Cold ischemia and the reduced long-term survival of cadaveric renal allografts

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Background. Prolonged cold ischemia time (CIT) is accompanied by delayed cadaveric renal allograft function and early allograft loss, but the effect of CIT on *long-term* allograft survival is less certain and has not been studied in detail.

Methods. Using data from the United Network for Organ Sharing, we identified 6465 patients who received a kidney-only transplant of cadaveric origin for the first time in 1995. We examined the effect of CIT on the 6-year survival of these kidneys using Cox proportional hazard analysis.

Results. The mean CIT of the kidney was 21 ± 7 hours (mean $\pm$ SD) and correlated with the serum creatinine on discharge ($R = 0.20$, $P < 0.001$) and the distance traveled by the kidneys ($R = 0.30$, $P < 0.001$). CIT had a significant effect on the 6-year allograft survival (a 10-hour increase in CIT was associated with a hazard risk ratio (RR) of 1.20 for graft failure ($P < 0.001$) that persisted (RR = 1.40, $P = 0.021$) after adjusting for donor age, recipient age and race, human leukocyte antigen (HLA) mismatch, panel reactive antibodies, and first 6 months' rejection treatments. Similarly, compared to CIT category of 0 to 10 hours, the 6-year graft survival was progressively worse for 11 to 20 hours (RR = 1.03), 21 to 30 hours (RR = 1.12), and, significantly so, for >30 hours (RR = 1.32; $P = 0.011$). The gain in HLA match with increasing CIT was not uniform; for instance, HLA match in >30 hours was lower than for 21 to 30 hours (2.4 ± 1.5 vs. 2.7 ± 1.6; $P < 0.001$).

Conclusion. (*1*) Cadaveric kidneys continue to undergo prolonged periods of cold ischemia; (*2*) prolonged cold storage is associated with longer distance traveled by the kidneys, but is not associated with any significant gain in tissue matching; and (*3*) prolonged cold ischemia is a significant predictor of long-term graft loss. Reducing prolonged cold ischemia by regional distribution of organs and less stringent tissue matching may reduce the persistent high rate of long-term loss of cadaveric renal allografts.

Sharing of cadaveric kidneys at national level improves tissue matching, but often lengthens the cold ischemia time (CIT). That prolonged CIT is a strong risk factor for delayed graft function (DGF) and graft loss is confirmed by a number of earlier analyses [1, 2]. In particular, Ojo et al demonstrated that DGF and acute transplant rejections were significant determinants of short- and long-term graft survival, and that CIT, among other covariates, was a significant factor for DGF and acute rejections [1]. In another study, Shoskes and Cecka examined the effect of acute rejection on DGF's influence on renal allograft survival and suggested a worse outcome for renal allografts with DGF and acute rejection [2]. Using CIT as a covariate, they also noted lower long-term survival for kidneys with longer CIT. Although there has been a substantial improvement in the acute survival of renal allografts, the chronic allograft loss, particularly those from cadaveric donors, continues to occur at an unacceptably higher rate [3]. The other parameter that has remained unchanged over the years is the CIT, which is again relevant to cadaveric kidneys. A reasonable supposition based on these two observations is that the higher long-term loss of cadaveric kidneys might be due to the persistence of prolonged CIT. In the studies mentioned above, CIT is essentially used as a covariate and the information provided on the effect of CIT on long-term graft survival is far from adequate. In contrast, we primarily focused on the effect of CIT on long-term graft survival. Unlike earlier studies, we characterized CIT in detail, examined the inter-relationships among CIT, tissue matching, distance traveled by the donor kidneys and the outcomes, and explored the effect of CIT both as a continuous as well as a categorical variable on long-term graft survival. Our analysis demonstrates that nearly half of the 6465 cadaveric kidneys transplanted in 1995 were cold stored for over 20 hours, and that prolonged cold ischemia remains a significant risk factor for long-term graft loss. Our analysis also suggests that cold ischemia time may correlate with the distance traveled by the kidneys, and may not be associated with significant gain in tissue matching.

METHODS

Study population

From the United Network for Organ Sharing (UNOS) registry, the patients who underwent cadaveric kidney-only transplantation for the first time in 1995 ($N = 6612$) were identified. The year 1995 was chosen because this allowed a 6-year follow-up. Patients with any form of previous transplantation were excluded to avoid introducing the confounding effects of previous immunosuppression and preformed antibodies on the allograft survival. A total of 6465 patients who had data on CIT, renal allograft status, and survival time formed the final subjects of this analysis.

Statistical analysis

Graft failure risks and survival rates were obtained from analyses based on Cox proportional hazard models. Effect of CIT on the graft failure risk was obtained by introducing CIT as a continuous variable, both in univariate and multivariate Cox models. In the multivariate model, known predictors of graft survival (i.e., donor age, recipient age and race, HLA mismatch, panel reactive antibody status, and first 6 months' rejection treatments) were included [1, 2, 4]. Analysis was repeated by introducing CIT as categorical variables, grouped at 10-hour intervals (i.e., 0 to 10 hours, 11 to 20 hours, 21 to 30 hours, and >30 hours), thus providing a clinically relatable time frame. The UNOS data provides information on patients who died with a functioning renal graft. This was approximately 12% of recipients used for our analysis. Therefore, for the survival analysis, we considered two definitions of an event in subsequent Cox models. In the first definition, events included both allograft failures and death, regardless of the status of kidney function. In the second definition, subjects who died with a functioning kidney were considered censored observations and therefore not included as an event. Little difference was observed in the relationship between CIT and survival using both definitions of event. Therefore, the results presented here are from the analysis using death with functioning graft considered as censored. Analysis was also repeated allowing left censoring of the graft time to the first 6 months (i.e., grafts that failed during the first 6 months of transplantation were excluded), to see whether the long-term effect of cold ischemia could be demonstrated without including the early graft loss.

All analyses were performed using the entire study population (i.e., 6465 recipients and graft survival time and status were used as recorded in the UNOS database). The results of the survival analysis are presented as hazard rate ratios with 95% confidence intervals (CI). Analyses of differences in covariates across CIT groups were carried out with analysis of variance (ANOVA) and reported as mean ± SD. Association between continuous
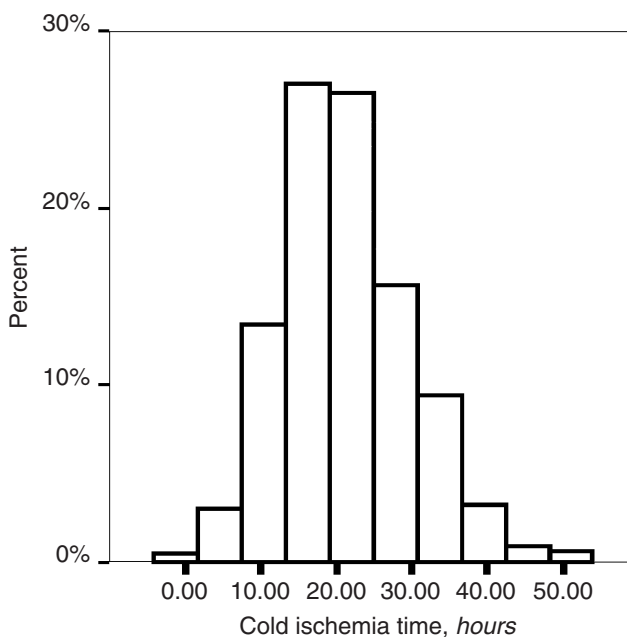

Fig. 1. Frequency distribution of the cold ischemia time sustained by cadaveric kidneys before transplantation.

variables was determined by simple correlation analysis. A probability value of $P < 0.05$ was considered statistically significant. The analysis was carried out using SPSS computer program, version 10.1.3 (Chicago, IL, USA) and the findings were independently verified by two of the authors.

RESULTS

Recipient characteristics

The mean age of the 6465 cadaveric renal allograft recipients was 44 ± 14 years; 62% were males. The race distribution was 66% white, 28% black, and 6% others. The reported causes of renal failure were diabetes mellitus in 24%, hypertension in 23%, glomerulonephritis in 25%, polycystic kidney disease in 10%, and others in 18%; the latter included renal failure from congenital, metabolic, obstructive, infective, and malignancy causes. These patients waited for an average 414 ± 396 days to obtain a kidney transplant. The HLA match and the mismatch out of a maximum of 6 were 2.1 ± 1.4 and 3.6 ± 1.5, respectively. The most recent panel reactive antibodies were positive (>10%) in 8% of recipients. The mean CIT of the kidney was 21 ± 7 hours and its frequency distribution is presented in Figure 1.

CIT and its effect on long-term graft survival

In the univariate analysis, increase in CIT as a continuous predictor was associated with a significant increase

Table 1. Hazard risk ratio (RR) of graft failure as a function of CIT in the univariate and multivariate Cox proportional hazard analysis

	RR	95% CI	*P* value
Univariate analysis			
CIT (10 hours)	1.120	1.06–1.18	<0.001
Multivariate analysis			
CIT (10 hours)[a]	1.140	1.02–1.25	0.020
Age, donor	1.015	1.009–1.020	<0.001
Age, recipient	0.980	0.973–0.986	<0.001
Race, recipient (black vs. white)	1.214	1.095–1.345	<0.001
HLA mismatch	1.131	1.064–1.202	<0.001
Panel reactive antibodies >10% vs. ≤10%	1.645	1.195–2.264	0.002
Number of rejection treatments in the first 6 months	1.617	1.334–1.961	<0.001

CIT is cold ischemia time. CIT is used as continuous variable and the observation begins with transplantation.

[a]The effect of CIT (10 hours) on multivariate graft survival after excluding the "number of rejection treatments in the first 6 months" variable from the model was an RR of 1.12 (95% CI: 1.06–1.19); *P* < 0.001.

Table 2. Characteristics of the recipients and donors based on kidneys' cold ischemia time subgrouped into 4 categories

Recipients' characteristic	Category of cold ischemia time *hours*			
	I	II	III	IV
	(0–10)	(11–20)	(21–30)	(>30)
Age *years*	44 ± 15	45 ± 14	45 ± 14	46 ± 13
Race %				
White	67	66	68	62
Black	25	28	28	32
Others	8	6	4	6
Male %	61	63	62	65
Primary kidney disease %				
Diabetes mellitus	20	22	22	22
Hypertension	22	22	23	24
Glomerulonephritis	25	23	27	27
Polycystic kidney disease	10	11	11	9
Others	23	21	17	18
Waiting time for transplantation *days*	380 ± 382	410 ± 388	428 ± 415	413 ± 415
HLA				
Match[a]	2.1 ± 1.4	2.5 ± 1.5	2.7 ± 1.6	2.4 ± 1.5
Mismatch[b]	3.6 ± 1.5	3.2 ± 1.6	3.0 ± 1.8	3.3 ± 1.6
Distance traveled by the kidneys *miles*[c]	116 ± 290	170 ± 340	429 ± 613	589 ± 725
Serum creatinine at post-transplant hospital discharge *mg/dL*[d]	2.2 ± 1.9	2.7 ± 2.3	3.2 ± 2.7	3.9 ± 3.0
Donors' characteristics				
Age *years*	32 ± 16	34 ± 17	34 ± 18	33 ± 18
Race %				
White	67	66	68	62
Black	9	12	12	12
Others	3	2	3	6
Male %	60	59	59	62
Head trauma %	36	37	37	37

[a]*P* < 0.001 by analysis of variance (ANOVA): Post-hoc Bonferroni: *P* < 0.05 in all interactions except II vs. IV, *P* = 0.14.

[b]*P* < 0.001 by ANOVA: Post-hoc Bonferroni: *P* < 0.05 in all comparisons except II vs. IV, *P* = 0.39.

[c]*P* < 0.001 by ANOVA: Post-hoc Bonferroni: *P* < 0.05 in all comparisons.

[d]*P* < 0.001 by ANOVA: Post-hoc Bonferroni: *P* < 0.01 in all comparisons.

in the RR for graft failure (Table 1). A 10-hour increase in CIT was attended by a 12% increase in the RR (RR = 1.12, 95% CI, 1.06–1.18; *P* < 0.001) for graft failure over the 6-year period. In the multivariate analysis, despite the inclusion of a number of known, strong predictors of graft survival (i.e., donor age, recipient age and race, HLA mismatch, panel reactive antibody status, and first 6 months' rejection treatments) CIT persisted (RR = 1.14; 95% CI, 1.02–1.25; *P* = 0.021) as a significant risk factor for long-term allograft failure. As expected, the covariates had significant effects on long-term graft failure in our analysis (Table 1). RR for long-term graft failure was significantly higher with higher donor age, HLA mismatch, panel reactive antibodies, and rejection treatments. Black recipients, compared to white, had significantly higher risk for graft failure, whereas recipients' age had a negative relationship with graft failure. In our analysis, 5% of patients were aged less than 18 years, 30% were 18 to 40 years, and 65% were 40 to 84 years. A univariate analysis of recipients' age against graft failure also showed a negative relationship (RR = 0.981, 95% CI, 0.981–0.987; *P* < 0.001). When this relationship was reanalyzed without accounting for the death-associated functioning grafts, the RR for the effect of age on graft failure was positive but did not reach statistical significance (RR = 1.002; 95% CI, 0.99–1.005; *P* = 0.112). It should also be noted that for multivariate analysis, we did not include any acute renal injury variables because these parameters are known to be strongly associated with CIT [1, 2]. Consistently, we also found that the discharge serum creatinine closely and directly correlated with CIT (Table II), and so, not surprisingly, due to colinearity, inclusion of discharge serum creatinine in the multivariate analysis had rendered the association between CIT and allograft survival insignificant.

The effect of CIT on graft survival was reanalyzed with CIT grouped at 10-hour intervals. Based on the 10-hour categorization, 9% of the kidneys were stored in the cold for 0 to 10 hours, 40% for 11 to 20 hours, 37% for 21 to 30 hours, and 14% for over 30 hours. The characteristics of the recipients and donors based on CIT categories are presented in Table 2.

Age, gender, primary renal disease, race, and wait of recipients for the transplantation were not different among the CIT categories. A significant correlation existed between CIT and HLA match or mismatch (both *r* = 0.30, *P* < 0.001). However, the extent of HLA match or mismatch with regard to CIT category was not uniform (Table 2).

The HLA match score in CIT category >30 hours was lower than 21 to 30 hours (2.4 ± 1.5 vs. 2.7 ± 1.6; *P* < 0.001) and not different from 11 to 20 hours (2.5 ± 1.5; *P* = 0.14). A finding consistent to HLA match score

was also observed with percent of transplantation with 6-antigen match. The matches were 2.5%, 3.9%, 7.2%, and 3.8% for 0 to 10 hours, 11 to 20 hours, 21 to 30 hours, and >30 hours CIT categories, respectively. Converse to match, the HLA mismatch was higher >30 hours than 21 to 30 hours (3.3 ± 1.6 vs. 3.0 ± 1.8; $P < 0.001$) and not different from 11 to 20 hours (3.2 ± 1.6; $P = 0.36$). A significant correlation existed between the distance traveled by the kidneys and the CIT ($r = 0.30$, $P < 0.001$), such that among the CIT categories the distance from the site of procurement of the kidney to transplantation progressively increased. The distances were 116 ± 290 miles, 170 ± 340 miles, 429 ± 613 miles, 589 ± 725 miles for CIT 0 to 10 hours, 11 to 20 hours, 21 to 30 hours, and >30 hours, respectively ($P < 0.001$ for all comparisons). The distance traveled by the kidney, in turn, correlated with HLA matching ($R = 0.30$; $P < 0.001$). Serum creatinine levels at the time of first hospital discharge after transplantation also showed a significant positive correlation with CIT ($R = 0.20$; $P < 0.001$), and were 2.2 ± 1.9 mg/dL, 2.7 ± 2.4 mg/dL, 3.2 ± 2.7 mg/dL, 3.9 ± 3 mg/dL for CIT 0 to 10 hours, 11 to 20 hours, 21 to 30 hours, and >30 hour, respectively ($P < 0.001$ for all comparisons). With regard to donors (Table 2), the donor characteristics of age, gender, race, and cause of death such as head trauma were not different among the CIT categories. When graft survival was reanalyzed using the CIT as categorical variables, the RR again increased with increasing CIT in the categories ($P = 0.008$) (Fig. 2). Compared to the referent group of 0 to 10 hours with an assigned RR of l, the 6-year survival was worse, but not statistically significant, for 11 to 20 hours CIT (RR = 1.03; 95% CI, 0.85–1.24; $P = 0.79$), 21 to 30 hours CIT (RR = 1.12; 95% CI, 0.92–1.35; $P = 0.27$), and significantly worse for >30 hours CIT (RR = 1.32; 95% CI, 1.07–1.63; $P = 0.011$).

When the analysis was repeated with accounting for left censoring of the graft time to first 6 months (i.e., by excluding 750 grafts that failed during the first 6 months of transplantation to see if the detrimental long-term effect of cold ischemia could be demonstrated without the early loss), the above finding was reproducible; compared to 0 to 10 hours, the 6-year survival was worse for 11 to 20 hours CIT (RR = 1.10; 95% CI, 0.86–1.38; $P = 0.47$), 21 to 30 hours CIT (RR = 1.19; 95% CI, 0.94–1.50; $P = 0.27$), and significantly worse for >30 hours CIT (RR = 1.32; 95% CI, 1.01–1.72; $P = 0.042$).

DISCUSSION

Our analysis demonstrates that nearly half of the 6465 cadaveric kidneys transplanted in 1995 were cold stored for over 20 hours, and that prolonged cold ischemia remains a significant risk factor for long-term allograft loss. Furthermore, prolonged cold ischemia was found to be a
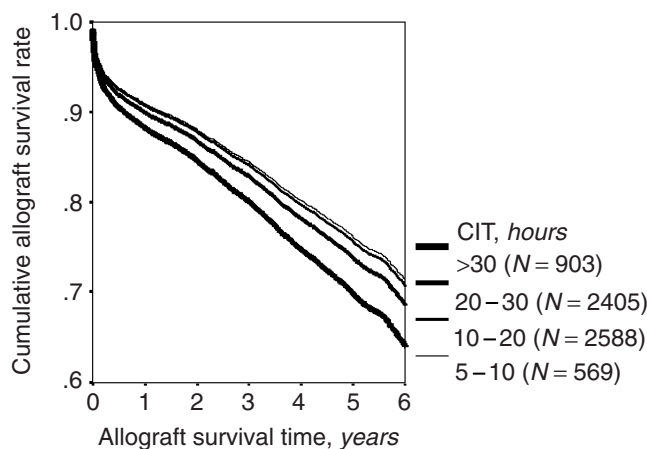

Fig. 2. Cadaveric renal allograft survival rates against 4 categories of cold ischemia time (CIT) based on Cox regression analysis. Overall, the survival rate was significantly different among the CIT categories ($P < 0.001$). Between specific groups, it was significantly lower for the CIT category of >30 hours versus 0 to 10 hours ($P = 0.011$), but not between CIT category of 0 to 10 hours and 11 to 20 hours ($P = 0.7920$) or 21 to 30 hours ($P = 0.265$).

function of distance traveled by the kidneys and, against expectation, was not associated with any significant gain in tissue matching.

Cadaveric renal allografts have shorter survival than renal allografts from live donors, irrespective of whether the live donor is related, unrelated, or well matched [5]. Donor factors such as brain death and CIT are unique to cadaveric donors, and their influence may account for much of the survival difference. Prolonged cold ischemia is strongly associated with early allograft dysfunction [1], and consistently in our analysis post-transplant discharge serum creatinine strongly and directly correlated with CIT. Thus, prolonged cold ischemia is attended by both acute, as well as chronic, renal injury. A strong colinearity between these two dependent measures on cold ischemic injury is suggested by the fact that introduction of acute injury variable such as discharge serum creatinine had rendered the relationship between CIT and graft survival insignificant. Based on the response-to-injury hypothesis [6–8], early injury from cold ischemia may set the stage for indolent, yet chronically progressive, damage leading to higher rates of chronic graft loss noted in this analysis of kidneys subjected to extended cold storage. Whether the chronic loss of graft is a direct effect of cold ischemia or through irreversible acute injury is an intriguing question that requires separate analysis using follow-up renal function.

The average CIT reported in the UNOS registry over the years has more or less remained unchanged around 20 hours. This was not different in our analysis, with nearly half of the kidneys stored in the cold for over 20 hours, and 14% over 30 hours. The lack of reduction in cold storage time over the years may partly explain for the

persistence of delayed graft function and the persistence of chronic allograft loss [1, 3]. In contrast, the striking improvement in early renal allograft survival is credited with refinement in immunosuppression therapy through reduced frequency of early renal allograft rejection [9]. However, our finding that CIT continues to exert negative influence on the long-term graft survival even after adjusting for the early episodes of rejection suggests that cold injury still remains a potentially modifiable risk factor for the long-term allograft failure. Although there are new insights into the mechanisms of cold ischemic renal injury, as well as of chronic allograft nephropathy [10–12], any clinical intervention to reduce chronic allograft loss other than reducing the cold storage time is unlikely in the near future. In our analysis, the best long-term survival was observed for kidneys with the least duration of cold ischemia. However, the relationship between CIT and long-term allograft failure was not strictly linear in that, although there was progressive increase in the failure rate with increase in cold storage time, appreciable increase in the failure rate was seen mainly in kidneys subjected to cold storage for over 20 hours, with statistically significant increase only for kidneys kept in the cold for over 30 hours. This suggests that a CIT less than 30 hours, preferably 20 hours, is less likely to be associated increased long-term allograft failure.

As noted in our analysis, shipping kidneys in the cold to further distances, presumably to increase HLA matching, increased the cold ischemia time. Yet kidneys that sustained prolonged cold ischemia did not have significantly higher HLA matching. It could be argued rightly that shipping further away from the site of procurement had, however, maintained the HLA matching on average of 2.5 antigens. However, with the use of more potent and precise immunosuppressants, the benefit of partial HLA matching on graft survival is less clear than before [13]. Thus, as noted in our analysis, the survival of less well-matched kidneys with shorter storage times may be better than that of well-matched kidneys with longer storage times. Therefore, strategies could be implemented by the kidney-sharing networks to avoid whenever possible prolonged cold storage by utilizing the kidneys closer to procurement sites, and, if necessary, with lower HLA match. With the increasing scarcity for donor kidneys, the criteria for useable kidneys have become less stringent [14]. In our analysis, although best survival was seen in kidneys subjected to least duration of cold storage, nearly 65% of grafts that underwent more than 30 hours of cold storage were still functional at 6 years. Thus, while prolonged cold storage should be avoided as a routine practice, any potentially viable kidney should be considered for transplantation, irrespective of cold storage time.

This study is undertaken with a database that uses nationwide sampling. It is in the public domain and therefore the validity of our analysis can be readily verified.

On the other hand, the data is observational and reported as they were presented to the UNOS by the participating transplant centers. Furthermore, our analysis could be carried out in many different ways. For example, one could begin at an early period with a longer follow-up or one could have a larger number of patients with a longer follow-up. A third approach could be to compare data of the late 1980s with the late 1990s to see if change in immunosuppression had any influence on cold ischemia's effect on graft survival. We also recognize that one could disagree with our approach of not including acute injury parameters in the multivariate analysis examining the effect of CIT on long-term graft survival, or, for that matter, dividing the cold ischemia time at 10-hour intervals. Although there is no specific reason to believe that immunosuppression will be any different among different CIT groups, one could argue that the interpretation would have been more meaningful with data on acute and chronic immunosuppression. We have used the first 6 months to account for acute allograft rejection, while others might have used the first 12 months. We have used rejection episodes based on both clinical and biopsy judgements; some would have used only biopsy-proven rejections, albeit small in number. Although it is beyond the immediate scope of this study, one would have liked data on serial renal function to determine whether cold ischemic acute injury leads to chronic injury. We recognize these and other potential limitations of our study and, therefore, we suggest that conclusions are to be drawn in the confines of our study. Our study, however, draws attention to a less widely discussed importance of cold ischemic injury on allograft injury, and in doing so, sheds light on the disturbing possibility that prolonged cold ischemia may not necessarily be associated with any better tissue matching. Our study also provides some clues as to what would be a safe duration for cold ischemia and suggests considering regional distribution of retrieved kidneys as a way to reduce cold ischemia time.

CONCLUSION

Using a subset of UNOS data on primary cadaveric kidney transplants performed in 1995, we demonstrated that cadaveric kidneys continue to be subjected to prolonged cold ischemia periods, and the latter remains a significant risk for long-term graft loss. Reducing cold ischemia time by less stringent tissue matching and regional distribution of organs may reduce the persistent high rate of long-term cadaveric renal allograft loss.

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