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Long-Term Survival After Retransplantation of the Liver

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Objective

The authors determined the long-term outcome of patients undergoing hepatic retransplantation at their institution. Donor, operative, and recipient factors impacting on outcome as well as parameters of patient resource utilization were examined.

Summary Background Data

Hepatic retransplantation provides the only available option for liver transplant recipients in whom an existing graft has failed. However, such patients are known to exhibit patient and graft survival after retransplantation that is inferior to that expected using the same organs in naïve recipients. The critical shortage of donor organs and resultant prolonged patient waiting periods before transplantation prompted the authors to evaluate the results of a liberal policy of retransplantation and to examine the factors contributing to the inferior outcome observed in retransplanted patients.

Methods

A total of 2053 liver transplants were performed at the UCLA Medical Center during a 13-year period from February 1, 1984, to October 1, 1996. A total of 356 retransplants were performed in 299 patients (retransplant rate = 17%). Multivariate regression analysis was performed to identify variables associated with survival. Additionally, a case–control comparison was performed between the last 150 retransplanted patients and 150 primarily transplanted patients who were matched for age and United Network of Organ Sharing (UNOS) status. Differences between these groups in donor, operative, and recipient variables were studied for their correlation with patient survival. Days of hospital and intensive care unit stay, and hospital charges incurred during the transplant admissions were compared for retransplanted patients and control patients.

Results

Survival of retransplanted patients at 1, 5, and 10 years was 62%, 47%, and 45%, respectively. This survival is significantly less than that seen in patients undergoing primary hepatic transplantation at the authors' center during the same period (83%, 74%, and 68%). A number of variables proved to have a significant impact on outcome including recipient age group, interval to retransplantation, total number of grafts, and recipient UNOS status. Recipient primary diagnosis, cause for retransplantation, and whether the patient was retransplanted before or after June 1, 1992, did not reach statistical

significance as factors influencing survival. In the case–control comparison, the authors found that of the more than 25 variables studied, only preoperative ventilator status showed both a significant difference between control patients and retransplanted patients and also was a factor predictive of survival in retransplanted patients. Retransplant patients had significantly longer hospital and intensive care unit stays and accumulated total hospitalization charges more than 170% of those by control patients.

Conclusions

Hepatic retransplantation, although life-saving in almost 50% of patients with a failing liver allograft, is costly and uses scarce donor organs inefficiently. The data presented define patient characteristics and preoperative variables that impact patient outcome and should assist in the rational application of retransplantation.

The only therapeutic option for patients with a failing liver allograft is retransplantation. Prior studies, however, have showed worse patient and graft survival after retransplantation when compared to primary grafting.[1–7] Although more recent data show improvement in survival after retransplantation,[8] the generally inferior outcome in this cohort has prompted some to question the appropriateness of hepatic retransplantation on both economic and ethical grounds.[9–12] These concerns assume even greater relevance when considered in the context of an ever-increasing shortage of donor organs and the growing financial constraints imposed by the deeper penetration of managed care into the transplant environment.

Previous reports usually have had insufficient follow-up and been comprised of too small a sample size to permit meaningful conclusions regarding the long-term efficacy of retransplantation. Moreover, the factors responsible for the poorer outcome of retransplanted patients are as-yet undefined. As with primary transplantation, a combination of overall recipient condition, quality of the donor organ, and conduct of the operation are important determinants of outcome.[13]

Operative complications clearly impact successful hepatic transplantation. However, most, but not all,[5] authors suggest that liver retransplantation technically is less demanding than primary transplantation owing to the simplicity of the recipient hepatectomy, as evidenced by a requirement for less intraoperative blood product administration.[1,13] This pertains to retransplants performed early in the postoperative period, whereas patients retransplanted after a prolonged delay may prove especially challenging.[7,14] Paradoxically, patients retransplanted late present the most arduous technical challenges, yet generally have shown better survival than those with a short interval between first and second transplants.[12,14]

In addition to operative explanations, it is possible that the inferior survival after retransplantation is a reflection of a sicker recipient population. It is well documented that outcome after primary grafting is correlated with the United Network of Organ Sharing (UNOS) status of the recipient,[15] and it is reasonable to assume that this also might apply to cases of retransplantation. Similarly, it is conceivable that sicker patients in desperate need of retransplantation more often receive grafts of marginal quality, further reducing the probability of optimal outcome.

In the current work, we examined the records of all patients retransplanted at our institution to define recipient, donor, and operative variables that adversely impact outcome. Based on long-term follow-up of a large patient population, our experience may prove useful as an objective measure for the selection of patients for retransplantation.

MATERIALS AND METHODS

Patients

From February 1, 1984, to October 1, 1996, a total of 2057 consecutive liver transplants were performed in 1701 patients at the Dumont-UCLA Transplant Center. Two hundred ninety-nine patients required retransplantation with 356 liver grafts: 250 patients received a total of 2 grafts, 43 patients received 3 grafts, and 6 patients received more than 3 grafts. Adult patients (18 years of age or younger at the time of transplant) comprised 72.2% of the series.

We performed a retrospective analysis of the records of these patients as well as the records of 150 control patients that were transplanted only once. Control patients were matched with the last 150 retransplanted individuals based on the nearest date of transplant, UNOS status, and age. Patients not seen in follow-up within 4 months of

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Table 1. DIAGNOSES IN PATIENTS UNDERGOING RETRANSPLANTATION

	Diagnosis	n	%
A. Primary transplant	Viral hepatitis	91	30.4
	Alcohol abuse	24	8.0
	Cholestatic	38	12.7
	Metabolic	18	6.0
	Biliary atresia	46	15.4
	Fulminant failure	23	7.7
	Hepatocellular cancer	5	1.7
	Miscellaneous	54	18.1
B. Retransplant	Primary nonfunction	77	27.9
	Delayed nonfunction	46	16.7
	Hepatic artery thrombosis	68	24.6
	Rejection	54	19.6
	Biliary	9	3.3
	Recurrent disease	10	3.6
	Miscellaneous	12	4.3

study date termination (October 1, 1996) were contacted by telephone. Two patients were lost to follow-up, and their date of last visit was recorded as date of last follow-up. For three patients known to have died but for whom the exact date of death could not be determined, the date of last contact was recorded as the date of death.

Study Design

A number of variables were studied for the entire cohort of 299 retransplanted patients including age group, primary diagnosis, diagnosis leading to retransplantation, interval to retransplantation, era in which the retransplant was performed, UNOS status, and total number of transplants. Age group was defined as either pediatric (younger than 18 years of age) or adult (18 years of age or older). Primary diagnoses are listed in Table 1A. Diagnoses leading to retransplantation are listed in Table 1B. Primary nonfunction is defined as graft failure requiring retransplantation within 1 week of prior transplant without other identifiable cause. Delayed nonfunction is defined as graft failure requiring retransplantation after 1 week without other definable cause. Era was defined as either retransplant before or after June 1, 1992. The UNOS status was defined as follows: UNOS status 1, patients in intensive care unit (ICU); status 2, hospitalized patients; and status 3, patients at home. For patients transplanted before April 1, 1995, the previously used UNOS classification was converted to the current system.

Case–Control Study

For the last 150 retransplanted patients and 150 matched control patients, additional donor, recipient, or intraoperative factors were determined and are summarized in Table 2. Endpoints under study included graft failure (defined as either patient death or retransplantation) and patient death. Additional outcome variables included length of hospital stay, length of ICU stay, and hospital charges incurred during the admissions required for the primary or retransplant or both. Charges were expressed as a ratio by dividing charges of control or retransplant patients by the mean charges accrued during admission by all patients at our institution undergoing transplantation during the period between July 1, 1992, to July 1, 1996. Charges are reported on a per-hospital admission basis and are summarized for control patients for a single admission and for retransplanted patients for one or two admissions depending on whether the patient was discharged before retransplantation. Length of stay and charges data were available for 148 of 150 control patients and for 133 of 150 of those retransplanted.

Cause of death was analyzed for retransplanted and control patients and recorded using standardized UNOS cause of death codes. For statistical comparison, codes were further grouped into either septic (bacterial or fungal) or nonseptic causes. Cause of death data were available for 56 of 59 deaths in the retransplant group and 31 of 35 control patient deaths. The cause of death was recorded as the primary factor responsible for the patient's death. Cases in which severe graft dysfunction or other organ system failure preceded sepsis were recorded as a nonseptic cause.

Statistical Analysis

Survival analysis was performed using the Kaplan–Meier method. Group survival curves were compared us-

Table 2. VARIABLES STUDIED

Donor	Operative	Recipient
Donor age	PRBCs	UNOS status
Hospital days	FFP	ICU
Dopamine dose	Cryoprecipitate	Hospital
Ischemia time	Platelets	Ventilator preoperation
	Aortic graft	Dialysis preoperation
	PV graft	Total bilirubin
	PV thrombectomy	Prothrombin time
	Venovenus bypass	BUN
	Other transplants	Creatinine
		Age group
		Primary diagnosis
		Retransplant diagnosis
		Retransplant interval
		Date of retransplant
		Total retransplants
		Immunosuppressant

PRBCs = packed red blood cells; FFP = fresh frozen plasma; PV = portal vein; UNOS = United Network of Organ Sharing.

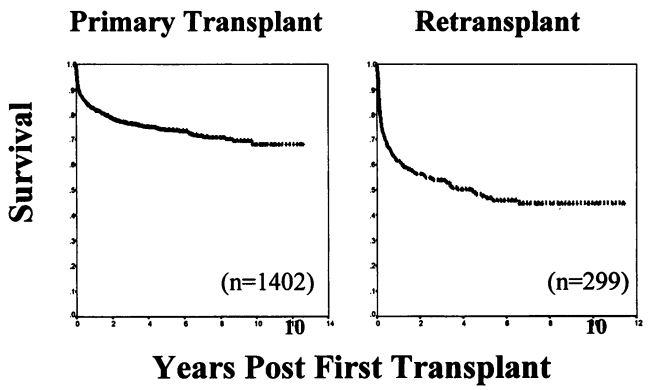

Figure 1. Kaplan–Meier survival estimates of patients undergoing primary transplantation (n = 1402) and retransplantation (n = 299) calculated from the date of the first transplant.

ing the log–rank test for nonparametric data. For survival analysis, continuous variables were dichotomized using the median value for the group. Variables found to impact significantly on survival then were analyzed by Cox multivariate regression. Continuous variables were compared using a two-tailed t test for independent samples. Categoric data were compared using a chi square test. Cox regression analysis was performed using JMP (SAS Institute Inc, Cary, NC). All other statistical analyses used the SPSS statistical software program (SPSS Inc, Chicago, IL).

RESULTS

Retransplanted Patient Survival

Kaplan–Meier survival estimates for the entire group of 299 retransplanted patients are shown in Figure 1. Survival from the date of the first transplant to 1, 5, and 10 years was 62%, 47%, and 45%, respectively, and from the date of the second graft was 55%, 47%, and 44%, respectively. This is less than that of the 1402 patients transplanted during the same period who required only 1 transplant (83%, 74%, and 68%). It also is lower that that reported in the UNOS registry for unselected first transplants at 1 and 5 years (79% and 66%, respectively).[15]

Of 299 retransplanted patients, 156 (52.2%) remain alive. Of 143 total deaths, 127 (89%) occurred during the first year after retransplantation. In patients surviving more than 1 year, the likelihood of continued survival is high. Three patients have survived more than 10 years postretransplant and remain alive and well. Of 55 patients surviving more than 5 years postretransplant, 52 are alive and well.

Bivariate and Multivariate Regression Analyses of Survival

A number of variables were studied for their impact on retransplant patient survival (Table 3). In a bivariate

Table 3. ANALYSIS OF PATIENT SURVIVAL AFTER RETRANSPLANTATION

Variable	Subgroup	(n)	Patient Survival (%)			p Value
			1 Year	5 Year	10 Year	
Age group	Pediatric	(83)	63	58	56	0.031
	Adult	(216)	52	42	38	
Retransplant interval	<7 days	(96)	58	47	40	0.005
	8–30 days	(100)	42	38	36	
	>30 days	(103)	64	55	—	
Total transplants	2	(250)	57	51	50	0.07
	3	(43)	50	35	—	
	>3	(6)	0	—	—	
UNOS status	1	(230)	52	45	42	0.015
	2	(36)	72	59	—	
	3	(14)	91	61	—	
Era of retransplant	Before 6/1/92	(149)	52	45	42	0.38
	After 6/1/92	(150)	58	—	—	
Retransplant indication	PNF	(77)	63	54	47	0.23
	HAT	(46)	67	53	—	
	DNF	(68)	40	32	—	
	Rejection	(54)	55	52	52	
	Recurrent disease	(10)	41	—	—	
	Biliary	(9)	25	—	—	
	Miscellaneous	(12)	64	64	—	

PNF = primary non-function; HAT = hepatic artery thrombosis; DNF = delayed non-function.

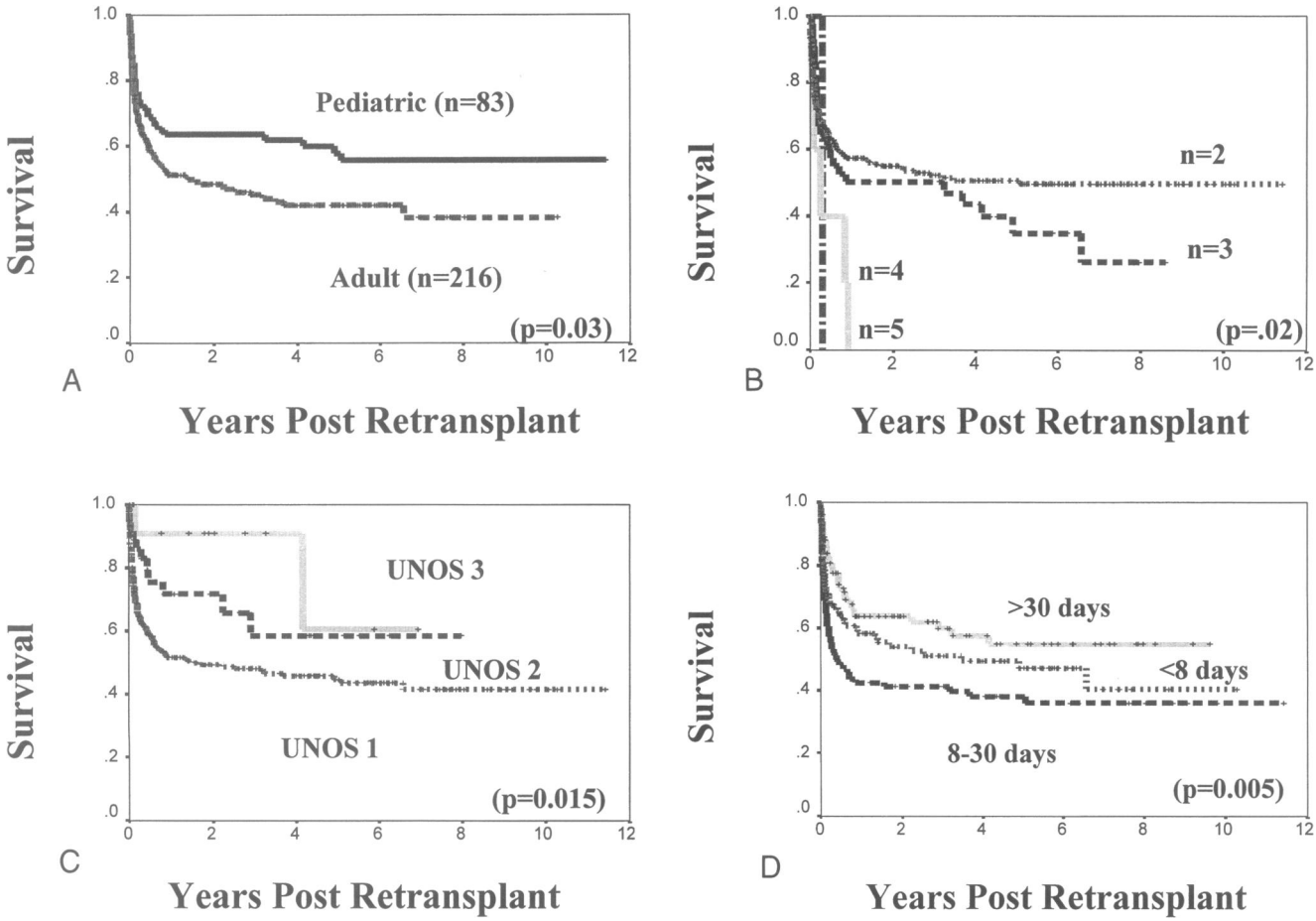

Figure 2. Survival of retransplanted patients stratified by age group (A), and total number of transplants in a single patient (B), United Network of Organ Sharing status (C), and interval to retransplantation (D). Data are calculated from the date of the first retransplant.

statistical analysis, age group, retransplant interval, total number of transplants, and UNOS status all reached statistical significance: pediatric patients showed markedly better survival than adults (Fig. 2A), and reduced survival correlated with an increasing total number of transplants (Fig. 2B) and higher UNOS status (Fig. 2C). Patients retransplanted more than 30 days after their initial transplant fared better than did those retransplanted between 8 and 30 days (Fig. 2D). The survival in patients transplanted within 1 week of the first graft was intermediate in the overall population. When these data were analyzed by age group, we found that survival in adults retransplanted within 1 week was nearly equivalent to that seen in those in the chronic group. In contrast, pediatric retransplants performed within 1 week of the first graft fared worse than did pediatric patients retransplanted between 8 and 30 days (data not shown).

Statistical significance between groups was not achieved when patient survival was stratified based on primary diagnosis (data not shown). A trend toward improved survival was observed in era 2 patients (*i.e.*, retransplanted after June 2, 1992), and when stratification was performed based on the indication for retransplantation, however, statistically significant differences were not detected.

The variables found significant in bivariate analysis were evaluated in forward and backward stepwise Cox regression models. All four variables (*i.e.*, age group, interval to retransplantation, total number of transplants, and UNOS status) were found to be independent risk factors for patient death with relative risks from 1.3 to 1.9 (data not shown).

Case–Control Analysis

In an attempt to control for the significant effects of age group and UNOS status in the survival of retransplanted patients and to determine the influence of other donor, recipient, and operative variables on outcome, a case–control analysis was performed. Control patients selected to match the last 150 retransplanted patients for UNOS status, age group, and era of transplant show significantly

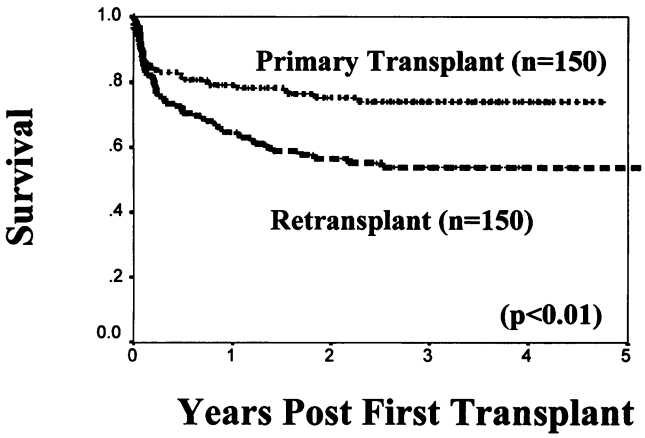

Figure 3. Comparison of survival in retransplanted patients and control patients matched for age group and United Network of Organ Sharing status who received a single transplant. Survival is calculated from the date of the first transplant.

better survival than do retransplanted patients ($p < 0.01$). Retransplanted patient survival at 1 year was 65% *versus* 79% for control patients (Fig. 3).

Case-Control Differences in Recipient, Operative, and Donor Variables

A panel of preoperative characteristics for both control and retransplant groups were studied to determine whether retransplanted patients were more seriously ill than were control patients despite matching for UNOS status. No differences were observed in mean recipient age, percentage of patients requiring preoperative dialysis, or in preoperative total bilirubin or serum creatinine (Table 4). Control patients had significantly higher prothrombin times. Retransplanted patients had higher average blood urea nitrogen levels and were more likely to require preoperative mechanical ventilator support than were control patients (46.7% *vs.* 26.7%). When survival curves for retransplanted and control patients were stratified to control for ventilator status, retransplanted patients still had a significantly worse survival than did control patients for both ventilated and nonventilated states. Control and retransplant groups also differed in the proportion of various diagnoses that lead to the primary transplant. However, primary diagnosis had no statistically significant impact on survival in either group (data not shown).

To evaluate whether differences in the donor organ graft might account for survival differences observed in the groups under study, we compared donor characteristics for the two groups. No differences were evident in donor age, the maximum dose of dopamine required, or the cold ischemia time (defined as the period from cross-clamping in the donor until portal reperfusion in the recipient). A modest but statistically significant difference was detected in the duration of preharvest hospital stay of the donor with control donor stay being slightly longer (Table 5). Even if clinically relevant, this difference would likely bias better survival against the control group and thus cannot help explain the poorer survival in the retransplanted group.

Control and retransplanted patients also were compared according to the surgical complexity of the transplant performed and the requirement for intraoperative blood product administration. Retransplanted patients were significantly more likely to require a Roux-en-Y hepaticojejunostomy than were control patients (47.7% *vs.* 18.8%; Table 6). Similarly, use of an arterial conduit from the aorta for revascularization of the liver was reported in 28.2% of retransplanted recipients but only 9.5% of control patients ($p < 0.05$). Despite this apparent increase in the technical complexity of the retransplant procedure,

Table 4. PREOPERATIVE RECIPIENT CHARACTERISTICS FOR CONTROL AND FOR PATIENTS WHO UNDERWENT RETRANSPLANTATION

	Controls	Retransplant	p Value
Recipient age (yr)	41.6 ± 1.7	42.3 ± 1.6	NS
UNOS (%)			
1	76.7	76.7	NS
2	12	12	NS
3	11.3	11.3	NS
Adults/Children (%)	83.3/16.7	83.3/16.7	NS
ICU (%)	76.7	76.7	NS
Ventilator (%)	26.7	46.7	
Dialysis (%)	14.0	14.7	NS
In hospital (%)	88.7	88.7	NS
Total bilirubin (mg/dL)	17.5 ± 1.2	15.8 ± 0.99	NS
Prothrombin time (seconds)	18.9 ± 0.65	16.8 ± 0.61	<0.05
BUN (mg/dL)	32.6 ± 2.3	46.1 ± 2.5	<0.001
Creatinine (mg/dL)	2.0 ± 0.16	2.1 ± 0.14	NS

NS = not significant; UNOS = United Network of Organ Sharing.

Table 5. DONOR CHARACTERISTICS FOR CONTROL AND PATIENTS WHO UNDERWENT RETRANSPLANTATION

	Control	Retransplanted	p Value
Donor age (yr)	33.5 ± 1.6	32.5 ± 1.6	NS
Dopamine dose (μg/kg/min)	8.0 ± 0.54	7.7 ± 0.47	NS
Hospital stay (days)	3.1 ± 0.26	2.5 ± 0.17	<0.05
Cold ischemia (hr)	8:36 ± 0:16	8:45 ± 0:14	NS

NS = not significant.

Table 6. OPERATIVE PARAMETERS FOR CONTROL AND PATIENTS WHO UNDERWENT RETRANSPLANTATION

	Control (%)	Retransplanted (%)	p Value
Roux-en-y	18.8	47.7	<0.001
Venovenous bypass	78.5	80.0	NS
Aortic graft	9.5	28.2	<0.05
Portal vein graft	1.4	2.7	NS
Portal vein thrombectomy	8.8	1.3	<0.05
In situ split graft	2.0	2.0	NS
Living related donor	1.3	0.7	NS
Ex vivo reduced graft	5.3	3.3	NS
Intraoperative deaths	2.0	0.7	NS

		Interval to Retransplant			
Blood Product	**Control**	**Retransplanted**	**≤30 Days**	**>30 Days**	**p Value***
PRBCs	9.7 ± 0.56	9.0 ± 1.2	5.6 ± 0.58	14.2 ± 2.8	<0.01
FFP	13.6 ± 0.80	11.3 ± 1.4	8.6 ± 0.80	15.5 ± 3.1	<0.05
Platelets	11.0 ± 0.85	8.8 ± 0.87	10.0 ± 0.89	7.0 ± 1.7	NS

PRBCs = packed red blood cells; FFP = fresh frozen plasma; NS = not significant.
* Comparing patients retransplanted either ≤30 days or >30 days after primary grafting.

the mean quantity of intraoperative blood products infused was similar between the control and retransplant groups (Table 6).

When retransplant patient blood product usage data were segregated based on the interval to retransplant being either <30 days or >30 days, a significant difference was observed (Table 6). Patients retransplanted late used significantly more packed red blood cells (PRBCs) and fresh frozen plasma, suggesting a higher degree of operative difficulty in this subgroup. This difference did not necessarily impact on survival as patients retransplanted after 30 days fared better than did those transplanted before 30 days.

Case–Control Survival Analysis

For the case–control portion of the study, additional donor, recipient, and operative factors were compared for their impact on retransplant patient survival (Table 7). The variables reaching bivariate statistical significance in predicting retransplant patient death included serum creatinine >1.6, interval to retransplant, ICU status, and preoperative requirement for dialysis or ventilator support. Cold ischemia time, retransplant diagnosis, and total bilirubin showed borderline statistical significance. Blood product usage was only analyzed for adult patients because it is not controlled for patient size or weight. Administration of more than 6 units of PRBCs, 8 units of fresh frozen plasma, or 10 units of platelets all had significant impact on survival. Cox regression analysis was performed using all variables found to have significant bearing on outcome by bivariate testing. When performed for retransplanted patients, we found ischemia time >12 hours, ventilator, age group, creatinine, and total bilirubin to be independent factors predictive of survival (relative risks for these factors are listed in Table 7). For regression analysis, both serum creatinine and bilirubin were found to have greater statistical significance when entered as continuous rather than categoric variables. Relative risk values for these two variables are expressed in Table 7 as relative risk per unit increase in their measured values. No significant interactions between these variables were identified, suggesting they each carried additive risk.

Case–Control Analysis of Cause of Death

The cause of death for control and retransplanted patients was categorized into either septic or nonseptic etiologies. The incidence of death secondary to sepsis was significantly higher in retransplanted patients compared with that of control patients (60.7% *vs.* 29%) (Table 8). Of retransplanted patients in whom sepsis was the primary cause of death, there was a striking incidence of fungal infection (16 of 34 patients) only infrequently seen in control patients who died of sepsis (1 of 9 patients).

Case–Control Outcome Analysis

Length of hospital stay, length of ICU stay, and hospital charges were compared for control and retrans-

Table 7. BIVARIATE AND MULTIVARIATE ANALYSIS OF DONOR, RECIPIENT, AND OPERATIVE VARIABLES IN SURVIVAL OF PATIENTS WHO UNDERWENT RETRANSPLANTATION

Variable		1 Year Survival (%)	p Value	Relative Risk (95% confidence interval)
Donor				
Cold ischemia time	<12 hr (127)	62	0.056	2.1 (1.0–3.9)
	>12 hr (18)	30		
Maximum dopamine	< or >10 μg/kg/min	—	NS	
Donor age	< or >50 yr	—	NS	
Donor hospital stay	< or >2 days	—	NS	
Recipient				
Age group	Pediatric	71	0.10	1.3 (0.88–2.1)
	Adult	56		
TOLT		—	NS	
Interval to retransplant	0–7 days (50)	57	0.005	
	8–30 days (40)	40		
	>30 days (60)	71		
Fk506 *vs.* cyclosporine			NS	
UNOS status		—	NS	
ICU	No (34)	73	0.03	
	Yes (116)	54		
Dialysis	No (129)	63	0.001	
	Yes (21)	29		
Ventilator	No (80)	68	0.002	1.8 (0.94–3.3)
	Yes (70)	46		
Retransplant diagnosis	PNF (46)	57	0.053	
	HAT (34)	74		
	DNF (24)	39		
	Rejection (22)	70		
	Recurrent disease (11)	49		
	Biliary (6)	60		
	Miscellaneous (7)	29		
Creatinine	<1.6 (74)	71	0.0004	1.22 (1.02–1.45)
	>1.6 (76)	46		
Prothrombin time	<14.5	—	NS	
Total bilirubin	<12.8 (76)	67	0.05	1.03 (1.01–1.05)
	>12.8 (74)	49		
Operative (adults only)				
PRBCs	<6 units (68)	67	0.008	
	>6 units (55)	38		
FFP	<8 units (64)	68	0.01	
	>8 units (59)	42		
Platelets	<10 units (96)	63	0.00001	
	>10 units (27)	31		
Type of biliary reconstruction		—	NS	
Use arterial conduit		—	NS	

UNOS = United Network of Organ Sharing; TOLT = total number of orthotopic liver transplants; PNF = primary non-function; HAT = hepatic artery thrombosis; DNF = delayed non-function; PRBCs = packed red blood cells; FFP = fresh frozen plasma; NS = not significant.

planted patients. Data also were compared to mean length of stay and charge data for a group consisting of all patients transplanted in fiscal year 1992–1993 through 1995–1996. Data were stratified by age group. Based on patients for whom complete data were available, the total average hospital and ICU stay for matched control patients was significantly ($p < 0.01$) shorter than that seen for both retransplanted adults and pediatric patients (irrespective of whether retransplantation was performed during the same or different admission, Table 9). Retransplanted pediatric patients incurred the greatest total charges and, when retransplanted in a separate admission, had the longest mean total stay in the hospital (107.5 days) and longest mean total ICU stay (49.1 days). Both retransplant groups accrued significantly higher total charges than did con-

Table 8. CASE-CONTROL CAUSE OF DEATH ANALYSIS

Group (n)	Nonsepsis	Sepsis*	Fungal Sepsis
Control (31)	22 (71.0%)	9 (29.0%)	1/9
Retransplanted (54)	22 (39.3%)	34 (60.7%)	16/34

* $p < 0.01$, control *vs.* retransplanted patients.

trol patients. Whereas control adult mean charges totaled 1.2 times that of all adult patients, those retransplanted accrued charges 2.1 and 1.9 times that of all patients depending on whether one or two admissions were involved.

DISCUSSION

Our study indicates that hepatic retransplantation is an effective therapy for patients with liver allograft failure. Long-term survival can be anticipated in nearly 50% of all those retransplanted. This represents a dramatic improvement in expected survival for many patients, given the fact that approximately 80% of those retransplanted are UNOS status 1 and face imminent death without urgent retransplantation. Hepatic retransplantation entails a massive consumption of health care resources, however,[7,9,14] and arguably an inefficient use of scarce donor organs.[11,12]

Despite the inferior results compared to primary grafting, hepatic retransplantation can not be abandoned for the ethical and practical reasons that have been detailed previously.[16] Thus, a rational approach to balancing the conflicting responsibilities to patients in need of retransplantation and those awaiting a primary liver allograft is to refine the technique of retransplantation so that it is used as efficiently as possible.

One approach to this end entails identifying subgroups of patients in whom outcome will be so poor as to make retransplantation unjustifiable. For example, in our own experience, we discovered that no patients requiring more than three total transplants survive a year from the time of their first retransplantation. Similar findings were reported in a recent extensive analysis from the University of Pittsburgh.[16] In addition, using a logistic regression model, they identified a number of independent risk factors that predicted poor outcome at 1 year postretransplantation. Specifically, donor variables (*e.g.*, age and gender) and recipient variables (*e.g.*, creatinine, bilirubin, preoperative mechanical ventilation, recipient age, and choice of immunosuppression) showed independent prognostic significance. Although the donor variables we identified differed from those in the Pittsburgh study, the recipient variables they found are remarkably similar to the recipient factors we identified as relevant by Cox regression (creatinine, bilirubin, ventilator, and age group). We did not find choice of primary immunosuppressant to impact significantly on survival in bivariate analysis.

The regression model we derived theoretically can be applied to predict relative outcome based on characteristic donor and recipient variables. For example, as extreme cases, an adult patient not requiring the ventilator, with a creatinine of 2.1 and bilirubin of >15.8 who receives a liver with <12 hours of ischemia time would have a predicted survival at 1 year of 64.9%. In contrast, an otherwise similar patient who requires the ventilator and

Table 9. CASE-CONTROL OUTCOME ANALYSIS

Patient Group	n	Length of Stay (days)	ICU Stay (days)	Relative Charges
Unselected patients				
Adult	709	30.1	10.5	—
Pediatric	153	33.7	14.0	—
Case-control adults				
Control	124	36.8 ± 2.4	20.7 ± 2.9	1.22
Retransplanted				
Single admission	81	47.4 ± 3.3	33.3 ± 3.6	2.10
Two admissions	34			
1st		24.8 ± 3.1	6.7 ± 1.7	0.76
2nd		35.5 ± 3.4	12.4 ± 2.6	1.11
Case-control pediatric				
Control	24	32.9 ± 4.4	15.9 ± 2.8	0.93
Retransplanted				
Single admission	9	53.0 ± 7.2	39.9 ± 10.5	2.26
Two admissions	8			
1st		48.8 ± 6.2	16.4 ± 5.2	1.00
2nd		58.7 ± 9.1	32.7 ± 5.6	1.52

receives a liver with >12 hours of ischemia has a predicted 1-year survival of 20.9%.

Another strategy is to develop methods to improve outcome in patients undergoing retransplantation. This mandates elucidation of the factors responsible for the inferior outcome observed in retransplanted patients. To be considered a valid factor in explaining the survival discrepancy between control and retransplanted groups, two conditions should be satisfied:

1. The variable should differ significantly between control and retransplant groups.
2. The factor should show a significant impact on retransplanted patient survival.

In our study, the only variable tested that fulfilled these requirements was preoperative ventilator dependence. Whether preoperative ventilator dependence is indicative of a meaningful difference in the level of illness in the retransplanted group or merely the result of the fact that many of these patients recently are postoperative from their prior transplant currently is unclear.

We are left with the question of what other, as-yet undefined, factors might be responsible for the inferior results with retransplantation. One unique characteristic of retransplanted patients not considered in the analysis above is that in addition to being critically ill and undergoing major surgery, they are highly immunosuppressed. The hypothesis that retransplanted patients fare worse because of excessive immunosuppression also is compatible with our observation, and that reported previously by others,[12,14] that survival in patients retransplanted after a long delay is better than during the early post-transplant period, which is the time of most intense immunosuppression. The relatively better survival in the patients retransplanted late is especially noteworthy given the marked technical challenge that these patients often pose, as is evident in an approximate doubling of blood products used at surgery (Table 6).

Indirect evidence also supporting the possibility that heavy immunosuppression contributes to the reduced survival in retransplanted patients is our observation of a higher incidence of death due to sepsis in this group. Death resulting from fungal infection was unusual in control patients (1 of 31 deaths) but relatively common in retransplanted patient deaths (16 of 56 deaths). A high incidence of graft loss due to sepsis in retransplanted patients also has been reported previously by others.[1,4] Doyle et al.[16] reported that sepsis was the most frequent cause of graft failure, accounting for 44% of all grafts that were lost. Collectively, these studies suggest that interventional strategies should be designed to reduce immunosuppression or to initiate more effective antimicrobial prophylaxis for patients undergoing retransplantation.

In summary, our data confirm the utility of retransplantation as well as its inherent inefficiency and cost. For these reasons, we conclude that retransplantation must be applied with some discretion. Retransplantation in subgroups of patients with little chance of successful outcome should be avoided. For example, transplantation with more than three grafts, although only infrequently practiced to date, only should be considered in exceptional circumstances. Transplantation of a third graft should be scrutinized carefully and considered only in otherwise good risk patients.

We identified a number of recipient traits having significant negative predictive impact on outcome after retransplantation. The variables serum creatinine, serum bilirubin, age group, and the need for preoperative mechanical ventilation also were deemed significant by the other large series on this topic.[16] If their value is confirmed by prospective analysis, these factors, whereas not in themselves adequate to differentiate patients suitable for retransplantation, may be of assistance in determining the appropriateness of borderline individual cases.

Finally, our results indicate a dramatic incidence of death from infection in retransplanted patients and suggest possible therapeutic avenues to improve survival in this cohort. Further analysis of degree of immunosuppression, type of infection, use of antimicrobials, and incidence of rejection as well as prospective studies of outcome will be required to validate our hypothesis.

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Discussion

DR. CLYDE F. BARKER (Philadelphia, Pennsylvania): I congratulate Dr. Markmann on a very nice presentation and congratulate Dr. Busuttil on another very large and informative series that is of considerable value.

One hears anecdotal reports that perhaps second liver transplants do as well as the first.

The explanation is sometimes used that there isn't as much dissection for a second liver transplant or as much blood loss. But when one sees the real data as we have seen it here it is obvious (and hardly surprising) that the results of a second transplant are worse than those of a first by some 20%. Dr. Markmann has given us the reasons; namely, that it is a big operation, in sick patients made sicker by a big operation performed before the additional insult of immunosuppression.

Only with a large series like this carefully studied with multivariate analysis could one hope to analyze the specific reasons for the increased risk and perhaps identify those patients in whom an outcome approaching the success of a first transplant might be anticipated.

The authors have in fact identified some of these factors, and this should be very useful.

I wonder now if, with the use of this information, they have been able to develop a formula to select those patients favorable for retransplantation or re-retransplantation, and if they are currently using such a formula. If so, their practice must be different than that of others who, although they have had the same kind of outcome information in front of them, have not learned from it.

At least in our hands and those of most, retransplantation of patients is often done realizing that the chances of success will be poor. The emotional and financial impact of this practice is suboptimal. It also becomes an ethical issue because of the shortage of livers and their use under circumstances that have little chance to benefit some recipients.

I am interested as to how the authors are listing their patients now. Has their experience had any impact on their relisting patients for transplantation? Are they confident enough of their ability to predict outcome that they could advocate a national policy for allocation of livers for retransplantation? Although there are technical explanations for poorer outcomes of repeat transplants and other obvious ones—such as immunosuppression, sicker patients, two big operations in sequence, and so forth, is there any suggestion that part of the explanation is immunologic? Certainly second kidney transplants after ones that have been rapidly rejected have a diminished likelihood of success, presumably in part because of sensitization by the first transplant.

In the case of a liver transplant, in which humoral factors are less important and even those transplanted across positive crossmatches may work out, this possibility seems less likely. But one wonders whether there may be some immunologic reasons that the second transplant would not be as likely to work as the first.

DR. GORAN B. KLINTMALM (Dallas, Texas): When performing liver transplantation, we offer a patient, already once blessed with a second chance at life, a third, fourth, fifth chance at life. While a large number of patients die without even having received the first liver transplant. Thus, the use of liver allografts must be continuously evaluated to ensure their optimal use.

What we have just heard is the largest and most complete analysis on this subject given to date. In addition, it is to me the best manuscript I have had the pleasure to review from the Busuttil group. There is very little criticism to give. However, because it is very unlikely that we will see additional complete data on this subject, I would like to press the authors for more on their conclusions and recommendations.

They recommended not to retransplant with more than two additional grafts. Is that one too many? What about patients on ventilators? What about those on dialysis? Combinations? Those in the intensive care units, all of them later on dialysis? What is the total maximum relative risk score that we should allow? Also, with the heavy impact of intraoperative blood loss that is outlined in the manuscript, should retransplantation be reserved to the most experienced surgeon on the team? Is there a subgroup of patients not analyzed in this study? In Dallas, our experience with retransplanting patients with primary diagnosis of hepatitis C who are in graft failure at the time of the retransplant is that they all have died in septic failures. What is the authors' experience for this and other subgroups? Finally, in our current donor crisis, a prospective study is actually urgently needed.

When will that be done?

DR. ROBERT J. CORRY (Pittsburgh, Pennsylvania): Dr. Busuttil had asked Dr. Starzl to discuss this eloquent paper. Unfortunately, Dr. Starzl had another commitment and handed the ball off to me on Fifth Avenue as I was leaving for the airport, so I will attempt very humbly to say briefly what I believe his views would be.

Dr. Busuttil and his team at UCLA represent one of the