Analysis of Long-term Outcomes of 3200 Liver Transplantations Over Two Decades

A Single-Center Experience

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Objective: Few studies have evaluated long-term outcomes after orthotopic liver transplantation (OLT). This work analyzes the experience of nearly 2 decades by the same team in a single center. Outcomes of OLT and factors affecting survival were analyzed.

Methods: Retrospective analysis of 3200 consecutive OLTs that were performed at our institution, between February 1984 and December 31, 2001.

Results: Of 2662 recipients, 578 (21.7%) and 659 (24.7%) were pediatric and urgent patients, respectively. Overall 1-, 5-, 10-, and 15-year patient and graft survival estimates were 81%, 72%, 68%, 64% and 73%, 64%, 59%, 55%, respectively. Patient survival significantly improved in the second (1992–2001) versus the era I (1984–1991) of transplantation ($P < 0.001$). Similarly, graft survival was better in the era II of transplantation ($P < 0.02$). However, biliary and infectious complications increased in era II. When OLT indications were considered, best recipient survival was obtained in children with biliary atresia (82%, 79%, and 78% at 1, 5, and 10 years, respectively), while malignant disease in adult patients resulted in the worst outcomes of 68% and 43% at 1 and 5 years, post-OLT. Further, patients <18 years and nonurgent recipients exhibited superior survival when compared with recipients >18 years ($P < 0.001$) or urgent patients ($P < 0.001$). Of 13 donor and recipient variables, era of OLT, recipient age, urgent status, donor age, donor length of hospital stay, etiology of liver disease, retransplantation, warm and cold ischemia, but not graft type (whole, split, living-donor), significantly impacted patient survival.

Conclusions: Long-term benefits of OLT are greatest in pediatric and nonurgent patients. Multiple factors involving the recipient, etiology of liver disease, donor characteristics, operative variables, and surgical experience influence long-term survival outcomes. By balancing and matching these factors with a given recipient, optimum results can be achieved.

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Although the first orthotopic liver transplantation (OLT), in an animal model, was performed by Cannon at the University of California, Los Angeles (UCLA) in 1956,[1] the clinical feasibility of the procedure was demonstrated by the pioneering work of Starzl et al[2] in the 1960s and later experiences by Rolles et al.[3] For 20 years, the operation was performed infrequently by a few centers in the United States,[4] Europe,[5] and Great Britain.[6] Results of these early trials were disappointing, with 1-year patient survival of approximately 30%.[7,8] Although many of the technical principles were developed and standardized, there remained fundamental shortcomings, including the lack of suitable and safe immunosuppressive drugs; inferior techniques for organ preservation; inadequate anesthesia and critical care monitoring, which were needed for patients with end-stage liver disease (ESLD); poor patient selection, particularly related to severity of disease and disease recurrence; and grave skepticism within the medical community regarding the value and risk-benefit of liver replacement.[9]

In the early 1980s, introduction of the immunosuppressive agent cyclosporine A (CYA), a calcineurin inhibitor, resulted in a dramatic improvement in graft and patient survival after OLT. With the use of CYA and steroids, 1-year

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patient survival doubled to nearly 70%.[10] This effect was also observed in other solid organ transplants, resulting in rapid and sustained proliferation of abdominal and thoracic transplant procedures.[11] In 1983, the National Institutes of Health Consensus Conference declared that liver transplantation was nonexperimental and should be considered a therapeutic modality for selected patients with ESLD.[12]

The UCLA liver transplant program was organized in February 1983 and performed its first OLT on an adult patient with an unresectable schwanoma on February 1, 1984. The patient was discharged on postoperative day 17 but died of recurrence 6 months later.[13,14] Since that time, the UCLA program has been in continuous operation under the same leadership and is the oldest liver transplant program west of the Mississippi without a hiatus of clinical activity.

During the past 20 years, the UCLA program has been at the forefront of many advances in liver replacement. These have included technical innovation in both adult and pediatric recipients;[15–17] development and application of immunosuppressive strategies;[18–21] establishment of protocols for prevention and treatment of transplant-associated viral and fungal diseases;[22–27] demonstration of the feasibility of segmental grafts (both deceased and living donors) to expand the donor pool;[28–31] elucidation of principles to allow safe use of extended-criteria donors;[32,33] and development of clinical models to predict survival after transplantation,[34] retransplantation,[35] and outcomes in patients with hepatitis C virus (HCV) infection.[36]

These advances have been made possible through a large accumulated experience over 2 decades in both children and adults, which is reported herein. Ours is 1 of only 2 reports[37] in which more than 2500 recipients have been analyzed with a median follow-up of over 6.5 years and for which management protocols have been uniform with a gradual evolution over time. The purpose of this work is to report our overall experience with 3200 consecutive liver transplants performed at UCLA between 1984 and 2001. In this analysis, we focus upon survival outcomes, incidence, and scope of complications, donor and recipient factors that influence patient survival. Finally, we analyze the modifications in our management that have had the greatest effects on outcome.

MATERIALS AND METHODS

Patients

All adult and pediatric OLT recipients that were transplanted at our center from 1984 through 2001 were included in the study. Demographic data, as well as morbidity and mortality, were obtained by retrospective review of inpatient and outpatient records, in addition to verification from our liver transplant database. Rigid criteria for organ acceptance were used in the first 100 donors.[14] Since then, absolute contraindications for donor organs included positivity of human immunodeficiency virus (HIV), human lymphotrophic virus, hepatitis B surface antigen, >40% macrovesicular steatosis, or presence of extracranial malignancies. All other donors were considered; livers were visualized and biopsied when deemed necessary during the donor operation before exclusion.

All patients with ESLD were evaluated for OLT regardless of age or cause of underlying liver disease. Active alcoholism and continued substance abuse were considered as contraindications to transplantation. HIV patients with ESLD were not accepted for OLT during the period of the study, since we were not a part of the Nationals Institutes of Health (NIH) consortium for transplantation of HIV-positive recipients. For the purpose of this study, OLT candidates were considered as urgent or nonurgent recipients, according to their medical condition prior to transplantation, as defined by the United Network for Organ Sharing (UNOS) categories. Urgent patients included recipients requiring support in the intensive care unit prior to OLT or those designated urgent by UNOS criteria. The current model for ESLD (MELD) scoring system[38] was not initiated during the period of this study.

Immunosuppression

Maintenance immunosuppression regimens consisted of a double regimen of CYA and prednisone from 1984 to 1987, triple CYA-based drug regimen that included azathioprine (Imuran, GlaxoSmithKline, Triangle Park, NC), and prednisone from 1987 to 1991, or dual immunosuppression that used tacrolimus (Prograf, Fujisawa Pharmaceutical Co, Deerfield, IL) and prednisone. In 1996, CYA preparation Neoral (Novartis, Basel, Switzerland) was routinely substituted for Sandimmune (Novartis). Routine use of tacrolimus was initiated at our institution in 1994 and has become the standard maintenance immunosuppressive agent. Supplemental immunosuppression, when required, has consisted of mycophenolate mofetil (CellCept, Hoffman-LaRoche, Inc, Nutley, NJ) with or without occasional induction therapy with OKT3 (Orthoclone, Ortho Biotech Products, Nutley, NJ) or anti-IL2 receptor antibody. On the day of transplantation, patients were begun on a rapid steroid taper according to our standard protocol. One gram of methylprednisolone (Solumedrol, Pfizer-Pharmacia Upjohn, Kalamazoo, MI) was administered intravenously for the first day and rapidly tapered to 20 mg/day over 1 week. Oral prednisone (20 mg/day) was started on day 8 and tapered over 2 months to 5 mg/day. Beginning in 1995, steroids were discontinued at 3 to 6 months in HCV patients who did not exhibit rejection episodes.

Statistical Analysis

Survival curves were computed using Kaplan-Meier methods and compared using log-rank tests. Medians were

compared via the log-rank test or the Wilcoxon test when data were not censored. Proportions were compared using the χ^2 test. The log-rank test for trend was used when comparing survival curves across ordered categories.

Univariate and multivariate analyses were conducted for the adult population only. For univariate screening purposes, continuous potential predictors of patient or graft survival were dichotomized at their overall median or polychotomized at clinically significant thresholds to form 2 or more groups of roughly equal size. All variables found to be univariately significant at $P < 0.20$ or those thought to be important on logical and/or biomedical grounds were entered into a backward stepdown Cox proportional hazard regression analysis. Variables with many missing values were not included. The methods of May and Hosmer were used to compute overall goodness of fit χ^2 measures for the final Cox models (SAS Institute Inc, Cary NC).

RESULTS

Recipient Characteristics

Over the 18-year period of the study, 2662 patients underwent 3200 OLTs with a median follow-up time of 6.7 years (range, 0–20 years) (Table 1). This cohort included 578 pediatric and 2084 adult (>18 years) recipients, with a male-to-female ratio of 1.1:1. The most common cause of ESLD of the entire cohort, that included both adult and pediatric recipients, was HCV (27%) followed by alcoholic liver disease (ALD 12%) and biliary atresia (10%). The most common cause of transplantation in children was biliary atresia (276 of 578, 47.5%), while HCV (718 of 2084, 37.4%) was the primary cause in adult patients.

Of the total 3200 transplants performed during this period, 2662 were primary transplants, while 450 recipients received 2, and 88 underwent 3 or more OLTs. Donor organs included whole deceased donor (DD, 2964), split DD (142), living donor (65), and reduced-size grafts.[29] A combined liver kidney procedure was performed in 62 patients who were included in the analysis. The yearly transplant activity at our center is shown in Figure 1.

Overall Survival Estimates

Kaplan-Meier patient and graft survival estimates for the entire adult and pediatric population included in the study period (1984–2001) are shown in Figure 2. Median follow-up was 78 months (range, 0–246 months). Overall patient survival rates at 1, 5, 10, and 15 years were 81%, 72%, 68%, and 64%, respectively. Graft survival analysis that included all causes of graft failure, need of retransplantation, and/or patient death demonstrated overall graft survival estimates of 73%, 64%, 59%, and 55%, at 1, 5, 10, and 15 years, respectively.

TABLE 1. Recipient Characteristics and OLT Indications

Characteristic	Variable	No. (%)
Total no. of recipients		2662
Recipient age (yr)	0–18	578 (21.7)
	18–55	1386 (52.1)
	>55	698 (26.2)
Gender	Male	1406
	Female	1256
Etiology of liver disease	HCV	718 (27)
	ALD	319 (12)
	Biliary atresia	276 (10.4)
	Cryptogenic cirrhosis	221 (8.3)
	HBV	193 (7.3)
	PSC	187 (7)
	PBC	177 (6.6)
	Fulminant failure	123 (4.6)
	Malignancy	106 (4.0)
	Metabolic	96 (3.6)
	AIH	87 (3.3)
	Other	159 (5.9)
Total no. of transplants		3200
No. of transplants/recipient	1 OLT	2662
	2 OLTS	450
	3+ OLTs	88
Type of donor grafts	Whole	2964
	Split	142
	Living donor	65
	Reduced-size	29

HCV indicates hepatitis C virus; ALD, alcoholic liver disease; HBV, hepatitis B virus; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis.

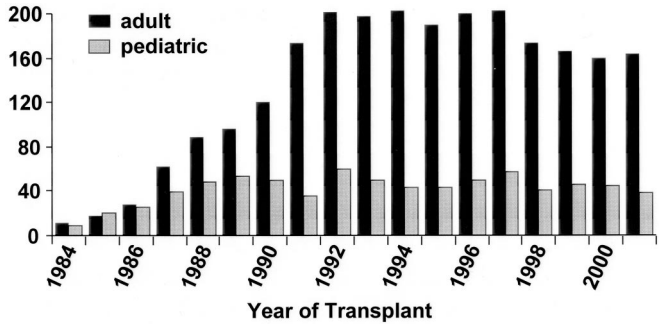

FIGURE 1. Number of yearly transplants performed in adults and pediatric recipients at UCLA.

Patient Survival

Actuarial patient survival rates were not uniform in our patient cohort that included adults and children. Comparing survival at 1, 5, and 10 years (Fig. 3A), best survival benefit

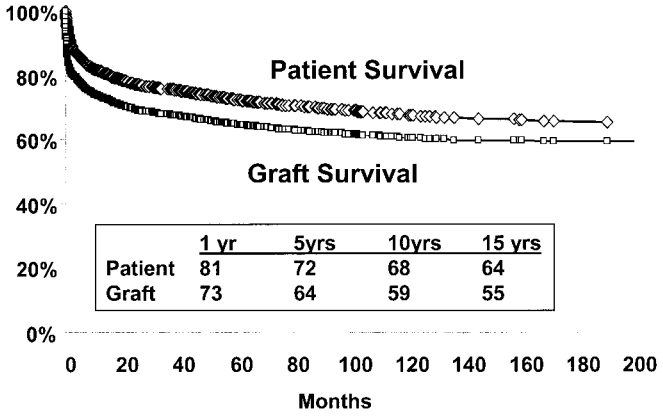

FIGURE 2. Kaplan-Meier overall patient and graft survival estimates following 3200 liver transplantations in 2662 adult and pediatric recipients.

of 86%, 82%, and 79%, was observed in recipients 1 to 18 years of age ($n = 316$), followed by 80%, 77%, and 75% in infants <1 year old ($n = 262$). Survival estimates were 83%, 73%, and 68% for recipients 18 to 55 years of age ($n = 1386$), compared with 77%, 65%, and 58% for patients >55 years of age ($n = 698$). Such difference in survival between these age groups was significant ($P < 0.001$). As expected, survival of nonurgent recipients was superior to that exhibited by urgent patients ($P < 0.001$, Fig. 3B). Recipients of younger organs appeared to exhibit long-term survival advantage over recipients of older donors (Fig. 3C). Best survival was obtained from donors 1 to 18 years of age, followed by donors <1 year old, and 18 to 55 years of age. Worst survival was seen with 55– to 60–year-old donors, while livers older than 60 years exhibited better survival benefit than the 55- 60-year age group ($P = 0.02$). Patients receiving a combined liver and kidney transplant procedure demonstrated equivalent survival to patients receiving OLT alone (P = not significant, Fig. 3D). Similarly, survival after partial liver transplantation using DD split or living donor liver allografts was equivalent to that for whole DD livers in both the adult and the pediatric recipients.

Long-term survival was significantly affected by etiology of ESLD (Fig. 4). Pediatric recipients with biliary atresia achieved the best survival of 82%, 79%, and 78% at 1, 5, and 10 years. In adult recipients, primary biliary cirrhosis, primary sclerosing cholangitis, and ALD exhibited superior survival outcomes of 82%, 77%, and 68%; 85%, 76%, and 70%; and 84%, 77%, and 70% at 1, 5, and 10 years, respectively. OLT survival estimates for hepatitis B virus were inferior to that of cholestatic liver disease but superior to the survival of HCV recipients who exhibited survival estimates of 81%, 68%, and 62% at 1, 5, and 10 years. As expected, OLT for malignant disease had the poorest survival (68%, 43%, and 36% at 1, 5, and 8 years, $P < 0.001$).

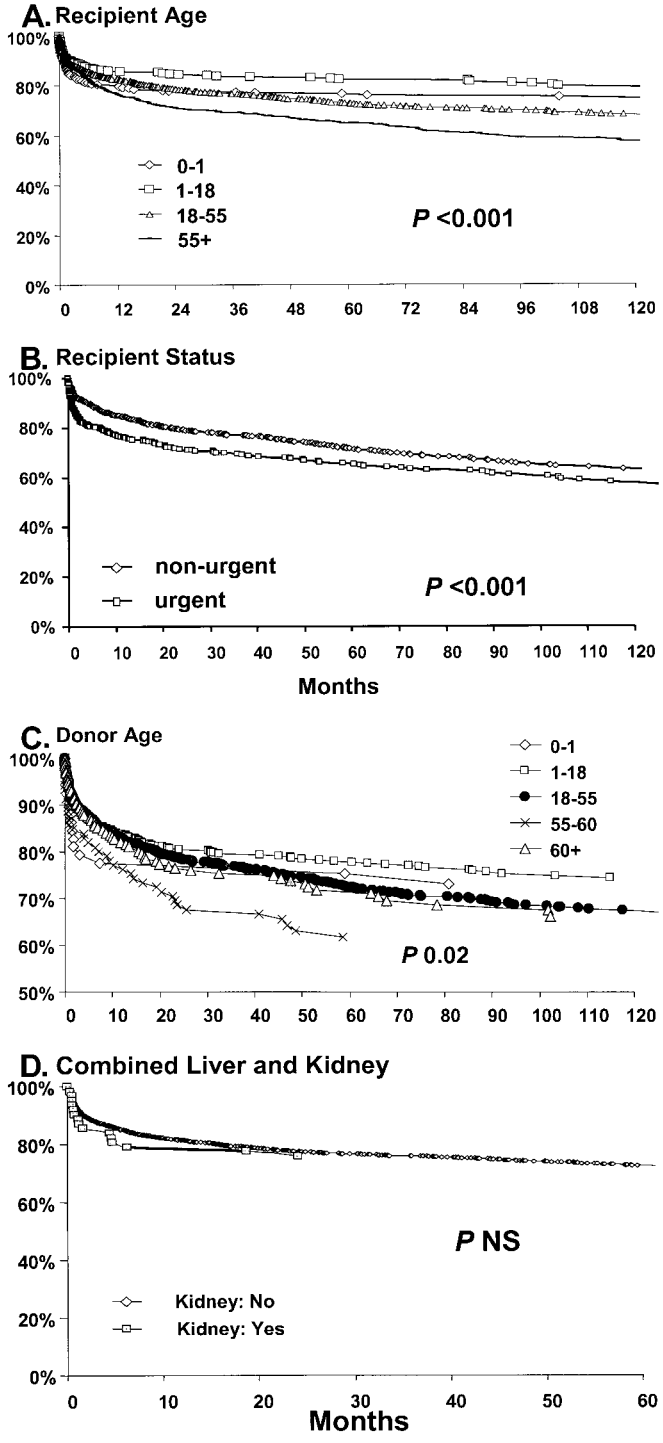

FIGURE 3. Patient survival estimates for different recipient populations based on (A) recipient age in years, (B) recipient urgent or nonurgent status, (C) donor age in years, and (D) requirement of renal graft.

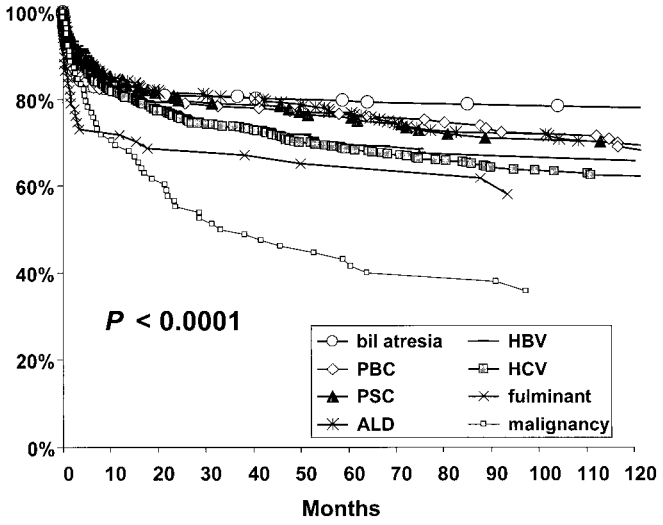

FIGURE 4. Kaplan-Meier patient survival estimates for different etiologies of end stage liver disease. Survival for biliary atresia is given for pediatric recipients. Survival for all other etiologies is provided in adult patients.

Recipient survival was also affected by operative parameters. Survivals at 1, 5, and 10 years for adult recipients were significantly better when cold ischemia time (CIT) was less than 6.5 hours ($P < 0.001$). Similarly, reduced warm ischemia time (WIT) less than 45 minutes improved patient survival after OLT ($P < 0.001$).

Eras of Transplantation

The study population was divided into 2 groups based on the time of transplantation (Table 2). From 1984 to 1991 (era I), 719 received an OLT; whereas in the era II (1992–2001), 1943 patients received an OLT.

Increasing complexity of OLT in the era II compared with the first was evidenced by increased transplantation of more urgent patients (26% versus 21% ($P < 0.001$), older adult recipients (median age 52 versus 47 years, $P < 0.001$), smaller children (median age 2 versus 3 years, $P < 0.001$), increased incidence of re-OLT for late graft loss (>30 days, 7% versus 5%; $P < 0.06$), and utilization of older donors (median adult donor age of 42 versus 36 years, $P < 0.001$). The era II also saw the introduction of partial graft transplantation in adult recipients and increased utilization of split left lateral segmental grafts in children. On the other hand, median WITs declined to 43 from 47 minutes ($P < 0.001$), CITs remained under a median of 7 hours, and incidence of re-OLT for early graft loss (<30 days) was reduced (9.5% versus 12.5%, $P < 0.01$) in the second era.

Overall patient survival estimates were compared for both eras (Fig. 5). Despite more challenging donors and recipients, overall patient survival estimates of 83%, 75%, and 71% achieved in the era II were significantly better than 76%, 66%, and 60% in the first (Fig. 5, $P < 0.001$). Similarly, Kaplan-Meier graft survival estimates improved from 66%, 56%, and 51% in the era I to 75%, 66%, and 62% at 1, 5, and 10 years, respectively, in the second ($P < 0.02$, Fig. 5B).

Complications for both eras are shown in Table 3. Biliary and infectious complications increased from 5% and 20% in era 1 to 15% and 33%, respectively, in the second era. Although graft nonfunction (primary and delayed) did not substantially change between both eras, the era II exhibited a slight increase in the incidence of hepatic artery thrombosis, while the incidence of portal vein thrombosis declined.

Retransplantation

In our patient cohort, 450 recipients were retransplanted, 73 underwent 3 transplantations, and 13 patients received 4 OLTs. Survival was markedly reduced in retransplanted patients (Fig. 6). A single re-OLT achieved 59%, 52%, and 48%, while 3 OLTs resulted in 44%, 36%, and 32%, patient survival at 1, 5, and 10 years, respectively. In 13 recipients who received 4 OLTs, 1-year survival was 31% ($P < 0.001$).

TABLE 2. Comparison of Transplantation in Two Eras

Variable	Level	Era I (1984–1991)	Era II (1992–2001)	*P*
No. of recipients		719	1943	
Urgent status (%)		21.2	26.0	<0.001
Median recipient age (yr)	Adult	47	52	<0.001
	Pediatric	3	2	<0.001
Median donor age (yr)	Adult	36 (19–71)	42 (19–82)	<0.001
	Pediatric	12 (0.17–18)	11 (0.08–18)	0.85
Retransplantation	<30 days	93 (12.9%)	184 (9.5%)	0.01
	>30 days	36 (5%)	137 (7.0%)	<0.06
Median WIT (min)		47	43	<0.001
Median CIT (hr)		6.2	7.1	<0.01

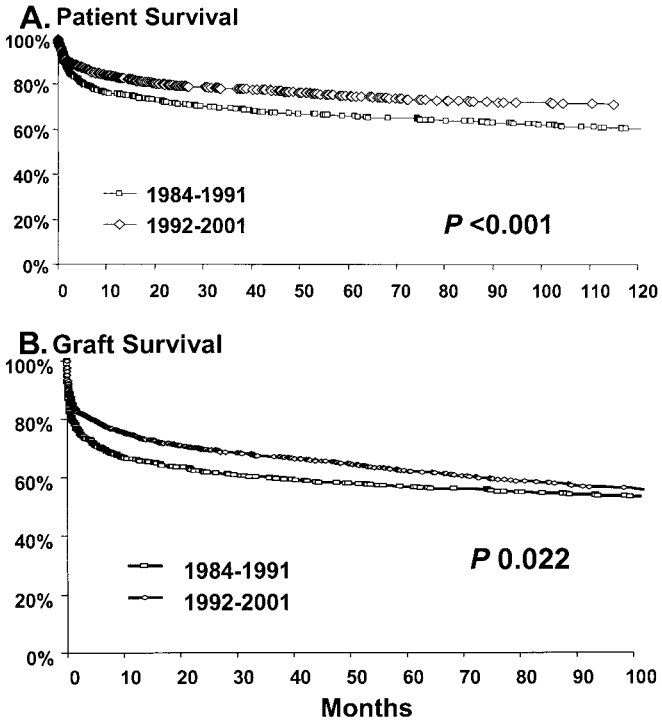

FIGURE 5. Survival outcomes of liver transplantation in 2 different eras of transplantation. The era I extended from 1984 to 1991, while the second ranged from 1992 to 2001. A, Patient survival. B, Graft survival.

TABLE 3. Complications Following Liver Transplantation in Adult and Pediatric Recipients

Complication	Era I (1984–1991)	Era II (1992–2001)	Overall (%)
GNF	8.4	9.4	9.17
HAT	1.25	3.8	3.1
PVT	2.36	0.72	1.16
Biliary complications <30 days	2	5	4.5
>30 days	2.6	9.5	7.6
Total	4.6	14.5	12.1
Infectious complications <30 days	10.5	14.9	13.7
>30 days	9.18	17.6	15.4
Total	19.6	32.5	29.1

GNF indicates graft nonfunction; HAT, hepatic artery thrombosis; PVT, portal vein thrombosis.

Risk of mortality following retransplantation also varied based on the time interval from primary transplantation (Table 4). Mortality risk ratios (MRR) of recipients retransplanted in the first week or after 30 days from primary OLT were equivalent at 1.00 and 0.858, respectively. The highest MRR occurred with retransplantation within 7 to 30 days from first OLT (MRR, 1.688; $P < 0.01$).

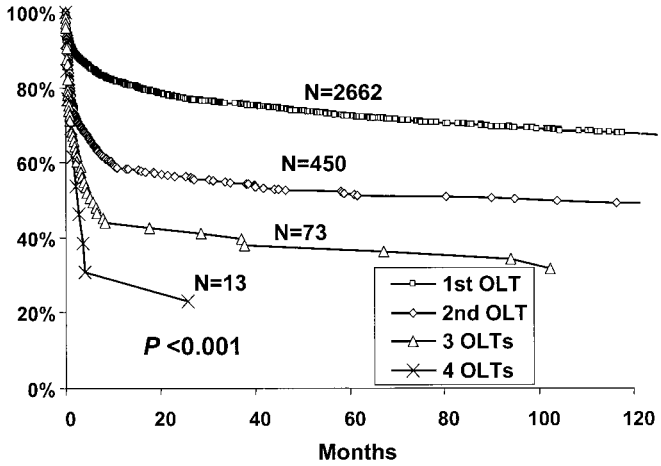

FIGURE 6. Survival estimates of recipients undergoing multiple liver transplantations. Recipient survival after primary OLT was compared with survival after retransplantation, 3 OLTs, or 4 OLTs.

TABLE 4. Effect of Time Interval to Retransplantation on Adult Recipient Survival

Interval (Days After 1-Year OLT)	Death Rate (100 Person-Months)	Mortality Risk Ratio	Survival at 60 Months (%)	*P*
0–7	0.802	1.00*	52.5	<0.01
8–30	1.337	1.668	39.7	
30 or more	0.688	0.858	57.0	

*Reference group for mortality risk ratio.

Univariate Predictors of Patient Survival

Recipient, donor, and operative variables were studied for their impact on patient survival following primary transplantation in adult recipients. The 5 recipient variables that were considered included era of transplantation, urgency status at time of transplantation, type of transplanted allograft, recipient age, and etiology of ESLD. Five donor variables included number of pressors, history of cardiac arrest, donor age, serum sodium, and days of hospitalization prior to procurement. The 2 operative variables examined were CIT and WIT.

By univariate comparison, 3 of 5 recipient variables significantly affected survival following transplantation (Table 5). These included recipient status, age, and cause of liver disease. Urgent recipients exhibited increased risk of death

TABLE 5. Univariate Summary of Adult Recipient Variables on Mortality After Liver Transplantation

Variable	Level	Death Rate (100 person-months)	Mortality Risk Ratio	Survival at 60 Months (%)	*P* Value
Era	1984–1991	0.441	1.00*	61.2	<0.0001
	1992–2001	0.414	0.94	73.3	
Urgency of OLT	Nonurgent	0.338	1.00	73.0	<0.0001
	Urgent	0.469	1.39	65.4	
Recipient age (yr)	18–55	0.361	1.00	73.0	<0.0001
	>55	0.575	1.59	65.2	
Etiology of ESLD	PBC	0.313	1.00	76.6	<0.0001
	Metabolic	0.284	0.905	76.7	
	PSC	0.314	1.002	76.4	
	ALD	0.322	1.029	77.2	
	AIH	0.353	1.127	72.7	
	HBV	0.420	1.339	69.8	
	Cryptogenic	0.485	1.54	65.8	
	HCV	0.479	1.530	68.4	
	Fulminant failure	0.612	1.952	65.1	
	Malignancy	1.090	3.478	43	
Graft type	Whole DD	0.367	1.00	70.3	0.2978
	In situ split	0.566	1.54	65.1	
	Living-donor	0.234	0.64	90.9	

*Reference group for mortality risk ratio.
ESLD indicates end-stage liver disease; DD, deceased donor.

(relative risk [RR], 1.39) and significantly lower survival ($P < 0.001$). Similarly, risk of death was elevated in patients older than 55 years of age (RR, 1.59; $P < 0.001$). Of all examined etiologies of ESLD, cryptogenic cirrhosis, HCV, fulminant failure, and malignancy showed elevated MRRs of 1.54, 1.530, 1.952, and 3.478, respectively ($P < 0.001$). For the era of transplantation and type of donor graft, the effects were less pronounced. Although patient survival was significantly improved in the era II when compared with era I ($P < 0.001$), MRRs of both eras were equivalent (0.94 versus 1.00). And while graft type did not significantly affect survival when all types of grafts were considered simultaneously (P 0.297), MRR was highest with split (1.54) and lowest with living donor (0.64), when compared with whole DD (1.00) grafts.

Only 2 of 5 donor variables affected posttransplant survival (Table 6). Number of donor pressors, serum sodium level, and history of cardiac arrest prior to donation were not significant predictors of post-OLT survival (P = not significant). In contrast, recipient survival declined as length of donor hospitalization increased. Donor hospitalization longer than 6 days was accompanied by a MRR of 1.627 ($P < 0.001$). MRR also increased with increasing donor ages but with marginal significance ($P = 0.12$). Mortality risk was lowest with donor age between 1 and 18 years (RR, 1.00) and highest with donors of ages 55 to 60 years (RR, 1.822). Surprisingly, recipients of livers from donors older than age 60 had a lower mortality risk than from donors between ages 55 to 60 years (MRR, 1.359 and 1.822, respectively).

The effects of operative parameters were pronounced (Table 7). Survival was adversely affected by increasing WITs and CITs. MRR was 1.349 for WIT over 45 minutes and 2.294 for WIT of 55 minutes or more ($P < 0.001$). CIT between 5 and 9.2 hours imposed minimal risks on patient survival (RR, 1–1.269). However, CIT greater than 9.2 hours increased mortality RR to 2.229 ($P < 0.001$).

Multivariate Analysis for Adult Patient Survival

Of the 12 factors considered for adult patient mortality, 8 were simultaneously significant by Cox multivariate regression analysis. Table 8 shows the adjusted RR of death with the corresponding 95% confidence bounds for each factor.

Recipient survival was improved in the era II compared with the first (RR, 0.62; $P < 0.001$). Urgent status at OLT (RR, 1.32) and advanced recipient age (>55 years; RR, 1.47) were associated with increased risk of death ($P = 0.02$ and <0.001, respectively). Hepatic malignancy increased mortality RR to 2.29 ($P < 0.001$). Risk of death was increased to 1.5 with fulminant liver failure but with borderline significance ($P = 0.12$).

TABLE 6. Univariate Summary of Effect of Donor Variables on Adult Recipient Mortality After Liver Transplantation

Variable	Level	Death Rate (100 person-months)	Mortality Risk Ratio	Survival at 60 Months (%)	*P* Value
No. of pressors	0	0.433	1.00*	69.3	0.24
	1	0.387	0.893	74.1	
	2	0.464	1.061	71.2	
	3+	0.399	0.922	76.9	
Cardiac arrest	No	0.424	1.00	71.5	0.14
	Yes	0.358	0.844	74.9	
Age (yr)	1–18	0.353	1.00	75.9	0.12
	18–32	0.394	1.114	71.7	
	32–48	0.442	1.251	71.0	
	48–55	0.381	1.079	73.9	
	55–60	0.644	1.822	59.2	
	>60	0.480	1.359	70.8	
Serum sodium	<142	0.382	1.00	74.1	0.464
	142–148	0.475	1.243	68.6	
	148–155	0.419	1.098	71.7	
	155–160	0.369	0.967	75.0	
	160+	0.370	0.969	75.2	
Hospital stay (days)	1–2	0.022	1.00	72.4	0.039
	3–4	0.038	1.105	72.9	
	5–6	0.057	0.905	75.9	
	6+	0.071	1.627	64.8	

*Reference group for mortality risk ratio.

TABLE 7. Univariate Analysis of Operative Variable Effect on Adult Recipient Survival After Liver Transplantation

Variable	Level	Death Rate (100 person-months)	Mortality Risk Ratio	Survival at 60 Months (%)	*P* Value
WIT (min)	<39	0.292	1.00*	80.0	<0.0001
	39–45	0.308	1.056	76.3	
	46–54	0.394	1.349	71.4	
	55+	0.669	2.294	58.2	
CIT (hr)	<5	0.324	1.00	78.4	<0.0001
	5.1–6.5	0.246	0.760	80.6	
	6.5–9.2	0.420	1.296	71.0	
	9.2–10	0.723	2.229	61.5	
	10+	0.595	1.834	64.0	

*Reference group for mortality risk ratio.
WIT indicates warm ischemia time; CIT, cold ischemia time.

Increasing donor age demonstrated a stepwise increase in risk of death with the highest mortality observed in donors 55 to 60 years of age (RR, 2.29; $P < 0.001$). Similarly, donor hospitalization for 6 or more days reduced recipient survival (RR, 1.39; $P = 0.02$). CIT beyond 10 hours elevated the risk of death to 1.4 ($P = 0.01$). Increased WIT beyond 45 minutes moderately elevated the death RR to 1.32 ($P = 0.06$), while increases beyond 55 minutes were detrimental to survival (RR, 2.1; $P = 0.0001$).

TABLE 8. Multivariate Estimate of Relative Mortality Risk in Adult Recipients

Variable	Level	Adjusted Relative Risk	95% Confidence Bounds	*P* Value
Era	1984–1991	1.0*		
	1992–2001	0.62	0.47–0.83	0.001
Urgency of OLT	Nonurgent	1.0		
	Urgent	1.32	1.04–1.67	0.02
Recipient age (yr)	18–55	1.0		
	>55	1.47	1.19–1.80	<0.001
Etiology of ESLD	PBC	1.0		
	Fulminant	1.52	0.89–2.61	0.12
	Malignancy	2.29	1.45–3.59	<0.001
Donor age (yr)	1–18	1.0		
	18–32	1.23	0.88–1.72	0.2
	32–48	1.40	1.02–1.92	0.03
	48–55	1.51	1.02–2.24	0.04
	55–60	2.29	1.48–3.55	<0.001
	>60	1.61	1.10–2.37	0.01
Hospital stay (days)	1–2	1.0		
	3–4	1.03	0.8–1.32	0.8
	5–6	0.9	0.6–1.35	0.59
	6+	1.39	1.03–1.86	0.02
CIT (hr)	<5.1	1.0		
	5.1–6.5	0.86	0.6–1.18	0.35
	6.5–9.2	0.94	0.7–1.26	0.67
	9.2–10	1.16	0.75–1.81	0.5
	10 or >	1.43	1.07–1.92	0.01
WIT (min)	<39	1.0		
	39–45	1.15	0.84–1.54	0.35
	46–54	1.32	0.99–1.76	0.06
	55+	2.14	1.60–2.87	0.0001

*Reference group for adjusted relative risk.

DISCUSSION

Over 2 decades have passed since liver transplantation was accepted as a therapeutic option for ESLD.[2,12] During that period, more than 250 centers practicing liver replacement have emerged throughout the world, and many have reported periodically on their series.[3,4,39] However, there are few single-center experiences,[37] which have chronicled outcomes for thousands of patients followed for close to 20 years. The present series of 3200 consecutive liver transplants performed at the Dumont-UCLA Transplant Center examines long-term outcome data, analyzes factors that influence results, and evaluates techniques to optimize outcomes.

When compared with our report of 1000 liver transplants at UCLA in the period ending in June 1992,[13] 1-year overall adult and pediatric patient survival has increased to 81% from 75% in our earlier series. Currently, long-term recipient survival is 81%, 72%, 68%, and 64%, while graft survival is 73%, 64%, 59%, and 55%, at 1, 5, 10, and 15 years, respectively. These results are somewhat improved from figures reported recently by Jain et al from Pittsburgh.[37] In the latter study, overall patient survival rates were 79%, 67%, 57%, and 50%, while graft survival was 70%, 59%, 49%, and 44% at 1, 5, 10, and 15 years, respectively. An important difference from our series is that the Pittsburgh report spanned an earlier era that began in 1981, when survival outcomes were inferior to their more recent results. However, both of these collective series show clearly that OLT is a very durable procedure that has benefited from improvements in immunosuppression, patient selection, and technical advances. Nevertheless, barriers that still need to be overcome include long-term chronic graft dysfunction, disease recurrence, and complications related to immunosuppression, specifically adverse cardiovascular, renal, and infectious events.

Analysis of survival outcomes achieved in the present series, although improved from our previous report, is con-

sonant in identifying the same factors that have demonstrated a negative influence on outcomes over this longer time period. These include recipient characteristics (age, diagnosis, and urgent status), need for retransplantation, donor age, and operative variables that perhaps are underestimated. Our results show that extended CITs or WITs were significant independent risk factors for mortality. Warm ischemia beyond 55 minutes doubled the risk, while cold ischemia greater than 10 hours substantially increased the risk of death (MRR, 2.14 and 1.43, respectively). Although increasing donor age resulted in stepwise progression of recipient mortality risk, it is interesting to note that the MRR associated with donors over age 60 (1.61) was lower than for donors between 55 and 60 years of age (2.29). This may be indicative of our cumulative experience in donor selection or the exercise of greater discrimination during selection of older donors that are traditionally considered in the extended category. Nevertheless, this finding needs further validation by larger databases to avoid statistical bias. Whereas other studies have suggested that number of DD pressors, cardiac arrest, and donor sodium levels may affect survival outcomes,[40] these factors did not pose a significant risk in our patient cohort. One explanation may be our diligent efforts to control CITs and WITs. Of donor variables, only donor age and donor hospitalization days were significant predictors of mortality.

The dynamic interactions of the identified risk factors underscore the critical, yet immeasurable, effect of extensive surgical experience to achieve a successful outcome. When we compared these parameters for the 2 eras (Table 2), we found that outcome was improved in the recent era, despite statistically significant increases across the board in negative variables. Although the reasons are undoubtedly multifactorial, we deduce that the most important factor is team experience. Although experience is difficult to quantify, it is our opinion that it represents a gradual evolution of treatment algothrims, which can only be realized over a long period of follow-up. One example of this is the virtually exclusive use of tacrolimus as baseline immunosuppression with maintenance of the lowest possible dose, usually without steroid supplement after 3 to 6 months. Maturation of experience in utilization of this immunosuppressive agent has allowed its application for maximum benefit with the fewest possible adverse effects. Other examples that are represented as a continuum in our series are meticulous antiviral/fungal prophylaxis and therapy; improved utilization of the extended donor; and conduct of the operative procedure to minimize cold and warm ischemia, overall operative time, blood loss, and eliminate operative "fussiness." Currently, veno-venous bypass is only used selectively; WIT is <43 minutes; CIT is 7 hours; and the surgical procedure is usually under 4 hours.

Our center has championed the use of partial grafts[28,29,31] and has the largest series of in situ splits.[30] The successful application of split grafts requires careful recipient and donor selection and a unique surgical repertoire to meet the distinctive challenges that these partial grafts present. Living donor grafts have also been used at our center with a philosophy that embodies the principle of nonmaleficence for living donors. We have therefore established rigid recipient and donor selection criteria for both adult-to-pediatric and adult-to-adult living donoation.[29,31] This may, in part, explain the excellent survival outcomes achieved in both the pediatric[29] and adult[31] living-donor recipients. Nevertheless, segmental transplantation has a higher risk of overall morbidity,[30,31] particularly biliary complications. This, in addition of increased rate of chronic re-OLT, may account for the increased biliary complications encountered in our era II of transplantation. Additionally, the observed increases in donor and recipient ages, higher rates of transplantation of urgent patients, and increased requirement of chronic retransplantations (7%) may account for the observed increase in infection rates seen in the second era. Graft nonfunction (GNF) rates were not substantially different between both eras with an overall rate of 9%. Adoption of stricter criteria for donor selection and reduction of urgent patient transplantation may arguably result in a lower rate of GNF and other complication rates. However, such restrictive policies further shrink an anemic donor pool and deprive many patients from chance for a lifesaving procedure, albeit at a higher complication rate.

The deleterious effects of retransplantation on survival outcomes have been investigated by many authors,[41,42] as well as by our group.[35,43–45] The current study demonstrates patient survival of 59%, 52%, and 48% at 1, 5, and 10 years, respectively. Although slightly better than our previous report,[35] re-OLT still carries a considerable mortality risk. Further, multiple re-OLTs were accompanied by progressively worsening survival outcomes. Our current policy therefore allows 1 retransplantation event with limited exceptions in the pediatric population. A difficulty often faced in evaluating retransplantation outcomes is the distinction between re-OLT performed for early graft failure versus delayed re-OLT undertaken for recurrent disease, chronic rejection, or other late complications of transplantation. This study demonstrates a relatively lower MRR for re-OLTs performed in the first 7 days (RR, 1) or after 30 days (RR, 0.858) from the date of the first transplant, when compared with retransplantations between 8 and 30 days (RR, 1.37). Such findings demand an earlier decision for re-OLT when faced with a poorly functioning graft after transplantation. Nevertheless, re-OLT at any time poses an enormous challenge to the transplant community.[43] On the one hand, concerns are based on poor survival outcomes following retransplantation, scarcity of DD organ resource, and the predicted increased requirements of re-OLT for recurrent HCV.[43,44] On the other hand, the arguments for re-OLT are the acceptable outcomes in selected recipients and limited antiviral efficacy for treatment of recurrent disease. Such difficult issues have been

actively addressed by our center through the development of retransplant survival models that accurately predict posttransplant survival to allow selection of re-OLT candidates.[34–36]

Etiology of liver disease continues to be an important variable affecting long-term outcomes, as demonstrated by a recent study that analyzed posttransplant survival in 17,044 adult recipients from the UNOS database.[47] In our study, the lowest mortality risk was seen in pediatric recipients with a diagnosis of biliary atresia. In the adult population, the lowest risk of death was achieved in patients with cholestatic liver disease, autoimmune liver failure, and ALD, followed by hepatitis B virus. The highest risk of death was for fulminant failure and malignancy. However, in the last 5 years, patient and graft survival after OLT for chronic hepatitis B is among the best. The improved results obtained in these patients is due to the systematic use of hyperimmune gammaglobulin and lamivudine.[46] Similarly, results after OLT for hepatocellular cancer since 1997 have improved dramatically with the adoption of the more selective Milan criteria,[48,49] and possibly because of the use of neoadjuvant ablation.[49] Although we[36] and others[39] have demonstrated that OLT for HCV achieved good short- and medium-term survival, our current long-term data confirm worsening long-term survival. Viral infection with hepatitis C, although the most common indication for OLT (27%), had the highest mortality risk ratio by univariate analysis, except for fulminant failure and malignancy. Unfortunately, we have not observed increased success with HCV patients despite the more frequent use of antiviral therapy. As has been shown previously,[50] these treatments are much less effective in the post-OLT setting. No doubt, HCV continues to represent a formidable challenge.

Perhaps a more challenging task is to fulfill the premise of the final rule, which is the guiding principle for organ allocation: "To avoid futile transplants and to promote the efficient use of our scarce organ resource."[51] Unfortunately, the sole adoption of the MELD score for organ allocation, which is an accurate predictor of pretransplant death but not of posttransplant survival,[42] implies more organ diversion to high-risk recipients, who are clearly shown herein to exhibit poor survival outcomes. Balancing disease severity, as provided by the MELD, with posttransplant outcome-predicting models has therefore become a critical pursuit. This study and our previous work[34] both emphasize the effects of donor organs and surgical parameters. Thus, for accurate assessment of posttransplant outcomes, survival models must account for surgical and allograft interactions in addition to recipient characteristics.

CONCLUSION

Liver transplantation in the modern era has conquered many barriers to achieve long-lasting survival benefits for our patients. Surgical perseverance has been the cornerstone on which many achievements were realized. However, much work is needed to combat recurrent disease, maximize utility of a scarce donor resource, inhibit side effects of immunosuppressive medications, develop new modalities for tolerance induction, and above all enhance the quality of life of transplant recipients.

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Discussions

DR. RICHARD J. HOWARD (GAINESVILLE, FLORIDA): We have just heard from one of the premier liver transplant programs in the world. Dr. Busuttil and his colleagues deserve our commendation. They have used this forum to present their transplant results over the years. And certainly their results are outstanding.

Transplantation is the only field of medicine I know where every procedure performed in the United States is maintained on a national database. And those data are published on the web so one can look at the results of every transplant center in the country, and that is transparency. Yet there is some advantage in having single-center results, as we have heard now, because many of the variables can be better controlled: patient selection, immunosuppression regimens, surgical techniques. I would like to ask Dr. Busuttil some questions.

When he divided the causes of liver failure, most were either hepatitis C or alcoholic liver disease. I am struck in our own population how many patients have both. In fact, we see few pure alcoholics. It seems most of our alcoholics also have hepatitis C. And how did he deal with patients who had both?

In the paper, he reported a 9.4% primary graft nonfunction rate where you transplant the graft and, for reasons that are unclear, it just doesn't work and the patient needs retransplantation within the immediate future. That seems a bit higher than our own series, which is 2% to 3%. I would like to ask: What in the patient selection led to such a high graft nonfunction rate?

I would like you also to address the final question about multiple transplants. We have many patients who could benefit from liver transplantation. What we don't have are enough grafts. And yet when you transplant a patient, you kind of buy into that person. If the graft doesn't work, you transplant them a second time, and if that doesn't work, or somewhere down the road, possibly a third transplant. The results diminish with every transplant. Is that a good use of resources? And where do you call it quits?

Some serious thinkers along that line have said that each patient should get one shot at a transplant and never another one. Because while patients are dying on the waiting list for lack of livers and other organs as well, for the sake of fairness, it is not right that someone should get a second, a third, or even a fourth graft, and yet they are denied even a first transplant. How do you address that issue?

Dr. Sander Florman (New Orleans, Louisiana): Dr. Busuttil, I also echo Dr. Howard's comments saying that you continue to honor this prestigious Society with your presentations, not only with your first 100, 1000, and now over 3000 transplants, but also with important experiences in transplantation for hepatitis B, hepatitis C, and fulminant hepatic failure.

Today's presentation was excellent. Today more than ever, there is tremendous pressure and need to have data such as this, and I am confident that this paper will be analyzed closely by everyone in the transplant field. There are so many aspects of this extraordinary single center experience that merit discussion.

The outcome for transplantation of pediatric patients is excellent, particularly considering that it was not long ago that most pediatric patients died on the waiting list. Your in vivo split experience has made death on the pediatric waiting list extremely uncommon and has maximized the utility of our limited organ supply. Why don't we see more centers splitting livers? And what, if anything, can we or should we do to encourage or even require this?

One of the more intriguing aspects of your experience, at least to me, is that it was done in the era prior to the implementation of our new allocation system, MELD, which, as you know, gives particular weight to renal dysfunction and to patients with hepatocellular carcinoma.

In addition, it is estimated that the need for transplant for hepatitis C over the next 15 years will increase by over 400%. I am very interested to know what your thoughts are for how MELD will affect future long-term outcomes in light of your analysis that identified things such as malignancy as strong prognostic indicators and knowing that because of MELD we will be transplanting sicker and sicker patients.

Furthermore, how will we be able to transplant our other patients, our cholestatic patients, most of whom, as your data show, have a considerably more favorable prognosis with transplantation than those with hepatitis C have?

I was very surprised actually reviewing your manuscript that graft type was not predictive of outcome. It seems, however, that your results for adult live donor transplant are better, at least seem to have a trend better, if not significantly so. Is this because the number of these transplants is relatively small and follow-up for them has also been relatively short at only 12 months?

Finally, congratulations to you and your entire team at UCLA for this extraordinary and important contribution. I am anxious to know what you think will be the most important developments in transplant as you do your next 1, 2, or even 3000 liver transplants. Will it be further improvements in immunosuppression, will we see zenotransplantation, will it be hepatocyte stem cells or something else?

Dr. Alan W. Hemming (Gainesville, Florida): Dr. Busuttil, a beautiful series. One of the things you showed was that malignancy was a negative predictor of survival. And yet we have several groups across the country right now who are trying to increase the indications for transplantation for malignancy, increase the size and the number of tumors, which presumably may lead to worse outcome. I would like to have you comment on increasing the indications for transplantation for HCC when we currently have such a shortage of grafts.

A second comment would be: most of us have seen a worsening result with transplantation for hepatitis C over the last decade with results for hepatitis C being worse now than a decade ago. We are not entirely sure whether it is differences in immunosuppression, differences in graft quality, or exactly what. I wondered if you saw the same thing in your series.

Dr. C. Wright Pinson (Nashville, Tennessee): This study is remarkable for its size and for its long-term follow-up. I am impressed with the less than 1% per year decrement in survival between 5 and 15 years of follow-up. The lack of impact of graft source (deceased donor, living donor, or split graft) is an important observation. I have 3 questions for the authors.

The increase in biliary complications from 4.6% in era 1 to 14.5% in era 2 and the increase in infectious complications in era 2, as well as the graft nonfunction rate overall, are

important observations. You mentioned this may be due to increasing donor complexity and use of segmental grafts. What implications do you feel this has on your donor selection policies now and for the future, especially with respect to marginal donors? For example, do you think that the stricter criteria that you mentioned applying to donors over 60, that you might apply to donors over age 55?

The second question is, given the sharp decrease in survival after retransplantation, just as Dr. Howard asked you, what do you feel is the appropriate current policy on multiple retransplantations?

Third, do you feel that the current allocation policies, based on the final rule, are impeding even better outcomes by limiting your ability to match donor and recipient factors optimally?

Dr. Ronald W. Busuttil (Los Angeles, California): I would like to thank all of the discussants for their comments. What I would like to do is to answer these questions in several broad categories, since many of the discussants asked similar questions.

Let me first discuss PNF, or primary nonfunction, in which we report an overall rate of 9.4%. First of all, this not only includes primary nonfunction, it also includes delayed graft function and it also includes technical complications resulting in early graft loss. Our actual PNF rate is probably closer to 5%.

The second issue is retransplantation. This is an extremely thorny issue that we have grappled with for many years. We have come to the conclusion that if one can achieve a 50% survival at 5 years, then that would be grounds enough to justify retransplantation. Unfortunately, we now know from our data that rarely do you achieve a 50% 5-year survival with more than one transplant.

We think that, when you correctly identify an appropriate candidate for retransplantation, 2 grafts are indicated; however, beyond 2 grafts, one has to think very long and hard before one offers that patient a third graft. Clearly, in the pediatric population, we are going to be more aggressive with retransplantation than we are in the adult population. Also, in the younger adult patient, we are going to be more apt to retransplant more than once.

Also, based on the data that I showed you, if we can retransplant these patients early on, we can usually achieve a 70% or more long-term survival. If you do it in that window of time between the first week and the first month in which there are infectious complications, usually multiorgan system failure, you are doomed to failure.

We presented several years ago, at the American Surgical Association meeting, a model that accurately predicted selection of patients for retransplantation based on several parameters. And I just refer you to that paper.

The next category of questions regarded the new allocation system, the MELD system. As you all know, MELD was a system that was shown to predict mortality while waiting for a transplant. MELD score does not accurately predict postoperative mortality.

I think one of the most important things that MELD has done is that it identified a group of patients that we should not be transplanting. And that is, if you have a MELD of 15 or less, your chances of having long-term survival are better without a transplant than they are with a transplant. That needs to be studied further.

In regard to how we match patients, Dr. Pinson, I think that the MELD system has taken that away from us. I think there is no question that optimum results are obtained by a seasoned matching of donors to recipients. Extended criteria donors can be used in fairly healthy recipients successfully. On the other hand, you can't put an extended donor into somebody who is in the ICU. Those patients don't do very well.

The question about hepatitis C and malignancy. These are clearly the most vexing problems that we have to deal with today. As I showed you in the data, the results of hepatitis C show an inexorable decline in survival because of disease recurrence. The reasons are clearly multifactorial. I think one of the most important reasons that has been recently shown by several groups is the impact of the donor organ on recurrence. If you put an extended criteria donor into one of these hepatitis C patients, for example, an older donor, or liver with long cold or warm ischemia times, they are not going to do as well. As Dr, Florman indicated, since we will be transplanting sicker patients because of the MELD, we may even see higher and quicker rates of recurrence in the future. The use of preemptive therapy or post-transplant therapy with interferon or ribavirin is extremely difficult to interpret. By and large, very few patients really tolerate this kind of therapy for a long period of time. Clearly, management of malignant disease and organ allocation to patients with HCC are difficult problems without good answer. Much work is needed to understand the biology of HCC and how to best select patients for transplantation to achieve better outcomes.

Regarding the living donor question by Dr. Florman, it is true that some results after living donation trend to be better than that of the deceased donor. However, these are carefully selected recipients. The optimum role of the adult living donor procedure will be determined by the ongoing NIH A2ALL study.

And one final note. Dr. Howard, I believe, was asking about our biliary complications. They are higher in the last era. And I think they are higher for a couple of reasons. Number 1, we are using more segmental grafts, we are using more extended criteria donors, and we are doing more living donor grafts. As you know, bile duct issues in adult living donor grafts are still the Achilles heel of that operation.