, such as reducing cold ischemia time and costs that are driven by awaiting histologic results.[37]

Transplant professionals may ask why existing tools to assess donated kidneys are so limited in their ability to forecast post-transplant outcomes. Indeed, the C statistics of KDRI and of all our models show only modest predictive accuracy. In addition to the low quality of allograft biopsies, other barriers may include excessive reliance on low-granularity cross-sectional data obtained from the donor. The field of kidney transplantation is in serious need of better tools to predict allograft outcomes. We propose that meaningful improvement in characterizing the quality of donor kidneys may require novel sources of data—such as more extensive and longitudinal information about donor health and kidney function, advanced imaging methods, or deep molecular and genetic phenotyping—all of which might be accomplished during the donor's terminal hospitalization.[38]

This study's strengths include highly detailed data about kidney transplant recipients from European centers where preimplantation biopsies are prospectively performed but do not guide the decision-making process for allocating kidneys. We leveraged a comprehensive database of discarded kidneys in the United States. Although prior investigators have highlighted the limitations of usual care procurement biopsies in predicting allograft outcomes, our study advances the field by revealing the plausible counterfactual outcomes if similar kidneys were actually transplanted in European centers and showing the size of the lost opportunity to the large population of patients who are wait listed.[9,15,39,40] We also acknowledge limitations. First, because of differences in the health care systems, the allograft survival in a European transplant population may be different from the survival that United States centers could achieve if they accepted similar kidneys.[41,42] Second, the allograft outcomes achieved at academic European transplant centers may not be generalizable to less-experienced centers elsewhere. Third, it is possible that some discarded kidneys had additional adverse characteristics—such as donor infections—that would have caused kidney discard regardless of histopathology. On the other hand, organ procurement organizations specifically reported discarding these kidneys because of biopsy findings, so it is likely that biopsy findings were a central feature of the discard decision. Additionally, we matched on KDRI; prior studies suggest that KDRI is a very robust predictor of kidney discard, even if KDRI's predictive accuracy for allograft survival is only modest.[7,31] Fourth, our study is observational and may be subject to unmeasured confounding. A randomized trial of the use of biopsies in organ acceptance—such as the Pre-Implantation Trial of Histopathology In Renal Allografts (PITHIA) trial in the United Kingdom—could overcome this problem, although trials typically also have limitations related to generalizability, and our high-quality observational data will complement any trial findings.[43] Fifth, although external validation in the Belgian cohort provides additional evidence against the incremental predictive value of biopsies, the Belgian cohort has some limitations; namely, this cohort did not have the same diversity in histologic findings as the

French cohort, and the Belgian centers only rarely transplanted patients with pretransplant DSA. Finally, it is possible that we were unable to detect a small incremental predictive benefit related to kidney pathology due to our sample size. However, transplant clinicians and organ procurement organizations know well that biopsies create expense, create logistical difficulties with allocation, and prolong cold ischemia time. As a result, biopsies need to add substantial value to justify all of these disadvantages.

In a large, well-phenotyped, multinational cohort, kidney biopsy results from deceased donor kidneys did not improve prediction of allograft survival beyond usual donor attributes. We also determined that about half of kidneys discarded due to biopsy findings could have instead been transplanted with acceptable 10-year outcomes. These results add to a growing body of evidence that a ready opportunity exists for United States centers to increase the number of kidney transplants by adopting evidence-based standards for organ acceptance.[7,44] This report provides a strong rationale for organ procurement organizations to reduce the routine practice of obtaining biopsies of deceased donor kidneys. Likewise, transplant center staff should view these biopsy results as limited in their ability to contribute meaningful information in their overall assessment of kidney quality.

DISCLOSURES

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The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the Agence de la Biomedicine (which maintains the CRISTAL database) or the French government. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government. Preliminary results were presented at the 2019 Annual Meeting of the American Society of Nephrology in Washington, DC.

O. Aubert, A. Loupy, and P. Reese designed the study; O. Aubert, G. Divard, E. Huang, A. Loupy, V. Potluri, M. Raynaud, and P. Reese analyzed the data; O. Aubert, Y. Bouatou, A. Bouquegneau, G. Divard, J.-P. Empana, D. Glotz, E. Huang, S. Jordan, X. Jouven, D. Kuypers, C. Lefaucheur, C. Legendre, A. Loupy, M. Naesens, V. Potluri, M. Raynaud, P. Reese, and A. Vo interpreted the data; O. Aubert, A. Loupy, V. Potluri, and P. Reese wrote the manuscript; and O. Aubert, Y. Bouatou, A. Bouquegneau, G. Divard, J.-P. Empana, D. Glotz, E. Huang, S. Jordan, X. Jouven, D. Kuypers, C. Lefaucheur, C. Legendre, A. Loupy, M. Naesens, V. Potluri, M. Raynaud, P. Reese, and A. Vo edited the manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020040464/-/DCSupplemental.

Supplemental Figure 1. Distributional balance of the donor's age and biopsy characteristics before and after matching French transplanted kidneys with kidneys discarded in the United States due to biopsy findings.

Supplemental Figure 2. Kaplan–Meier curves of allograft survival rates for kidneys transplanted in France and kidneys transplanted matched to United States discarded kidneys using donor's age instead of KDRI for matching.

Supplemental Material. Methods, interpretation of statistical analyses, and kidney donor risk index calculation.

Supplemental Table 1. Association of day 0 biopsy results with kidney allograft loss.

Supplemental Table 2. Factors associated with kidney allograft loss in univariate analysis in the validation cohort.

Supplemental Table 3. Baseline characteristics of the United States discarded kidneys matched to transplanted French kidneys on the basis of histology and KDRI and the unmatched United States and French kidneys.

Supplemental Table 4. Distribution of KDRI and biopsy characteristics in the pre- and postmatch cohorts.

Supplemental Table 5. Determinants of nondeath-censored kidney allograft loss in the derivation cohort: univariate and multivariable analyses.

Supplemental Table 6. Distribution of donor age and biopsy characteristics in the pre- and postmatch cohorts.

Supplemental Table 7. Baseline characteristics of the United States discarded kidneys matched with transplanted French kidneys on the basis of histology and the donor's age and the unmatched transplanted French kidneys.

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