

## A COMPARISON OF THE SURVIVAL OF SHIPPED AND LOCALLY TRANSPLANTED CADAVERIC RENAL ALLOGRAFTS

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**ABSTRACT**

**Background** The effect on allograft survival of the shipment of cadaveric renal allografts from one organ-procurement organization to another is uncertain.

**Methods** Using data from the Organ Procurement and Transplantation Network of the United Network for Organ Sharing, we identified 5446 pairs of cadaveric kidneys (10,892 allografts) in which one kidney was shipped and the other was transplanted locally. We compared the risk of graft failure using statistical models that accounted for confounding variables, including the degree of HLA mismatching.

**Results** After adjustment for the degree of HLA mismatching, shipped organs had a significantly higher rate of allograft failure than locally transplanted organs in the first year after transplantation (adjusted hazard ratio, 1.17; 95 percent confidence interval, 1.05 to 1.31;  $P=0.004$ ), but not thereafter. An association between the shipment of organs with no HLA mismatches and allograft failure was not confirmed.

**Conclusions** The shipment of cadaveric renal allografts increases the risk of failure of HLA-mismatched grafts during the first year after transplantation. (N Engl J Med 2001;345:1237-42.)

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**T**HE policy of giving priority to potential recipients of cadaveric renal allografts who are matched with the donor at all six HLA loci (henceforth referred to as HLA-matched) has been in place since 1990 and is supported by a repeatedly demonstrated survival advantage.<sup>1-3</sup> By necessity, national sharing of organs prolongs the duration of cold ischemia, but whether this affects the survival of the graft is unclear.<sup>1-3</sup> We assessed whether the shipment of cadaveric renal allografts between organ-procurement organizations affects allograft survival.

**METHODS**

Patients who received a cadaveric renal transplant between January 1, 1990, and December 31, 1998, were eligible. To minimize a selection bias for organs to be shared nationally on the basis of observed characteristics of the donors, we identified pairs of kidneys from cadaveric donors in which one kidney was used within an organ-procurement organization's local service area and the other was shipped by the organ-procurement organization for transplantation at a center served by another procurement organization. Patients who received multiorgan transplants were excluded. Follow-up continued through May 31, 2000.

Data were provided by the United Network for Organ Sharing. Variables that were considered potential confounders of the association between shipment and allograft survival were the age, sex, and race (black or nonblack) of the donor and the recipient; the cause of end-stage renal disease (diabetes, hypertension, glomerulonephri-

tis, chronic interstitial nephritis, cystic kidney disease, or other); prior renal transplantation; the peak level of panel-reactive antibodies before transplantation (defined as the percentage of a panel of normal-donor cells that reacted with the recipient's serum); the year of transplantation; the number of cadaveric transplantations performed annually at the transplantation center; the use of antibody-induction therapy; and the duration of cold ischemia. The covariates considered after transplantation were delayed allograft function (defined by the use of dialysis within the first week) and acute rejection within the first year.

We compared the relevant characteristics of the donor, the recipient, and the graft between the group of patients who received shipped organs and the group of patients who received locally transplanted organs, with the use of the chi-square test for categorical variables and the t-test for continuous variables. The rate of allograft failure — defined by death, the initiation of long-term dialysis, or repeated transplantation — was compared between pairs of patients with a common donor. Log-rank statistics were used with the Kaplan-Meier product-limit method to evaluate the associations of individual covariates with allograft survival. The covariates with P values of less than 0.10 by the log-rank test were then entered in a forward and stepwise fashion into a multivariate Cox regression model to adjust for their relation with allograft survival.<sup>4,5</sup> Variables remained in the multivariate model if their P values were less than or equal to 0.05 according to the Wald test. Because of the hypothesis that delayed allograft function, long duration of cold ischemia, or HLA mismatching may explain any differences observed between shipped and locally shared kidneys, these covariates were forced sequentially into the model.

Multivariate models were fitted with the results from pairs of patients who had complete data on all the covariates (95.6 percent of the eligible patients). No data were imputed. Curves for predicted allograft survival were then generated from the multivariate Cox models. The nonindependence of the kidneys from the same donor was accounted for in all analyses with the use of robust methods to provide a better estimate of the standard error of the hazard ratio.<sup>6</sup> The assumption of proportional hazards was examined by weighted residual testing.<sup>7</sup> We also assessed whether there was an interaction between shipment and HLA-matched transplants. All P values were two-sided. All analyses were performed with the use of Stata software (Stata, version 6.0, College Station, Tex.).

**RESULTS****Frequency of HLA Mismatching and Shipment of Organs**

A total of 11,400 eligible patients, or 5700 pairs of patients, underwent transplantation from 1990 through 1998. Fifty-two patients (26 pairs) were excluded because of missing follow-up data, and 456 patients (228 pairs) were excluded because of missing information on the duration of cold ischemia. The known characteristics of the excluded pairs of patients

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were not significantly different from those of recipients included in these analyses, and the missing data were not related to shipment. In the cohort of 10,892 patients, 17.7 percent received an allograft with no HLA mismatches (9.1 percent of all patients received a graft with six HLA matches); 88.4 percent of these allografts were shipped. Among the shipped renal allografts, 31.4 percent were transplanted into recipients with no HLA mismatches. The proportion of shipped renal allografts transplanted into recipients with no HLA mismatches in this study increased from 17.4 percent in 1990 to 43.5 percent in 1998.

**Characteristics of the Recipients**

The relevant characteristics of the patients are presented in Table 1. In addition, recipients of shipped organs had a higher incidence of delayed graft function than recipients of locally transplanted organs (28.0 percent vs. 23.5 percent, P=0.001), and the two groups had similar unadjusted survival rates at five years (64.7 percent and 62.7 percent, P=0.50).

**TABLE 1. CHARACTERISTICS OF THE DONORS AND RECIPIENTS, ACCORDING TO WHETHER THE RENAL ALLOGRAFT WAS SHIPPED OR TRANSPLANTED LOCALLY.\***

CHARACTERISTIC	SHIPPED ALLOGRAFT (N=5446)	LOCALLY TRANSPLANTED ALLOGRAFT (N=5446)	P VALUE
Sex of donor and recipient (%)			0.30
Female/female	15.7	16.2	
Female/male	23.3	22.8	
Male/female	23.3	24.5	
Male/male	37.7	36.5	
Race of donor and recipient (%)			0.001
Nonblack/nonblack	74.3	70.6	
Nonblack/black	16.7	20.3	
Black/nonblack	4.2	4.3	
Black/black	4.8	4.8	
Difference in age between donor and recipient (yr)	-10.3±20.2	-9.7±20.3	0.15
Cause of end-stage renal disease in recipient (%)			0.17
Diabetes mellitus	18.7	19.5	
Hypertension	19.0	18.4	
Glomerulonephritis	30.1	30.1	
Chronic interstitial nephritis	6.1	6.3	
Cystic kidney disease	10.2	9.9	
Other	15.9	15.8	
Peak level of panel-reactive antibodies (%)	18.1±29.6	16.9±27.3	0.03
Prior kidney transplantation (%)	17.2	14.0	0.001
Duration of cold ischemia (hr)	26.7±9.53	19.7±8.94	0.001
No. of HLA matches (%)			0.001
>6	82.8	98.9	
6	17.2	1.1	
No. of HLA mismatches (%)			0.001
0	31.4	4.1	
>0	68.6	95.9	
Use of antibody induction (%)	20.7	22.2	0.04

\*Plus-minus values are means ±SD.

**Allograft Survival and Shipment**

An unadjusted univariate analysis showed that the following covariates were significantly associated with allograft failure (Table 2): the age, sex, and race of the donor and the recipient; the peak levels of panel-reactive antibodies; and the cause of end-stage renal disease. Therefore, these variables, in addition to the number of transplantations performed annually at the center and the year of transplantation, were entered into a multivariate Cox model and graft-survival curves were plotted (Fig. 1). In contrast to the unadjusted analysis (Fig. 1A), the adjusted analysis showed that the shipped allografts had a higher rate of failure than the kidneys that were transplanted locally, particularly within the first year after transplantation (Fig. 1B). The higher rate of allograft failure associated with shipped renal allografts was more distinct after adjustment was also made for the degree of HLA mismatching (Fig. 1C). The association between shipment and an in-

**TABLE 2. UNIVARIATE ASSOCIATIONS OF RELEVANT FACTORS WITH THE LIKELIHOOD OF ALLOGRAFT FAILURE.\***

VARIABLE	HAZARD RATIO (95% CI)	P VALUE
Overall likelihood of failure of shipped grafts (vs. locally transplanted grafts)		
≤1 yr after transplantation	1.04 (0.94–1.14)	0.46
>1 yr and ≤3 yr after transplantation	0.87 (0.76–0.98)	0.03
>3 yr after transplantation	0.88 (0.78–0.98)	0.02
Sex of donor and recipient		0.001
Female/female	1.00	
Female/male	1.10 (0.99–1.22)	
Male/female	0.94 (0.84–1.04)	
Male/male	0.96 (0.87–1.06)	
Race of donor and recipient		0.003
Nonblack/nonblack	1.00	
Nonblack/black	1.55 (1.44–1.68)	
Black/nonblack	1.11 (0.95–1.30)	
Black/black	1.59 (1.38–1.83)	
Difference in age between donor and recipient		0.001
First quintile (donor ≥28 yr younger)	1.00	
Second quintile (donor 16 to 27 yr younger)	0.94 (0.84–1.04)	
Third quintile (donor 4 to 15 yr younger)	1.03 (0.93–1.14)	
Fourth quintile (donor 3 yr younger to 8 yr older)	1.17 (1.05–1.29)	
Fifth quintile (donor >8 yr older)	1.32 (1.19–1.46)	
Peak level of panel-reactive antibodies (per 10% increase)	1.04 (1.03–1.05)	0.01
Cause of end-stage renal disease in the recipient		0.001
Diabetes mellitus	1.00	
Hypertension	1.00 (0.91–1.11)	
Glomerulonephritis	0.80 (0.73–0.87)	
Chronic interstitial nephritis	0.66 (0.57–0.77)	
Cystic kidney disease	0.63 (0.55–0.72)	
Other	0.80 (0.72–0.89)	

\*Hazard ratios are for the comparison of shipped renal allografts with locally transplanted allografts and are derived from the stratified Cox models. CI denotes confidence interval.

creased risk of allograft failure was attenuated once the duration of cold ischemia was added to the variables adjusted for in the analysis, including the number of HLA mismatches (Fig. 1D). These results suggest that HLA mismatching and the duration of cold ischemia are both important factors in the observed differences in survival between shipped and locally transplanted allografts, but they offset each other.

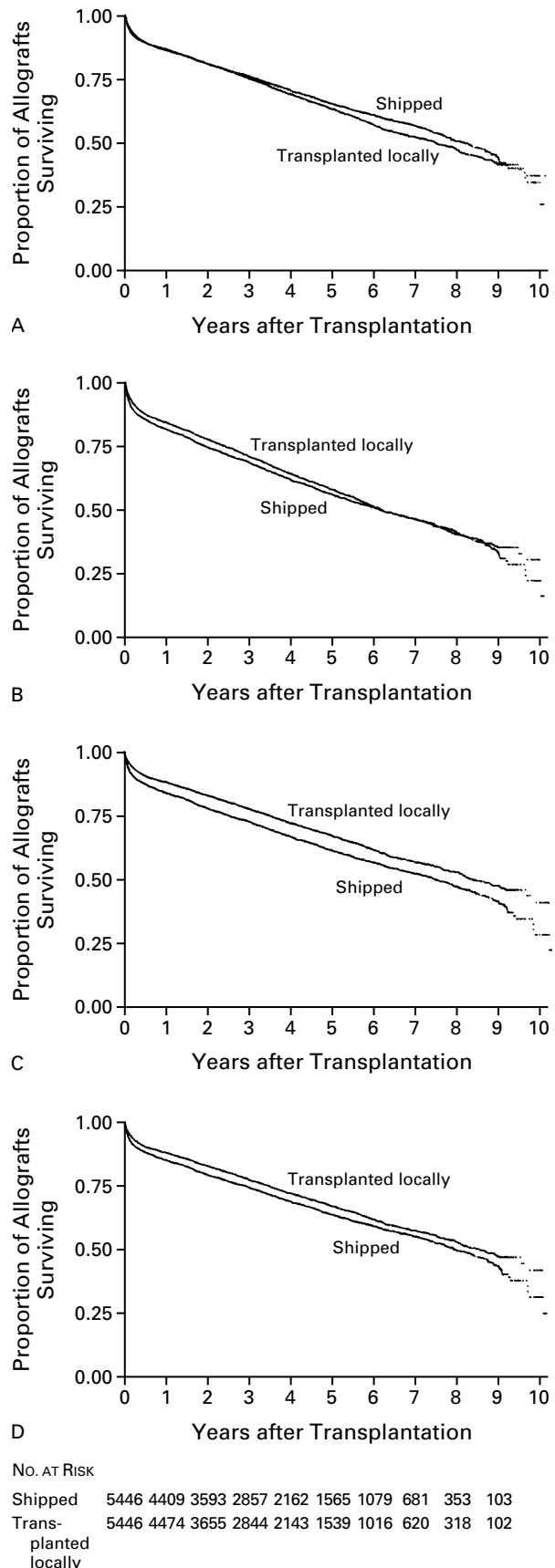
Since the proportional-hazards assumption was violated by the weighted residual testing, the Cox models were then stratified according to the time after transplantation (one year or less, more than one but no more than three years [contingent, or “conditioned,” on allograft survival at one year], and more than three years [contingent on allograft survival at three years]) to accommodate the inconstant relation of shipment with allograft survival (i.e., the fact that the hazard ratio changes over time).<sup>8</sup> After adjustment for the age, sex, and race of the donor and the recipient; the cause of end-stage renal disease; the peak levels of panel-reactive antibodies; the number of transplantations performed annually at the center; and the year of transplantation, there was no significant increase in the risk of the failure of shipped allografts in the first year, as compared with locally transplanted allografts (adjusted hazard ratio, 1.06; 95 percent confidence interval, 0.96 to 1.18;  $P=0.27$ ) (Table 3).

After further adjustment was made for the number of HLA mismatches, however, the shipment of kidneys was associated with a 17 percent increase in the risk of allograft failure in the first year after transplantation (adjusted hazard ratio, 1.17; 95 percent confidence interval, 1.05 to 1.31;  $P=0.004$ ). Adjustment for the duration of cold ischemia attenuated the increased risk of allograft failure in the first year that appeared to be associated with shipment (adjusted hazard ratio, 1.11; 95 percent confidence interval, 0.98 to 1.25;  $P=0.08$ ) after HLA mismatching was taken into account.

These changes in the adjusted hazard ratios suggest that the degree of HLA mismatching and the duration of cold ischemia influence the survival of shipped allografts in the first year after transplantation, but these variables have offsetting effects on allograft survival.

**Figure 1.** Estimated Rates of Graft Survival before and after Adjustment for Various Factors, According to Whether the Graft Was Transplanted Locally or Shipped.

Panel A shows unadjusted survival rates. Panel B shows the survival rates adjusted for the concordance for sex, age, and race of the donor–recipient pairs; the cause of end-stage renal disease in the recipient; the peak level of panel-reactive antibodies; the number of transplantations performed annually in the center; and the year of transplantation. Panel C shows survival rates adjusted for all the preceding factors as well as number of HLA mismatches. Panel D shows the survival rates adjusted for all the preceding factors as well as the duration of cold ischemia.



**TABLE 3.** RESULTS OF THE MULTIVARIATE MODEL OF THE LIKELIHOOD OF THE FAILURE OF SHIPPED ALLOGRAFTS AS COMPARED WITH LOCALLY TRANSPLANTED ALLOGRAFTS, ACCORDING TO THE TIME AFTER TRANSPLANTATION.\*

TYPE OF ANALYSIS	FAILURE ≤1 YR AFTER TRANSPLANTATION		FAILURE >1 TO 3 YR AFTER TRANSPLANTATION		FAILURE >3 YR AFTER TRANSPLANTATION†	
	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE
Unadjusted	1.06 (0.96–1.17)	0.28	0.86 (0.75–0.97)	0.02	0.89 (0.79–1.00)	0.05
Adjusted for the following initial factors: concordance for sex, age, and race of donor–recipient pairs; peak level of panel-reactive antibodies; cause of end-stage renal disease in recipient; year of transplantation; number of transplantations performed annually at the center; and nonindependence of donors	1.06 (0.96–1.18)	0.27	0.91 (0.80–1.04)	0.15	0.94 (0.83–1.06)	0.29
Adjusted for the initial factors plus duration of cold ischemia	1.00 (0.89–1.12)	0.98	0.90 (0.78–1.03)	0.13	0.93 (0.82–1.06)	0.28
Adjusted for the initial factors plus number of HLA mismatches	1.17 (1.05–1.31)	0.004	0.96 (0.83–1.11)	0.59	0.91 (0.79–1.03)	0.14
Adjusted for the initial factors plus number of HLA mismatches and duration of cold ischemia	1.11 (0.98–1.25)	0.08	0.95 (0.82–1.11)	0.55	0.89 (0.78–1.03)	0.11
Adjusted for the initial factors plus presence or absence of treatment for rejection by 1 yr	—	—	0.93 (0.82–1.06)	0.28	0.92 (0.82–1.04)	0.19

\*CI denotes confidence interval.

†Acute rejection is a fixed variable for this period.

Beyond the first year after transplantation, there was no statistically significant association between shipment and allograft failure in the adjusted analyses. Acute rejection within the first year did not affect the risk of failure of shipped kidneys that survived for a minimum of one year. Because of the correlation between the duration of cold ischemia and delayed allograft function, we entered delayed allograft function into a separate model that included only patients who survived for the first seven days after transplantation and found that the associations were similar.

#### Survival According to the Number of HLA Mismatches

We investigated whether there was an interaction between the shipment of organs and the presence or absence of any HLA mismatches in terms of allograft survival. After we detected such an interaction ( $P=0.02$ ), we then stratified the multivariate models according to the presence or absence of HLA matching in the two groups of allografts as a whole (shipped or locally transplanted) rather than in the groups of paired recipients (Tables 4 and 5). Shipment was associated with a significant increase in the risk of failure of HLA-mismatched organs (adjusted hazard ratio, 1.17; 95 percent confidence interval, 1.04 to 1.30;  $P=0.006$ ) in the first year after transplantation, as compared with locally transplanted HLA-mismatched organs (Table 4). This effect was related to the longer duration of cold ischemia of shipped organs and to the more frequent loss of allografts to acute rejection in

the first year (20.5 percent, as compared with 17.3 percent in the group of locally transplanted allografts with HLA mismatches;  $P=0.06$ ). Beyond the first year after transplantation, shipment was unrelated to the survival of either HLA-mismatched allografts (Table 4) or HLA-matched allografts (Table 5). The absolute rates of allograft survival were lower for shipped allografts irrespective of the degree of HLA matching (Table 6).

#### DISCUSSION

We found a significantly higher rate of allograft failure (17 percent) within the first year among recipients of shipped allografts with HLA mismatches, an effect that can be explained by the longer duration of cold ischemia and by more frequent loss of allografts in the first year as a result of acute rejection.

Takemoto et al.<sup>2</sup> recently reported that HLA-matched allografts have an estimated half-life of 12.4 years, as compared with an estimated half-life of 8.6 years for HLA-mismatched allografts. They suggested that the decreased frequency of acute rejection explained this difference. Held et al. also found that the survival of renal allografts with no HLA mismatches was longer than that of allografts with any degree of HLA mismatching<sup>3</sup>; the risk of allograft failure increased by 6 percent for every increase in the number of HLA mismatches. Held et al. also reported that the adjusted risk of allograft failure increases by 8 percent for every 12 hours of cold ischemia and concluded

**TABLE 4.** RESULTS OF THE MULTIVARIATE MODEL OF THE LIKELIHOOD OF THE FAILURE OF SHIPPED ALLOGRAFTS WITH AT LEAST ONE HLA MISMATCH AS COMPARED WITH LOCALLY TRANSPLANTED ALLOGRAFTS WITH AT LEAST ONE HLA MISMATCH, ACCORDING TO THE TIME AFTER TRANSPLANTATION.\*

TYPE OF ANALYSIS	FAILURE ≤1 YR AFTER TRANSPLANTATION		FAILURE >1 TO 3 YR AFTER TRANSPLANTATION		FAILURE >3 YR AFTER TRANSPLANTATION	
	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE
Unadjusted	1.10 (0.98–1.23)	0.09	0.96 (0.83–1.10)	0.58	0.85 (0.40–0.97)	0.01
Adjusted for the following initial factors: concordance for sex, age, and race of donor–recipient pairs; peak level of panel-reactive antibodies; cause of end-stage renal disease in recipient; year of transplantation; number of transplantations performed annually at the center; and nonindependence of donors	1.17 (1.04–1.30)	0.006	1.00 (0.87–1.16)	0.99	0.92 (0.80–1.05)	0.21
Adjusted for the initial factors plus duration of cold ischemia	1.09 (0.97–1.23)	0.15	1.00 (0.85–1.16)	0.96	0.90 (0.78–1.04)	0.15
Adjusted for the initial factors plus presence or absence of treatment for rejection by 1 yr	—	—	1.02 (0.88–1.18)	0.79	0.89 (0.77–1.02)	0.09

\*The analysis includes 3736 shipped allografts and 5223 locally transplanted allografts. Analyses accounted for differences in the extent of HLA mismatching. CI denotes confidence interval.

**TABLE 5.** RESULTS OF THE MULTIVARIATE MODEL OF THE LIKELIHOOD OF THE FAILURE OF SHIPPED ALLOGRAFTS WITH NO HLA MISMATCHES AS COMPARED WITH LOCALLY TRANSPLANTED ALLOGRAFTS WITH NO HLA MISMATCHES, ACCORDING TO THE TIME AFTER TRANSPLANTATION.\*

TYPE OF ANALYSIS	FAILURE ≤1 YR AFTER TRANSPLANTATION		FAILURE >1 TO 3 YR AFTER TRANSPLANTATION		FAILURE >3 YR AFTER TRANSPLANTATION	
	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE
Unadjusted	1.07 (0.56–2.05)	0.84	0.71 (0.33–1.55)	0.39	0.87 (0.42–1.83)	0.72
Adjusted for the following initial factors: concordance for sex, age, and race of donor–recipient pairs; peak level of panel-reactive antibodies; cause of end-stage renal disease in recipient; year of transplantation; number of transplantations performed annually at the center; and nonindependence of donors	1.19 (0.76–1.87)	0.45	0.63 (0.54–1.62)	0.34	0.82 (0.48–1.39)	0.46
Adjusted for the initial factors plus duration of cold ischemia	1.17 (0.73–1.89)	0.52	0.64 (0.23–1.83)	0.41	0.85 (0.49–1.49)	0.58
Adjusted for the initial factors plus presence or absence of treatment for rejection by 1 yr	—	—	0.64 (0.23–1.77)	0.39	0.59 (0.20–1.76)	0.34

\*The analysis includes 1710 shipped allografts and 223 locally transplanted allografts. CI denotes confidence interval.

that the actual benefit of HLA matching would be small, because of the attendant increases in the duration of cold ischemia and its relation with decreased allograft survival.

Our findings suggest that the degree of HLA mismatching and the duration of cold ischemia are important determinants of the survival of shipped allografts, but the effect of one offsets the effect of the other. HLA-mismatched allografts also had a higher rate of acute rejection leading to the loss of the allograft in the first year. These findings are similar to findings in animal models, in which a prolonged du-

ration of cold ischemia increased the severity of the immune response to the transplanted organ.<sup>9-11</sup> We did not find a significant association between shipment and the one-year rate of allograft survival among kidneys with no HLA mismatches. Beyond the first year after transplantation, there were no significant associations between shipment and allograft survival for kidneys with or without HLA mismatches. We suggest that the survival of shipped allografts could be increased by better matching of HLA antigens.

Allograft survival appeared to be unrelated to whether the left or right kidney was transplanted, sug-

**TABLE 6.** PREDICTED ABSOLUTE RATES OF ALLOGRAFT SURVIVAL IN THE FIRST YEAR AFTER TRANSPLANTATION.\*

VARIABLE	SURVIVAL	
	SHIPPED ALLOGRAFTS	LOCALLY TRANSPLANTED ALLOGRAFTS
	%	
Unadjusted analysis	85.0	85.4
Analysis adjusted for the following initial factors: concordance for sex, age, and race of donor–recipient pairs; peak level of panel-reactive antibodies; cause of end-stage renal disease in recipient; year of transplantation; number of transplantations performed annually at the center; number of HLA mismatches; and nonindependence of donors	86.7	90.3
Allografts with $\leq 2$ HLA mismatches	86.3	90.5
Allografts with $> 2$ HLA mismatches	79.0	83.0
Analysis adjusted for the initial factors plus duration of cold ischemia	88.5	92.0

gesting that anatomical factors are not significant. Because we did not classify shipped allografts according to the distance they were shipped, the effect of shipment may have been underestimated.

We conclude that the shipment of renal allografts is associated with an increased rate of organ failure in the first year after transplantation, but not subsequently. Shipped allografts that are better matched may have

a short-term survival benefit as compared with organs that are less well matched and transplanted locally.

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