Title

The evolution of liver transplantation during 3 decades: analysis of 5347 consecutive liver transplants at a single center.

Journal

Annals of surgery, 258(3)

ISSN

0003-4932

Authors

Agopian, Vatche G
Petrowsky, Henrik
Kaldas, Fady M
et al.

Publication Date

2013-09-01

DOI

10.1097/sla.0b013e3182a15db4

Peer reviewed

The Evolution of Liver Transplantation During 3 Decades

Analysis of 5347 Consecutive Liver Transplants at a Single Center

Vatche G. Agopian, MD, Henrik Petrowsky, MD,* Fady M. Kaldas, MD,* Ali Zarrinpar, MD, PhD,* Douglas G. Farmer, MD,* Hasan Yersiz, MD,* Curtis Holt, PharmD,* Michael Harlander-Locke, BS,* Johnny C. Hong, MD,* Abbas R. Rana, MD,* Robert Venick, MD,† Sue V. McDiarmid, MD,† Leonard I. Goldstein, MD,‡ Francisco Durazo, MD,‡ Sammy Saab, MD,‡ Steven Han, MD,‡ Victor Xia, MD,§ Jonathan R. Hiatt, MD,¶ and Ronald W. Busuttil, MD, PhD, FACS**

Objective: To analyze a 28-year single-center experience with orthotopic liver transplantation (OLT) for patients with irreversible liver failure.

Background: The implementation of the model for end-stage liver disease (MELD) in 2002 represented a fundamental shift in liver donor allocation to recipients with the highest acuity, raising concerns about posttransplant outcome and morbidity.

Methods: Outcomes and factors affecting survival were analyzed in 5347 consecutive OLTs performed in 3752 adults and 822 children between 1984 and 2012, including comparisons of recipient and donor characteristics, graft and patient outcomes, and postoperative morbidity before (n = 3218) and after (n = 2129) implementation of the MELD allocation system. Independent predictors of survival were identified.

Results: Overall, 1-, 5-, 10-, and 20-year patient and graft survival estimates were 82%, 70%, 63%, 52%, and 73%, 61%, 54%, 43%, respectively. Recipient survival was best in children with biliary atresia and worst in adults with malignancy. Post-MELD era recipients were older (54 vs 49, $P < 0.001$), more likely to be hospitalized (50% vs 47%, $P = 0.026$) and receiving pretransplant renal replacement therapy (34% vs 12%, $P < 0.001$), and had significantly greater laboratory MELD scores (28 vs 19, $P < 0.001$), longer wait-list times (270 days vs 186 days, $P < 0.001$), and pretransplant hospital stays (10 days vs 8 days, $P < 0.001$). Despite increased acuity, post-MELD era recipients achieved superior 1-, 5-, and 10-year patient survival (82%, 70%, and 65% vs 77%, 66%, and 58%, $P < 0.001$) and graft survival (78%, 66%, and 61% vs 69%, 58%, and 51%, $P < 0.001$) compared with pre-MELD recipients. Of 17 recipient and donor variables, era of transplantation, etiology of liver disease, recipient and donor age, prior transplantation, MELD score, hospitalization at time of OLT, and cold and warm ischemia time were independent predictors of survival.

Conclusions: We present the world's largest reported single-institution experience with OLT. Despite increasing acuity in post-MELD era recipients, patient and graft survival continues to improve, justifying the "sickest first" allocation approach.

Keywords: liver transplantation, MELD score, survival outcomes, single-center

(*Ann Surg* 2013;258:409–421)

From the *Department of Surgery, Dumont-UCLA Transplant and Liver Cancer Centers, Pfleger Liver Institute, Los Angeles, CA; and Departments of †Pediatrics, ‡Medicine, §Anesthesiology, and ¶Division of General Surgery, David Geffen School of Medicine at University of California, Los Angeles, CA.

Disclosure: The authors declare no conflicts of interest.

Reprints: Ronald W. Busuttil, MD, PhD, FACS, Division of Liver and Pancreas Transplantation, Department of Surgery, David Geffen School of Medicine at UCLA, University of California, 10833 Le Conte Ave, Room 77-120 CHS, Box 957054, Los Angeles, CA 90095. ; E-mail: rbusuttil@mednet.ucla.edu.

ISSN: 0003-4932/13/25803-0409
DOI: 10.1097/SLA.0b013e3182a15db4

In 1968, 5 years after Thomas Starzl performed the first human liver transplant,[1] Fonkalsrud and Longmire attempted the procedure at the University of California, Los Angeles (UCLA).[2] The recipient was a 46-year-old man who underwent a heterotopic transplant in the right renal fossa after nephrectomy, with retention of the native liver. The patient expired on the 12th postoperative day with a nonfunctioning graft because of arterial thrombosis. Despite the clinical success achieved by Starzl in 1967 and other favorable reports of human liver replacement by Calne,[3] Bismuth,[4] Pichlmyer,[5,6] and Krom[7] in the 1970s, liver transplantation was still considered an experimental procedure.

One of the major obstacles for expansion and acceptance of liver transplantation was poor immunosuppression that resulted in an unacceptably high rate of allograft rejection and failure. Introduction of the calcineurin inhibitor cyclosporine in the early 1980s significantly improved both graft and patient survival, with 1-year patient survival approaching 70%.[8]

In 1983, UCLA initiated a new program in liver transplantation, beginning with a comprehensive laboratory effort with porcine liver replacement.[9] Our first clinical case was performed on February 1, 1984, and 33 months later, we reported our first 100 liver transplants with 2-year actuarial patient survival of 73%.[10]

During the past 30 years, the liver transplant program at UCLA has been directed by the same team and has grown into one of the world's largest, caring for both adults and children. During this period, there have been significant changes in virtually all aspects of the discipline, including patient selection, immunosuppressive protocols, strategies to prevent infection and disease recurrence, operative approaches, use of graft variants, and postoperative care, among many others.

In 2002, the model for end-stage liver disease (MELD) scoring system for priority of liver transplant candidacy was put into practice.[11] This system was designed to select patients who would derive the greatest benefit from liver transplantation and has also resulted in transplantation for the sickest patients in a given geographic area, with potential increase in transplant futility, postoperative morbidity, and cost.[12–14]

Analysis of a single-center experience with more than 5000 transplants by the same team provides a unique perspective on the status of liver transplantation and with greater uniformity and accuracy than can be gleaned from registry data. This study was undertaken to (1) analyze our 28-year experience with 5347 consecutive liver transplants to identify the multiple, specific factors that influence short- and long-term survival and (2) characterize the effects of the MELD allocation system on recipient, donor, and operative characteristics; graft and patient outcomes; and the scope of postoperative complications.

METHODS

Using a prospectively collected transplant database, we performed a retrospective review of all adults (aged ≥18 years) and

children (<18 years) who underwent orthotopic liver transplantation (OLT) at the UCLA between February 1984 and August 2012. This study was approved by the UCLA Institutional Review Board.

Patients with irreversible liver failure were evaluated for OLT regardless of age or cause of underlying liver disease. Absolute contraindications to transplantation included active alcoholism and substance abuse and untreated extrahepatic malignancy. Before February 2002, allocation of organs was determined using defined United Network for Organ Sharing categories, stratified according to the medical acuity of recipients before transplantation. Beginning in February 2002, the current MELD scoring system was used for organ allocation.[15] Recipients were grouped accordingly into pre-MELD (1984–2001) and post-MELD (2002–2012) eras.

Recipient, donor, operative, and postoperative variables were obtained from review of inpatient and outpatient records, verification from our transplant database, and United Network for Organ Sharing donor charts. MELD scores were calculated for all recipients on the basis of laboratory values.

Variables collected for analysis for both recipients and donors included age and sex; for recipients, etiology of liver disease, MELD score at the time of transplantation, serum bilirubin, international normalized ratio, serum creatinine, hospitalization status, pretransplant length of hospitalization (LOS), and time from listing to transplantation; for donors, serum sodium, length of hospital stay, number of vasopressors, cardiac arrest, and graft type, including heartbeating cadaveric, non–heartbeating cadaveric for donation after circulatory death (DCD), cadaveric split,[16] cadaveric reduced,[17] and living donors. Operative variables included cold ischemia time (CIT), warm ischemia time (WIT), use of venovenous bypass, transfusion of packed red blood cell units (uPRBCs), biliary reconstruction, arterial reconstruction, and postreperfusion syndrome.[18]

Variables collected as measures of postoperative morbidity included the development of graft nonfunction (GNF), hepatic artery thrombosis (HAT), portal vein thrombosis (PVT), biliary complications, and infectious complications. GNF was defined as the need for retransplantation during the index admission or recipient death due to all-cause graft failure and included true primary nonfunction and graft loss due to HAT, PVT, and other perioperative factors. Outcome measures included LOS, incidence of graft rejection, need and indication for early (<30 days) and late (>30 days) retransplantation, 30-day mortality, and overall graft and patient survival. Explant pathology was reviewed for the presence of malignancy in all patients with end-stage liver disease, and the effects of the Milan criteria[19] on recipient survival were examined for these patients.

Immunosuppression

From 1984 to 1987, we used a double regimen of cyclosporine and prednisone; from 1987 to 1991, we used either a triple cyclosporine-based regimen including azathioprine (Imuran; Glaxo-SmithKline, Triangle Park, NC) and prednisone or a double regimen with tacrolimus (Prograf; Astellas Pharmaceutical Co, Deerfield, IL) and prednisone. In 1994, we began routine use of tacrolimus as the primary immunosuppressive agent in maintenance regimens. Since 2001, a triple regimen using tacrolimus, mycophenolate mofetil (CellCept; Hoffman-LaRoche, Inc, Nutley, NJ), and prednisone has become the standard for maintenance immunosuppression.

Supplemental induction therapy has been used selectively. Muromonab CD3 (Orthoclone OKT3; Ortho Biotech Products, Bridgewater, NJ) was used historically for perioperative T-cell depletion but has been unavailable commercially since 2009. Other induction agents included the anti-IL2 receptor antibodies daclizumab (Zenapax; Hoffman-LaRoche, Nutley, NJ) or basiliximab (Simulect; Novartis, Basel, Switzerland) used selectively since 2001 as calcineurin-sparing agents in patients with severe underlying renal dysfunction at the time of transplantation. Daclizumab also was removed from the commercial market in 2009. Sirolimus (Rapamune; Wyeth, Madison, NJ) has been used selectively in patients with refractory rejection, tacrolimus induced nephro- or neurotoxicity, or hepatocellular carcinoma.

Our standard corticosteroid regimen includes 1 g of methylprednisolone (Solumedrol; Pfizer-Pharmacia Upjohn, Kalamazoo, MI) administered intravenously for the first day and rapidly tapered to 20 mg/d over 1 week. Oral prednisone (20 mg/d) is started on day 8 and tapered over 2 months to 5 mg/d. Acute cellular rejection episodes are treated using methylprednisolone boluses with a rapid taper or by increasing maintenance immunosuppression. Biopsy-proven steroid-resistant rejection was treated historically with muronomab CD3 and currently with anti-thymocyte globulin; rabbit (Thymoglobulin; Sanofi-Aventis, Bridgewater, NJ).

Antimicrobial Prophylaxis

Routine perioperative bacterial prophylaxis currently includes intravenous ampicillin plus sulbactam (Unasyn; Pfizer, Irvine, CA), whereas piperacillin plus tazobactam (Zosyn, Wyeth, Madison, NJ) is used empirically for bacterial infections in the early posttransplant period. Oral fluconazole (Diflucan; Pfizer, Irvine, CA) is used for systemic antifungal prophylaxis for 42 days after transplantation.[20] In high-risk patients (retransplant, previous use of corticosteroids, mold colonization, additional immunosuppression with T-cell depleting agents), voriconazole (Vfend; Pfizer, Irvine, CA) may be substituted for fluconazole. Antifungal strategies before 1993 included superficial prophylaxis with oral nystatin and clotrimazole troches. For cytomegalovirus prophylaxis, all patients currently receive intravenous ganciclovir during their hospital stay and oral valganciclovir (Valcyte, Genetech, Oceanside, CA) on discharge to complete 100 days of antiviral therapy.[21,22] Before 1995, we utilized intravenous and oral acyclovir or ganciclovir, followed by oral acyclovir.

Trimethoprim/sulfamethoxazole (Bactrim; Mutual Pharmaceutical Company, Philadelphia, PA) is the first choice for pneumocystis carinii pneumonia (PCP) prophylaxis and is continued for 1 year after transplantation, or longer with a change in clinical status or immunosuppressive antirejection therapy. Alternative agents for PCP prophylaxis include dapsone, atovaquone, or pentamidine.

Statistical Analysis

Continuous variables were compared using the Student *t* test and summarized as means or medians. Categorical variables were compared using χ^2 test and summarized as percentages and frequencies. Graft and patient survival curves were computed using the Kaplan-Meier methods and compared using log-rank tests.

Univariate and multivariate analyses were performed for the adult population only. For univariate screening purposes, continuous potential predictors of overall patient survival were polychotomized by quartiles or at clinically significant thresholds to form 2 or more groups of roughly equal size. Overall mortality rates were computed empirically by dividing the total number of deaths by the total number of person-months of follow-up. For each variable, mortality rate ratios (MRR) were constructed using these empirically derived mortality rates. For multivariate analyses, all variables found to be univariately significant at $P < 0.20$ or those thought to be important on clinical grounds were entered into a backward step-down Cox proportional hazard regression analysis. To account for the same recipient receiving multiple grafts, the Cox model allowed for time-varying covariates. For the multivariate Cox regression model, the pre-MELD era was further stratified into pre-MELD era 1 (1984–1991) and pre-MELD era 2 (1992–2002) to control for the significant differences that were observed in overall patient survival in our prior study of 3200 pre-MELD era patients.[23]

RESULTS

Over the 28-year period of the study, 4574 patients underwent 5347 OLTs with a mean follow-up time of 8.3 years (Table 1). The group included 3751 adult and 823 pediatric recipients, with a male-to-female ratio of 1.3:1. The most common indication for OLT was hepatitis C virus (HCV, 33%), followed by alcoholic liver disease (12%) and biliary atresia (8.1%). The most common indication for OLT was biliary atresia in children (45%) and HCV in adults (40%). Nonalcoholic steatohepatitis (NASH) was a rare indication before 2002 but has become the second leading indication for primary OLT, comprising 19% of all adult transplants at our center in 2011.[24]

Of the 5347 OLTs, 4574 were primary transplants, whereas 657 recipients received 2, 101 recipients received 3, and 15 recipients received 4 or more transplants. Donor organs included whole heartbeating cadaveric grafts (n = 4820), cadaveric split grafts (n = 271), non–heartbeating cadaveric grafts procured by donation after circulatory death (DCD, n = 121), living donors (n = 103), and reduced-size grafts (n = 31). Combined liver-kidney transplantation was performed in 214 patients.

Malignancy was identified in 955 of 4574 recipients (20.8%) and included hepatocellular carcinoma (n = 869), cholangiocarcinoma (n = 40), hepatoblastoma (n = 30), and other rare tumors (n = 16) including hepatic schwannoma, hemangioendothelioma, leiomyosarcoma, rhabdomyosarcoma, and neuroendocrine tumors. Malignancy was seen most frequently in recipients with hepatitis B virus (n = 132, 38.5%), HCV (n = 497, 33.2%), and NASH (n = 35, 22.7%), and less frequently in recipients with other diagnoses.

TABLE 1. Recipient Characteristics and OLT Indications

Characteristic	Variable	No.	%
Total no. of transplants		5347	
Total no. of recipients		4574	
Recipient age (yr)	Adult (>18)	3751	82
	Pediatric (0–18)	823	18
Sex	Male	2604	57
	Female	1970	43
Etiology of liver disease	HCV	1496	32.7
	ALD	533	11.7
	Biliary atresia	370	8.1
	HBV	343	7.5
	Fulminant failure	321	7.0
	Cryptogenic cirrhosis	273	6.0
	PSC	238	5.2
	PBC	227	5.0
	NASH	154	3.4
	Metabolic	144	3.1
	AIH	134	2.9
	Other	341	7.4
No. of transplants/recipient	1 OLT	4574	85.5
	2 OLTs	657	12.3
	3 OLTs	101	1.9
	4+ OLTs	15	0.3
Type of donor grafts	Whole	4820	90.1
	Split	271	5.1
	DCD	122	2.3
	Living donor	103	1.9
	Reduced size	31	0.6

AIH indicates autoimmune hepatitis; ALD, alcoholic liver disease; DCD, donation after circulatory death; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Overall Survival Estimates

Kaplan-Meier patient and graft survival estimates for all patients in the study period are shown in Figure 1. Overall patient and graft survival rates at 1, 5, 10, and 20 years were 82%, 71%, 63%, and 52% and 73%, 61%, 54%, and 43%, respectively.

Patient and Graft Survival

Actuarial patient and graft survival rates were different for adults and children. Compared with adult recipients, pediatric recipients had better overall 1, 5, 10, and 20-year patient and graft survival (Fig. 2), with the exception of slightly inferior 1-year graft survival (71% vs 73%). The overall 20-year patient and graft survivals in pediatric recipients were 69% and 53% compared with 47% and 41% in adults ($P < 0.001$).

Long-term survival was significantly related to the etiology of liver disease (Fig. 3A). Pediatric recipients with biliary atresia had the best survival of 84%, 82%, 80%, and 71% at 1, 5, 10, and 20 years. In adult recipients, outcomes were best for primary sclerosing

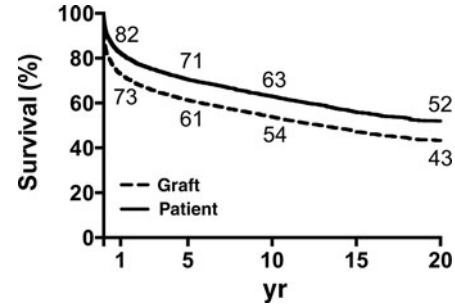

FIGURE 1. Kaplan-Meier overall patient and graft survival estimates after 5347 liver transplantations in 4574 adult and pediatric recipients from 1984 to 2012.

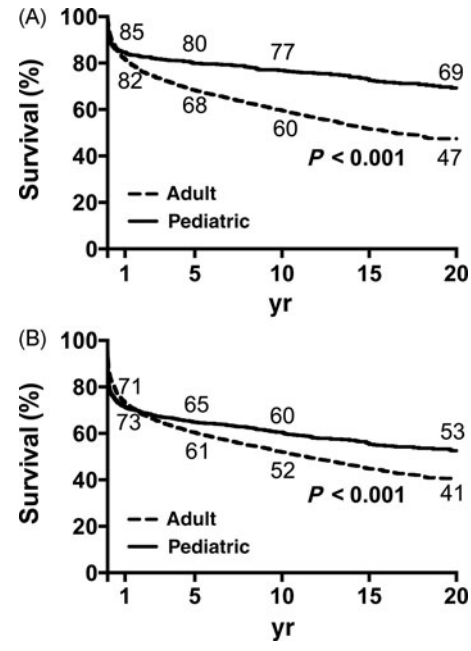

FIGURE 2. Kaplan-Meier patient (A) and graft (B) survival comparing adult and pediatric recipients.

cholangitis, with survival of 85%, 76%, 69%, and 57%. Survival in recipients with primary biliary cirrhosis, alcoholic liver disease, hepatitis B virus, and NASH was similar, with ranges from 61% to 66% at 10 years. Survival at 1, 5, 10, and 20 years was poorest after OLT for HCV (80%, 65%, 56%, 43%) and malignancy (82%, 62%, 54%, 42%). Regarding the latter group, survival at 1, 5, and 10 years for recipients with cancer was significantly improved after adoption of the Milan criteria (n = 802) compared with 132 recipients who received OLT before Milan criteria (83%, 66%, and 60% vs 69%, 43%, and 30%, $P < 0.001$; Fig. 3B).

Recipient MELD score significantly affected long-term survival. When stratified by quartiles (Fig. 4), adult recipients with MELD scores of 6 to 13, 14 to 21, and 22 to 33 had survival outcomes of 88%, 86%, and 83% at 1 year; 74%, 71%, and 70% at 5 years; and 65%, 62%, and 62% at 10 years. Compared with recipients in the lower MELD quartiles, patients with a MELD score of 34 or greater had lower survival estimates of 73%, 63%, and 54% at 1, 5, and 10 years ($P < 0.001$). As shown in Figure 4, this survival difference can be attributed to a higher 1-year mortality in recipients with the highest MELD scores. After 1 year, recipient MELD score did not affect mortality rates, with parallel survival curves across all MELD groups.

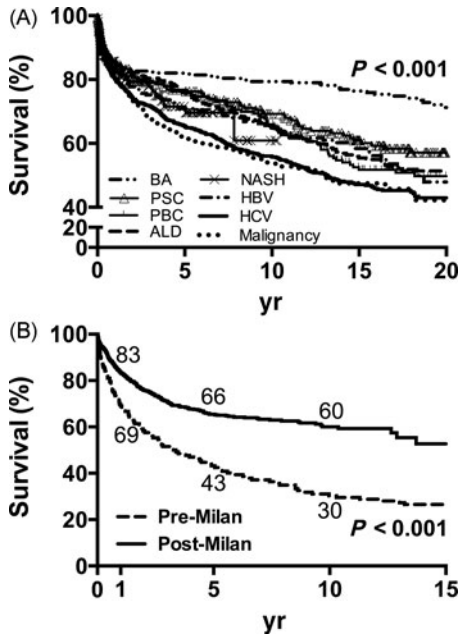

FIGURE 3. Kaplan-Meier patient survival estimates for (A) different etiologies of liver disease and (B) for cancer recipients before and after institution of Milan criteria. ALD indicates alcoholic liver disease; BA, biliary atresia; HBV, hepatitis B virus; PSC, primary sclerosing cholangitis.

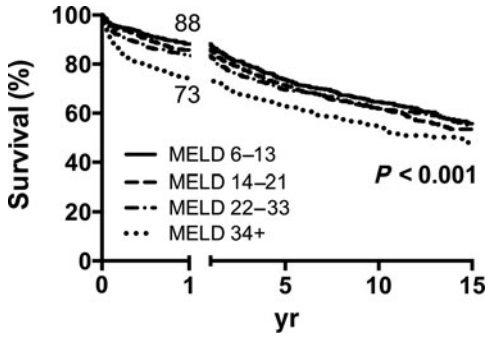

FIGURE 4. Kaplan-Meier patient survival estimates after primary liver transplantation in adult recipients stratified by MELD score.

Eras of Transplantation

In the pre-MELD era, 2678 recipients received 3218 transplants compared with 1896 recipients and 2129 transplants in the post-MELD era. Recipient characteristics in the pre- and post-MELD eras are compared in Table 2.

Recipients were more complex in the post-MELD era, with older adults (mean age, 54 vs 49 years, $P < 0.001$), higher median MELD scores (28 vs 19, $P < 0.001$), greater fraction of recipients with MELD score of 35 or greater (37.3% vs 13%, $P < 0.001$) and MELD score of 40 or greater (21.9% vs 5.9%, $P < 0.001$), more frequent need for pretransplant hemodialysis (34% vs 12%, $P < 0.001$) and pretransplant hospitalization in adult recipients (50% vs 46%), longer pretransplant hospitalization in adults (9 vs 7 days, $P < 0.001$) and children (15 vs 10 days, $P = 0.004$), longer wait-list times for adults (289 vs 217 days, $P < 0.001$) and children (159 vs 59 days, $P < 0.001$), and a 3-fold greater need for combined liver and kidney transplantation (6.8% vs 2.1%, $P < 0.001$). Moreover, the illness acuity has increased across the post-MELD era: 29.2% of our adult recipients in 2010 and 42.9% in 2011 had a MELD score of 40 or greater.

Comparing post-MELD with pre-MELD eras, a number of significant changes were observed in donor and operative characteristics

TABLE 2. Comparison of Recipient Characteristics in Pre- and Post-MELD Eras

Variable	Level	Pre-MELD Era	Post-MELD Era	*P*
No. of recipients	All	2678	1896	
	Adult	2108	1643	
	Pediatric	570	253	
No. of transplants	All	3218	2129	
	Adult	2480	1825	
	Pediatric	738	304	
Mean age (yr)	Adult	49	54	<0.001
	Pediatric	5	4	0.337
Total bilirubin (mg/dL)		9	15	<0.001
INR		1.7	1.8	0.405
Creatinine (mg/dL)		1.7	2.2	<0.001
Match MELD	Adult	. . .	30	
Laboratory MELD	Adult	19	28	<0.001
	≥35	13%	37%	<0.001
	≥40	5.9%	22%	<0.001
Hemodialysis (%)	Adult	12	34	<0.001
Hospitalization (%)	All	47	50	0.026
	Adult	46	50	0.004
	Pediatric	52	50	0.706
Pretransplant stay (d)	All	8	10	<0.001
	Adult	7	9	<0.001
	Pediatric	10	15	0.004
Time from listing to OLT (d)	All	186	270	<0.001
	Adult	217	289	<0.001
	Pediatric	59	159	<0.001
Liver/kidney n (%)		69 (2.1)	145 (6.8)	<0.001

(Table 3). Donor quality deteriorated, with increasing adult donor age (41.1 vs 39.6 years, $P = 0.001$), higher fraction of donors older than 55 years (21.8% vs 18.2%, $P = 0.005$), longer donor hospitalization (4.3 vs 3.2 days, $P < 0.001$) with a greater proportion of donors hospitalized for more than 5 days (25% vs 13%, $P < 0.001$)[25] and with predonation cardiac arrest (27% vs 16%, $P < 0.001$), and greater utilization of DCD grafts (4.6% vs 1%, $P < 0.001$). Operative variables included decreases in CIT (433 vs 404 minutes, $P < 0.001$), WIT (49 vs 41 minutes, $P < 0.001$), and utilization of venovenous bypass (85% vs 39%, $P < 0.001$); decrease in use of T-tubes (49% vs 66%, $P < 0.001$), despite an increase in the use of choledochocholedochostomy for biliary reconstruction (81 vs 73%, $P < 0.001$); and higher operative blood transfusion requirements (15 vs 11 uPRBC, $P < 0.001$) and rates of postreperfusion syndrome (30% vs 15%, $P < 0.001$).

Graft and patient survivals for both eras are compared in Figure 5. Despite more challenging donors and recipients, post-MELD era recipients achieved better 1-, 5-, and 10-year graft survival (78%, 66%, and 61% vs 69%, 58%, and 51%); Fig 5A and patient survival (82%, 70%, and 65% vs 77%, 66%, and 58%); Fig 5B than pre-MELD era patients ($P < 0.001$). Improved post-MELD era graft and patient survival were observed in both adults (Fig. 5C, D) and children (Figs. 5E, F). Overall survival in adults undergoing primary OLT was similar for recipients with MELD scores of 21 or lower in both eras (graphs not shown) but significantly better for patients with MELD scores of 22 or higher in the post-MELD era, with differences most pronounced in the highest MELD group (Figs. 6A, B).

TABLE 3. Comparison of Donor and Operative Characteristics in Pre- and Post-MELD Eras

Variable	Level	Pre-MELD Era	Post-MELD Era	*P*
Donor				
Mean donor age	Adult	39.6	41.1	0.001
	Pediatric	9.3	8.7	0.123
Donor age >55 yr (%)		18.2	21.8	0.005
Serum sodium		149	149	0.334
Hospital stay (d)		3.2	4.3	<0.001
Hospital stay >5 d (%)		13	25	<0.001
Cardiac arrest (%)		16	27	<0.001
Split graft (%)		9	8	0.161
DCD (%)		1	4.6	<0.001
Operative				
Cold ischemia time (min)		433	404	<0.001
Warm ischemia time (min)		49	41	<0.001
Venovenous bypass (%)		85	39	<0.001
Transfusion (uPRBC)		11	15	<0.001
Biliary reconstruction				
Choledochoje-junostomy	Adult	16	9	<0.001
	Pediatric	84	81	0.437
Choledochocholedochostomy		71	83	<0.001
T-tube used (%)		66	49	<0.001
Arterial conduit (%)	Adult	11.3	8.6	<0.001
Postreperfusion syndrome (%)	Any	15	30	<0.001
	Major	3.3	7.0	<0.001

Operative complications for both eras are shown in Table 4. GNF was significantly less frequent in the post-MELD era (6.8% vs 9.5%, $P < 0.001$), particularly in adult recipients (6.0% vs 9.1%, $P < 0.001$). There were no significant differences in either early (<30 days) or late (>30 days) HAT or PVT in adult or pediatric recipients in the 2 eras. The overall rates of HAT and PVT for all recipients were 4.8% and 2.1%, with higher rates of early HAT (6.1% vs 2.4%, $P < 0.001$) and early PVT (3.2% vs 0.6%, $P < 0.001$) in pediatric recipients than in adults. However, total biliary and infectious complications increased from 12.2% and 34.5% in the pre-MELD era to 21.2% and 51.7% in the post-MELD era ($P < 0.001$).

Posttransplantation LOS, rates of rejection, need for retransplantation, and 30-day mortality rates for both eras are shown in Table 5. Despite significantly longer LOS (34 vs 29 days, $P < 0.001$), post-MELD era recipients suffered fewer episodes of acute rejection (19% vs 28%, $P < 0.001$), required less frequent early (4.5% vs 9.9%, $P < 0.001$) and late (3.2% vs 9.1%, $P < 0.001$) retransplantation, and had a significantly lower 30-day mortality (5.7% vs 9.8%, $P < 0.001$) than patients in the pre-MELD era.

Retransplantation

Retransplantation was performed in 773 recipients, with 3 transplants in 101 patients and 4 or more in 15 patients. Survival was markedly reduced by each retransplantation (Fig. 7A). Patient survival estimates at 1, 5, and 10 years were 82%, 71%, and 66% after primary transplantation but decreased to 63%, 53%, and 43% after retransplantation and 47%, 42%, and 31% for recipients of a third allograft. For the 15 recipients who received 4 or more transplants, 1-year survival was 20%.

The most common indication for retransplantation (Table 6) was graft failure (40.4%), followed by vascular complications (21.1%), chronic rejection (14.5%), recurrent disease (11.8%), acute rejection (5.1%), biliary complications (4.1%), and de novo disease (3%). Of the 91 and 23 recipients who required retransplantation for recurrent and de novo disease, 59 (65%) and 13 (57%) were due to HCV. In pediatric recipients, vascular complications were the leading cause for retransplantation (33%), followed by graft failure (29%). Compared with the pre-MELD era, recipients in the post-MELD era were less likely to require retransplantation for graft failure (34% vs 43%) and acute rejection (2% vs 6%) but significantly more likely to require retransplantation for recurrent disease (21% vs 8%, $P < 0.001$).

Survival at 1, 5, and 10 years after retransplantation was better for pediatric than for adult recipients (63%, 58%, and 51% vs 58%, 48%, and 40%, $P = 0.014$; Fig. 7B) and for recipients in the post-MELD era than for recipients in the pre-MELD era (68%, 60%, and 57% vs 56%, 47%, and 39%, $P < 0.001$; Fig. 7C). Considering indications for retransplantation (Fig. 7D), 1-, 5-, and 10-year survival estimates were best for chronic rejection (73%, 63%, and 53%) and lowest for recurrent disease (65%, 44%, and 38%, $P = 0.053$).

Univariate Predictors of Adult Patient Survival

Eight recipient variables (era of transplantation, age, sex, MELD score, etiology of liver disease, prior liver transplant, hospitalization at time of OLT, and simultaneous liver/kidney transplantation), 7 donor variables (age, graft type, cardiac arrest, sex, hospital stay, serum sodium, and number of vasopressors), and 2 operative variables (WIT and CIT) were studied for their effects on patient survival after liver transplantation in adult recipients. The pre-MELD era was stratified into pre-MELD era 1 (1984–1991) and pre-MELD era 2 (1992–2002). By univariate comparison, 6 of 8 recipient variables significantly affected survival after transplantation (Table 7), including era of transplantation, recipient age, MELD score, etiology of liver disease, prior transplant, and hospitalization.

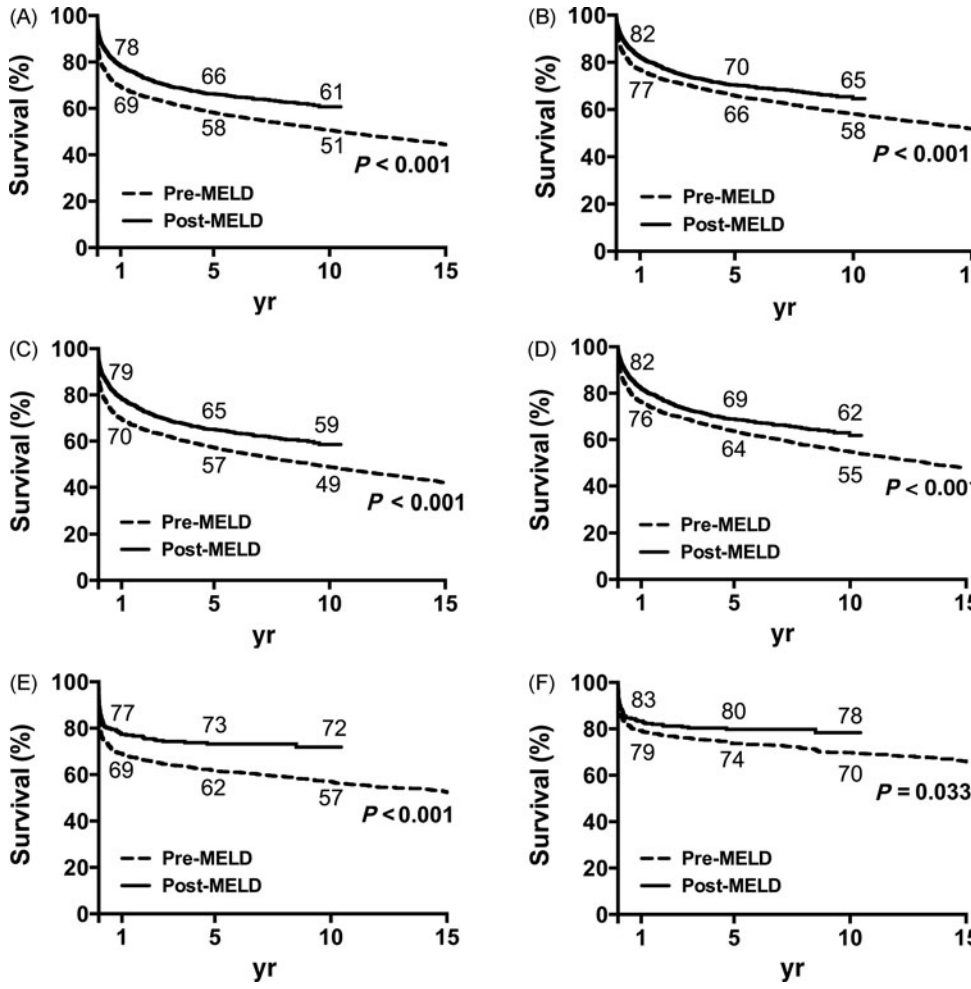

FIGURE 5. Kaplan-Meier survival estimates in the pre- and post-MELD era comparing (A) overall graft survival, (B) overall patient survival, (C) adult graft survival, (D) adult patient survival, (E) pediatric graft survival, and (F) pediatric patient survival.

The MRR was most pronounced for prior transplantation (MRR 2.01, $P < 0.001$), MELD score of 34 or greater (MRR 1.83, $P < 0.001$), and hospitalization at the time of transplantation (MRR 1.59, $P < 0.001$), with more modest effects seen for age (MRR 1.5 for age >55 years, $P < 0.001$) and era of transplantation (MRR 1.31 for pre-MELD era 1, $P < 0.001$). Comparing different etiologies of liver disease, recipients with malignancy (MRR 1.77) and HCV (MRR 1.56) had the highest MRRs. Of 7 donor variables (Table 8), only donor age affected posttransplant survival, with the highest risk in donors older than 60 years (MRR 1.50; $P = 0.003$). Both operative factors significantly affected posttransplant survival (Table 8), with the effect seen primarily in the highest quartile for both WIT (MRR 1.3 for WIT >49 minutes, $P = 0.001$) and CIT (MRR 1.23 for CIT >8.9 hr, $P = 0.002$).

Multivariate Analysis for Adult Patient Survival

Of the 17 factors considered for adult patient mortality, 9 were simultaneously significant by Cox multivariate regression analysis. Table 9 shows the adjusted relative risk (RR) of death, with the corresponding 95% confidence intervals for each factor.

Recipient survival was significantly improved across each era of transplantation, with worse survival for recipients in pre-MELD

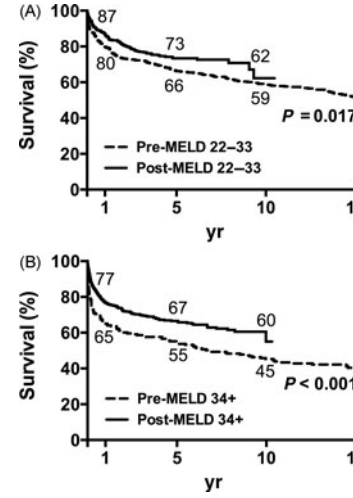

FIGURE 6. Comparison of pre- and post-MELD Kaplan-Meier patient survival estimates based on recipient MELD score (A) MELD score of 23 to 33 and (B) MELD score of 34 or greater.

TABLE 4. Complications After Liver Transplantation in Adult and Pediatric Recipients

Complication	Level	Pre-MELD	Post-MELD	*P*	Overall (%)
GNF	All	9.5	6.8	0.001	8.4
	Adult	9.1	6.0	<0.001	7.8
	Pediatric	10.7	12.4	0.454	11.1
HAT <30 d	All	3.4	2.8	0.223	3.1
	Adult	2.4	2.5	0.942	2.4
	Pediatric	6.5	5	0.441	6.1
HAT >30 d	All	1.6	1.7	0.659	1.7
	Adult	1.3	1.7	0.309	1.5
	Pediatric	2.5	2.1	0.812	2.4
PVT <30 d	All	1.2	1	0.50	1.1
	Adult	0.6	0.7	0.872	0.6
	Pediatric	3.2	3.3	0.930	3.2
PVT >30 d	All	0.9	1.1	0.562	1.0
	Adult	0.4	0.6	0.365	0.5
	Pediatric	2.6	4.6	0.139	3.1
Biliary <30 d	All	4.9	6.8	0.003	5.6
	Adult	5.2	6.9	0.022	5.9
	Pediatric	3.8	6.2	0.104	4.4
Biliary >30 d	All	7.4	14.4	0.001	10.2
	Adult	8	14.5	<0.001	10.8
	Pediatric	5.4	13.3	<0.001	7.4
Biliary—total	All	12.2	21.2	<0.001	15.8
	Adult	13.1	21.4	<0.001	16.7
	Pediatric	9.2	19.5	<0.001	11.8
Infectious <30 d	All	17.7	25.5	0.001	20.8
	Adult	16.1	23.8	<0.001	19.4
	Pediatric	22.9	38.3	<0.001	26.8
Infectious >30 d	All	16.8	26.3	<0.001	20.6
	Adult	16.2	25.3	<0.001	20.1
	Pediatric	18.9	33.8	<0.001	22.6
Infectious—total	All	34.5	51.7	<0.001	41.3
	Adult	32.3	49	<0.001	39.5
	Pediatric	41.9	72.1	<0.001	49.4

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

TABLE 5. Comparison of Posttransplantation Outcomes in Pre- and Post-MELD Eras

Variable	Level	Pre-MELD Era	Post-MELD Era	*P*
Posttransplant stay (d)	All	29	34	<0.001
	Adult	28	33	<0.001
	Pediatric	35	42	0.004
Acute rejection (%)	All	28	19	<0.001
	Adult	25	16	<0.001
	Pediatric	37	41	0.285
Retransplantation <30 d	All	9.9	4.5	<0.001
	Adult	7.2	2.8	<0.001
	Pediatric	15.6	5.3	<0.001
Retransplantation >30 d	All	9.1	3.2	<0.001
	Adult	17	7	<0.001
	Pediatric	27	12	<0.001
30-d mortality (%)		9.8	5.7	<0.001

eras 1 (RR, 1.79; $P < 0.001$) and 2 (RR, 1.24; $P = 0.001$) compared with post-MELD era recipients (Fig. 8). Prior transplantation (RR, 2.18; $P < 0.001$), recipient age more than 55 years (RR, 1.48; $P < 0.001$), MELD score of 34 or greater (RR, 1.39; $P < 0.001$), and hospitalization at the time of OLT (RR, 1.32; $P < 0.001$) were all independent predictors of mortality. Mortality risk was highest for recipients with malignancy (RR, 1.82; $P < 0.001$) and HCV (RR, 1.52; $P = 0.001$). An increased risk of death was seen with increasing donor age, with the highest mortality observed in donors older than 55 years (RR, 1.49; $P < 0.001$). Risk of death was also increased with WIT of more than 49 minutes (RR, 1.28; $P < 0.001$) and CIT of more than 8.9 hours (RR, 1.33; $P < 0.001$).

DISCUSSION

Fifty years have passed since Starzl[1] first reported liver transplantation in humans and 3 decades since the introduction of calcineurin inhibitors that transformed the procedure into the durable and widely accepted gold standard for all patients with irreversible liver failure.[8] During this period, more than 300 centers have performed more than 200,000 transplants throughout the world, with many authors periodically reporting on their experience.[23,26] This study represents the largest reported single-institution experience with liver transplantation, chronicling the outcomes of more than 5300 transplants in adult and pediatric recipients over nearly 30 years.

Over these 3 decades, there have been significant improvements in perioperative care, modification of surgical technique, and short- and long-term management of transplant recipients. A major change that has altered recipient selection is the MELD scoring system,[11,15] which was implemented in 2002 and created a fundamental shift in donor liver allocation in the United States. An accurate predictor of 3-month mortality in patients with end-stage liver disease, the MELD system prioritized liver allocation to the sickest recipients to minimize wait-list mortality. With illness acuity being the primary determinant of organ allocation and as a result of transplanting for the sickest recipients, concerns about posttransplant survival emerged. One year after MELD was implemented, Freeman et al[27] reported a 3.5% reduction in wait-list mortality, a 10.2% increase in cadaveric transplants, and 1-year graft and patient survival that remained unchanged compared with the pre-MELD era. Subsequent large population studies based on national registry data reported similar short- and long-term survival despite an increase in MELD score from 17 to 20 in the pre- versus post-MELD recipients,[28,29] justifying the "sickest first" allocation policy. However, an assessment of the outcome in the sickest patients with MELD scores greater than 34 was lacking.

One of the most striking findings of our study was the effect of MELD on recipient acuity, particularly at our transplant center. Compared with the pre-MELD era, our post-MELD recipients were older, had greater median MELD scores (28 vs 19), greater need for pretransplant hemodialysis (34% vs 12%), and higher rates and duration of pretransplant hospitalization. More than one-third of our adult recipients in the post-MELD era received pretransplant renal replacement therapy compared with 21% in other regional centers and 11% nationally.[30,31] The magnitude of the MELD system's effect on recipient illness has increased significantly over its first decade of use. In 2011, the median MELD score for adult recipients at our center was 38, compared with 22 nationally, and was 35 or greater in 64%, compared with only 18.4% nationally.[30] Despite the increasing acuity of recipients and deterioration of donor quality, post-MELD recipients achieved better overall graft and patient survival, with significant reductions in 30-day mortality and the need for early retransplantation.

In our study, the improved survival in the post-MELD era was most profound in recipients with cancer and high acuity. Widespread adoption of the Milan criteria[19] in 1996 has led to better selection of cancer recipients and dramatic improvements in long-term survival, with post-Milan cancer recipients achieving an excellent 60% survival at 10 years compared with a dismal 30%

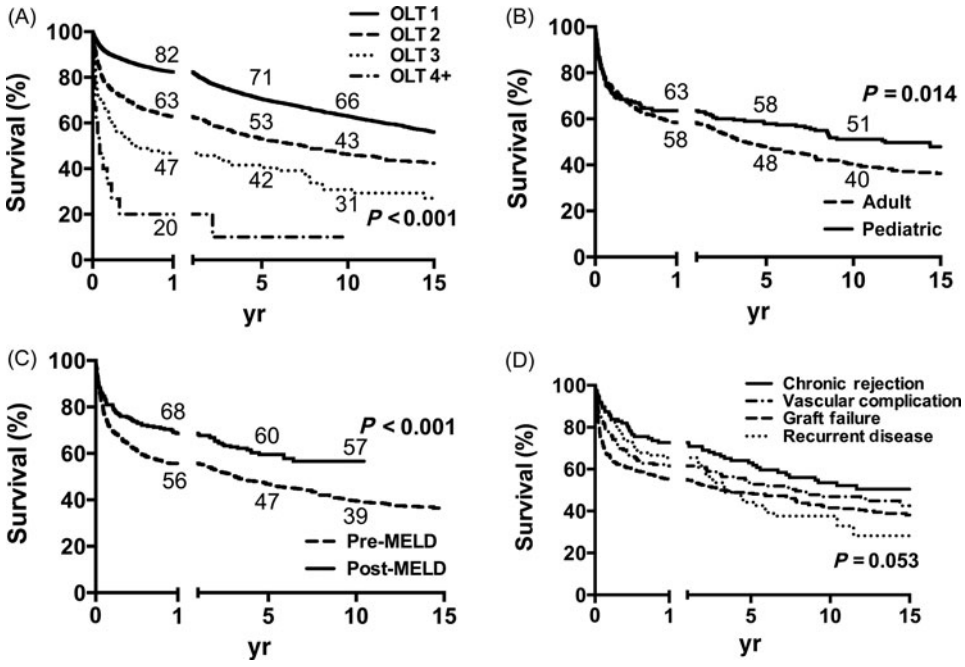

FIGURE 7. Kaplan-Meier patient survival estimates after retransplantation based on (A) number of transplants, (B) recipient age, (C) era of transplantation, and (D) indication for retransplantation.

TABLE 6. Comparison of Indications for Retransplantation in Adult and Pediatric Recipients and Pre- and Post-MELD Eras

Indication	Total (n = 772) N	Total (n = 772) %	Adult (n = 566) N (%)	Pediatric (n = 206) N (%)	Pre-MELD (n = 529) N (%)	Post-MELD (n = 243) N (%)
Graft failure	312	40.4	252 (45)	60 (29)	229 (43)	83 (34)
Vascular complications	163	21.1	96 (17)	67 (33)	116 (22)	47 (19)
Chronic rejection	112	14.5	68 (12)	44 (21)	78 (15)	34 (14)
Recurrent disease*	91	11.8	85 (15)	6 (3)	40 (8)	51 (21)
Acute rejection	39	5.1	29 (5)	10 (5)	34 (6)	5 (2)
Biliary complications	32	4.1	22 (4)	10 (5)	18 (3)	14 (6)
De novo disease†	23	3	14 (3)	9 (4)	14 (3)	9 (4)

*Hepatitis C virus accounts for 59 of 91 (65%).
†Hepatitis C virus accounts for 13 of 23 (57%).

in the pre-Milan era ($P < 0.001$). Although pre- and post-MELD survival was similar in less acute recipients (MELD ≤22), recipients with greater MELD scores had dramatically improved outcomes in the post-MELD era, as did technically challenging retransplant recipients. Although the reasons for improvements in posttransplant outcome are undoubtedly multifactorial, cumulative team experience in both the operative techniques and perioperative management of complex patients has certainly played a role. Examples include optimization of immunosuppressive regimens leading to less acute and chronic rejection, improved donor-to-recipient matching leading to significantly fewer early graft failures and retransplantations, and increased surgical efficiency resulting in shorter CIT and WIT.

Current long-term recipient and graft outcomes, as reported in our study, strongly support the lifesaving durability of liver transplantation. Analysis of survival outcomes in the post-MELD era, although improved in comparison with pre-MELD patients, identified many of the same factors that have been shown to impair long-term survival. These include recipient factors (age, etiology of liver disease, retransplantation), donor factors (age), and operative factors (ischemia times). Although the MELD score is more accurate in predicting wait-list mortality than posttransplant survival, it has been shown to be a risk factor for death after liver transplantation.[32,33] In our present study, a MELD score of 34 or greater was an independent predictor of long-term survival, posing a 39% increase in the risk of death.

One criticism of our pre- and post-MELD comparisons may be that grouping all of the pre-MELD era patients together biases the outcome results, as we have previously reported worse survival outcomes for recipients in the earlier pre-MELD era, 1984 to 1991, compared with the later pre-MELD era from 1992 to 2001.[23] This is a valid concern as transplantation has seen significant advances in immunosuppression, patient management, and cumulative center experience that would certainly influence outcomes. For this reason, our multivariate regression for patient survival divided the pre-MELD era into earlier and later periods and found that era of transplantation was an independent risk factor for mortality, with increased mortality risk of 71% in pre-MELD era 1 and 23% in pre-MELD era 2 compared with the post-MELD era (Fig. 8).

TABLE 7. Univariate Summary of Adult Recipient Variables on Mortality After Liver Transplantation

Variable	Level	Death Rate (100 Person-Mo)	Mortality Risk Ratio	Survival at 60 Mo (%)	*P*
Era	Pre-MELD 1 (1984–1991)	0.783	1.31	63.1	<0.0001
	Pre-MELD 2 (1992–2001)	0.560	0.94	69.1	
	Post-MELD (2002–2012)	0.597	1.00*	70.2	
Recipient age (yr)	18–55	0.517	1.00*	72.2	<0.0001
	>55	0.774	1.50	63.1	
Sex	Male	0.595	1.00*	69.1	0.3052
	Female	0.619	1.04	68.1	
MELD score	6–13	0.449	1.00*	75.2	<0.0001
	14–21	0.524	1.17	72.2	
	22–33	0.614	1.37	67.8	
	≥34	0.821	1.83	62.7	
Etiology of liver disease	PSC	0.425	1.00*	77.8	<0.0001
	Metabolic	0.347	0.82	77.8	
	PBC	0.523	1.23	74.8	
	ALD	0.522	1.23	75.7	
	Fulminant	0.528	1.24	71.8	
	HBV	0.511	1.20	71.3	
	NASH	0.645	1.52	71.9	
	AIH	0.595	1.40	69.6	
	HCV	0.661	1.56	66.3	
	Cryptogenic	0.659	1.55	65.3	
	Malignancy	0.750	1.77	62.2	
Prior transplant	No	0.549	1.00*	71.4	<0.0001
	Yes	1.102	2.01	50.7	
Hospitalization	No	0.483	1.00*	74.5	<0.0001
	Yes	0.770	1.59	62.5	
Liver/kidney	No	0.605	1.00*	68.6	0.7800
	Yes	0.603	1.00	70.9	

*Reference group for mortality risk ratio.

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

The post-MELD era has also seen significant maturation in the technical conduct of the operation, resulting in a very low incidence of hepatic artery and portal venous thrombosis despite increased recipient acuity. In 2002, we implemented early atraumatic common hepatic artery occlusion at the outset of the porta hepatic dissection, resulting in a significant decrease in the incidence of hepatic artery subintimal dissection and need for aortohepatic grafting and a decreased incidence of posttransplant HAT.[34] In this current series, our overall incidence of early HAT in adults and children was 2.5% and 5.0%, respectively, compared with 2.9% and 8.3% in a systematic review of 21,822 liver transplants performed in adults and children from 1990 to 2007.[35] Similarly, maturation of surgical experience with portal thromboendovenectomy in adults with preexisting PVT[36] who are at highest risk for posttransplant PVT has nearly eliminated the occurrence of early posttransplant PVT in adult recipients (27 of 4251, 0.6%). Our overall incidence of posttransplant PVT in children was higher at 6.3% (3.2% early, 3.1% late), well below the reported rates of 8% to 12% in the literature.[37,38]

Post-MELD era improvements in graft and patient survival did not come without a price. In our institution, 1 day in the intensive care unit and ward costs $10,000 and $4000, respectively. With the post-MELD era recipients requiring an average of 5 days longer posttransplant hospitalization, this amounts to approximately a $20,000 to $50,000 increased cost directly attributable to the longer hospitalization. Our findings are consistent with several large reports demonstrating increased lengths of hospitalization and excessive costs directly attributable to increasing recipient MELD scores.[12,39]

Post-MELD compared with pre-MELD era recipients also had greater overall biliary complication rates (21.2% vs 12.2%), similar to other large series reporting increasing biliary complication rates of 20.4% to 22.5% in the post-MELD era.[40,41] Increasing donor and recipient age and MELD score,[42] use of DCD grafts,[43] and the use of T-tubes[44] have all been associated with increased rates of biliary complications. Although these factors have certainly contributed to higher biliary complications in our post-MELD patients, they are not the only cause. We speculate that our overall reduction in the use of T-tubes in the post-MELD era has had 2 effects: an increase in late biliary strictures in patients without T-tubes and an increase in late bile leaks in recipients with T-tubes, as expertise with T-tube removal has diminished. In this era of increasing recipient acuity and extended criteria donor grafts, we use T-tubes liberally to monitor early graft function. Our strategy is supported by a recent prospective randomized trial showing less severe biliary complications when a T-tube is used.[40]

Results of liver retransplantation are inferior to results after primary transplantation.[23,45] We recently reported a clinical index that accurately predicts the 5-year survival after retransplantation and can be used as a practical guide to avoid futile retransplantation.[46] Similar to our prior report, we show that survival after retransplantation diminishes with each subsequent transplant, with recipients of a third transplant failing to achieve the 50% 5-year survival that represents a threshold to justify use of scarce donor resources. Although GNF remains the most common indication for retransplantation, GNF and early retransplantation were less common in post-MELD era recipients. We attribute these improved results to our center experience with the perioperative management of complex retransplant patients and to improved donor-recipient matching.

TABLE 8. Univariate Summary of Adult Donor and Operative Variables on Mortality After Liver Transplantation

Variable	Level	Death Rate (100 Person-M)	Mortality Risk Ratio	Survival at 60 Mo (%)	*P*
Donor					
Age (yr)	≤32	0.515	1.00*	71.8	0.0003
	33–48	0.589	1.14	69.2	
	49–55	0.665	1.29	67.7	
	56–60	0.722	1.40	62.2	
	>60	0.771	1.50	62.7	
Graft type	Cadaveric whole	0.602	1.00*	68.4	0.1340
	In situ split	0.655	1.09	66.6	
	Living donor	0.313	0.52	80.1	
	DCD	0.519	0.86	75.6	
Cardiac arrest	No	0.609	1.00*	69.1	0.4168
	Yes	0.607	1.00	68.1	
Sex	Male	0.575	1.00*	69.4	0.6969
	Female	0.595	1.03	69.1	
Hospital stay (d)	0–2	0.555	1.00*	69.6	0.9483
	3–4	0.605	1.09	68.8	
	5–6	0.619	1.12	68.3	
	6+	0.629	1.13	69.8	
Serum sodium	≤142	0.573	1.00*	70.2	0.9724
	143–148	0.597	1.04	68.8	
	149–155	0.589	1.03	67.9	
	156–160	0.600	1.05	70.5	
	≥160	0.541	0.94	70.9	
No. of vasopressors	0	0.609	1.00*	68.3	0.4515
	1	0.560	0.92	69.8	
	2	0.580	0.95	69.4	
	3+	0.689	1.13	69.4	
Operative					
WIT (min)	<37	0.537	1.00*	71.1	0.0001
	37–42	0.515	0.96	73.2	
	42–49	0.558	1.04	69.9	
	>49	0.705	1.31	65.9	
CIT (hr)	<5	0.545	1.00*	71.0	0.0023
	5–6.7	0.503	0.92	75.7	
	6.7–8.9	0.558	1.02	70.4	
	>8.9	0.672	1.23	64.2	

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

Retransplant recipients with chronic rejection achieved a remarkable 53% 10-year survival, a tribute to the optimization of immunosuppression protocols that have led to significant reductions in episodes of acute rejection. Unfortunately, recipients retransplanted for recurrent disease, usually recurrent HCV, had a discouraging 44% 5-year survival. Recurrent HCV remains one of the major challenges limiting liver transplantation, and the transplant community anxiously awaits data regarding effects of the newly approved protease inhibitors on disease recurrence after OLT.[47,48]

The increasing acuity of recipients and a deteriorating donor pool pose significant challenges to the future of liver transplantation. More work is needed on tolerance induction to mitigate the long-term side effects of immunosuppressive medications that add morbidity and expense. Recurrent disease continues to be a significant problem, especially in HCV. Finally, the growing epidemic of obesity and diabetes will elevate NASH to the leading indication for OLT in the next few years[24] and has significantly affected the quality of an already limited donor pool. Preliminary studies in donor organ resuscitation and minimization of ischemia-reperfusion injury may lead to meaningful expansion of the donor pool.[49–51]

CONCLUSIONS

In summary, the durability of liver transplantation for the treatment of irreversible liver disease has benefited greatly from improvements in patient selection, perioperative management, immunosuppression, and technical advancements. Improved long-term survival outcomes despite significant challenges of increasing recipient acuity and a deteriorating donor pool have justified the "sickest first" allocation policy in the post-MELD era. However, despite the advantage of the MELD score to identify patients most in need of liver transplantation, safeguards must be developed to avoid futile transplants in high MELD recipients. Finally, strategies to induce tolerance, expand and resuscitate the donor pool, and mitigate the long-term side effects of immunosuppression will lead to further reductions in wait-list mortality and improvements in posttransplantation outcomes.

ACKNOWLEDGMENTS

The authors express their deepest gratitude to all of the past and present transplant faculty and fellows, transplant coordinators, nursing staff, and administrative personnel, without whom this work would not have been possible.

TABLE 9. Multivariate Estimate of Relative Mortality Risk in Adult Recipients

Variable	Level	Adjusted Relative Risk	95% Confidence Intervals	*P*
Era	Post-MELD (2002–2012)	1.00*		
	Pre-MELD 2 (1992–2001)	1.24	1.09–1.42	0.001
	Pre-MELD 1 (1984–2001)	1.79	1.51–2.12	<0.001
Recipient age (yr)	18–55	1.00*		
	>55	1.48	1.33–1.65	<0.001
Etiology of liver disease	PSC	1.00*		
	HCV	1.52	1.18–1.94	0.001
	Malignancy	1.82	1.40–2.36	<0.001
MELD score	≤33	1.00*		
	34+	1.39	1.21–1.58	<0.001
Prior transplant	No	1.00*		
	Yes	2.18	1.89–2.51	<0.001
Hospitalization	No	1.00*		
	Yes	1.32	1.17–1.49	<0.001
Donor age (yr)	≤32	1.0*		
	33–55	1.23	1.10–1.37	<0.001
	>55	1.47	1.27–1.69	<0.001
WIT (min)	≤49	1.0*		
	>49	1.27	1.13–1.43	<0.001
CIT (hr)	≤8.9	1.0*		
	>8.9	1.34	1.20–1.50	<0.001

*Reference group for adjusted relative risk.
CIT indicates cold ischemia time; PSC, primary sclerosing cholangitis; WIT, warm ischemia time.

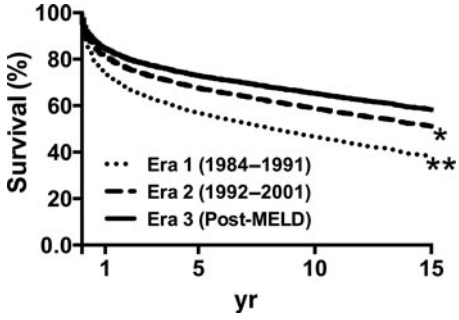

FIGURE 8. Adjusted patient survival by era of transplantation controlling for all independent predictors of survival from Cox multivariate model. $^{*}P = 0.001$ compared with post-MELD era. $^{**}P < 0.001$ compared with post-MELD era.

REFERENCES

1. Starzl TE, Marchioro TL, Vonkaulla KN, et al. Homotransplantation of the Liver in Humans. *Surg Gynecol Obstet*. 1963;117:659–676.
2. Fonkalsrud EW, Joseph WL, Tocornal JA, et al. Allogeneic hepatic transplantation using cadaveric donors with clinical application. *J Pediatr Surg*. 1968;3:300–308.
3. Calne RY, Williams R. Liver transplantation in man. I. Observations on technique and organization in five cases. *Br Med J*. 1968;4:535–540.
4. Houssin D, Franco D, Berthelot P, et al. Heterotopic liver transplantation in end-stage HBsAg-positive cirrhosis. *Lancet*. 1980;1:990–993.
5. Pichlmayr R, Brolsch C, Wonigeit K, et al. Experiences with liver transplantation in Hannover. *Hepatology*. 1984;4(suppl):56S–60S.
6. Pichlmayr R, Brolsch C, Neuhaus P, et al. Report on 68 human orthotopic liver transplantations with special reference to rejection phenomena. *Transplant Proc*. 1983;15:1279–1283.
7. Krom RA, Gips CH, Houthoff HJ, et al. Orthotopic liver transplantation in Groningen The Netherlands (1979–1983). *Hepatology*. 1984;4(suppl):61S–65S.
8. Starzl TE, Klintmalm GB, Porter KA, et al. Liver transplantation with use of cyclosporin a and prednisone. *N Engl J Med*. 1981;305:266–269.
9. Memsic L, Quinones-Baldrich W, Kaufman R, et al. A comparison of porcine orthotopic liver transplantation using a venous-venous bypass with and without a nonpulsatile perfusion pump. *J Surg Res*. 1986;41:33–40.
10. Busuttil RW, Colonna JO, II, Hiatt JR, et al. The first 100 liver transplants at UCLA. *Ann Surg*. 1987;206:387–402.
11. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003;124:91–96.
12. Axelrod DA, Koffron AJ, Baker T, et al. The economic impact of MELD on liver transplant centers. *Am J Transplant*. 2005;5:2297–2301.
13. Dutkowski P, Oberkofler CE, Bechir M, et al. The model for end-stage liver disease allocation system for liver transplantation saves lives, but increases morbidity and cost: a prospective outcome analysis. *Liver Transpl*. 2011;17:674–684.
14. Petrowsky H, Rana A, Kaldas FM, et al. Liver transplantation in highest-acuity recipients: identifying factors to predict success. *Ann Surg*. 2013. Accepted for publication.
15. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. *Liver Transpl*. 2001;7:567–580.
16. Yersiz H, Renz JF, Farmer DG, et al. One hundred in situ split-liver transplantations: a single-center experience. *Ann Surg*. 2003;238:496–505; discussion 506–507.
17. Farmer DG, Yersiz H, Ghobrial RM, et al. Early graft function after pediatric liver transplantation: comparison between in situ split liver grafts and living-related liver grafts. *Transplantation*. 2001;72:1795–1802.
18. Paugam-Burtz C, Kavafyan J, Merckx P, et al. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. *Liver Transpl*. 2009;15:522–529.
19. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693–699.
20. Winston DJ, Pakrasi A, Busuttil RW. Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1999;131:729–737.
21. Seu P, Winston DJ, Holt CD, et al. Long-term ganciclovir prophylaxis for successful prevention of primary cytomegalovirus (CMV) disease in CMV-seronegative liver transplant recipients with CMV-seropositive donors. *Transplantation*. 1997;64:1614–1617.
22. Winston DJ, Wirin D, Shaked A, et al. Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver-transplant recipients. *Lancet*. 1995;346:69–74.

23. Busuttil RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3200 liver transplantations over two decades: a single-center experience. *Ann Surg*. 2005;241:905–916; discussion 916–918.
24. Agopian VG, Kaldas FM, Hong JC, et al. Liver transplantation for nonalcoholic steatohepatitis: the new epidemic. *Ann Surg*. 2012;256:624–633.
25. Cameron AM, Ghobrial RM, Yersiz H, et al. Optimal utilization of donor grafts with extended criteria: a single-center experience in over 1000 liver transplants. *Ann Surg*. 2006;243:748–753; discussion 753–755.
26. Jain A, Reyes J, Kashyap R, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. *Ann Surg*. 2000;232: 490–500.
27. Freeman RB, Wiesner RH, Edwards E, et al. Results of the first year of the new liver allocation plan. *Liver Transpl.* 2004;10:7–15.
28. Kanwal F, Dulai GS, Spiegel BM, et al. A comparison of liver transplantation outcomes in the pre- vs. post-MELD eras. *Aliment Pharmacol Ther*. 2005;21:169–177.
29. Yoo HY, Thuluvath PJ. Short-term postliver transplant survival after the introduction of MELD scores for organ allocation in the United States. *Liver Int.* 2005;25:536–541.
30. Kim WR, Stock PG, Smith JM, et al. OPTN/SRTR 2011 Annual Data Report: liver. *Am J Transplant*. 2013;13(suppl 1):73–102.
31. Thuluvath PJ, Guidinger MK, Fung JJ, et al. Liver transplantation in the United States, 1999–2008. *Am J Transplant*. 2010;10(4 pt 2):1003–1019.
32. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg*. 2011;254:745–753; discussion 753.
33. Rana A, Hardy MA, Halazun KJ, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant*. 2008;8:2537–2546.
34. Duffy JP, Hong JC, Farmer DG, et al. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg*. 2009;208:896–903; discussion 903–905.
35. Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant*. 2009;9:746–757.
36. Seu P, Shackleton CR, Shaked A, et al. Improved results of liver transplantation in patients with portal vein thrombosis. *Arch Surg*. 1996;131:840–844; discussion 844–845.
37. Buell JF, Funaki B, Cronin DC, et al. Long-term venous complications after full-size and segmental pediatric liver transplantation. *Ann Surg*. 2002;236:658–666.
38. Jensen MK, Campbell KM, Alonso MH, et al. Management and long-term consequences of portal vein thrombosis after liver transplantation in children. *Liver Transpl*. 2013;19:315–321.
39. Buchanan P, Dzebisashvili N, Lentine KL, et al. Liver transplantation cost in the model for end-stage liver disease era: looking beyond the transplant admission. *Liver Transpl*. 2009;15:1270–1277.
40. Lopez-Andujar R, Oron EM, Carregnato AF, et al. T-tube or no T-tube in cadaveric orthotopic liver transplantation: the eternal dilemma: results of a prospective and randomized clinical trial. *Ann Surg*. 2013;258(1):21–29.
41. Sundaram V, Jones DT, Shah NH, et al. Posttransplant biliary complications in the pre- and post-model for end-stage liver disease era. *Liver Transpl*. 2011;17:428–435.
42. Welling TH, Heidt DG, Englesbe MJ, et al. Biliary complications following liver transplantation in the model for end-stage liver disease era: effect of donor, recipient, and technical factors. *Liver Transpl*. 2008;14:73–80.
43. Hong JC, Yersiz H, Kositamongkol P, et al. Liver transplantation using organ donation after cardiac death: a clinical predictive index for graft failure-free survival. *Arch Surg*. 2011;146:1017–1023.
44. Scatton O, Meunier B, Cherqui D, et al. Randomized trial of choledochocholedochostomy with or without a T tube in orthotopic liver transplantation. *Ann Surg*. 2001;233:432–437.
45. Doyle HR, Morelli F, McMichael J, et al. Hepatic retransplantation—an analysis of risk factors associated with outcome. *Transplantation*. 1996;61:1499–1505.
46. Hong JC, Kaldas FM, Kositamongkol P, et al. Predictive index for long-term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. *Ann Surg*. 2011;254:444–448; discussion 448–449.
47. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364:1195–1206.
48. Wertheim JA, Petrowsky H, Saab S, et al. Major challenges limiting liver transplantation in the United States. *Am J Transplant*. 2011;11:1773–1784.
49. Busuttil RW, Lipshutz GS, Kupiec-Weglinski JW, et al. rPSGL-Ig for improvement of early liver allograft function: a double-blind, placebo-controlled, single-center phase II study. *Am J Transplant*. 2011;11:786–797.
50. Henry SD, Nachber E, Tulipan J, et al. Hypothermic machine preservation reduces molecular markers of ischemia/reperfusion injury in human liver transplantation. *Am J Transplant*. 2012;12:2477–2486.
51. Hong JC, Koroleff D, Xia V, et al. Regulated hepatic reperfusion mitigates ischemia-reperfusion injury and improves survival after prolonged liver warm ischemia: a pilot study on a novel concept of organ resuscitation in a large animal model. *J Am Coll Surg*. 2012;214:505–515; discussion 515–516.

DISCUSSANTS

A. Humar (Pittsburgh, PA):

The UCLA program has been integrally involved in the development and advancement of liver transplant for more than 30 years, taking it from an experimental procedure to what is now considered standard of care.

This program represents the gold standard of what a modern top caliber program is capable of achieving, namely, the ability to offer adult and pediatric patients all options for transplant: live donor, split, domino, and donation after death. The UCLA data show how problems such as rejection, infection, and technical complications can be minimized, leaving the organ shortage as the greatest barrier to transplantation.

I have 2 questions.

First, patients with high scores on the model for end-stage liver disease (MELD) do not do as well when looking purely at patient and graft survival outcome. However, these patients derive the greatest benefit from this procedure. Would quality of life years gained be a better measure of outcome to use in convincing others of the benefits of transplant in these acutely ill patients? Second, the Asian centers have adopted live donor transplantation with great fervor, although in the United States, this option seems to be in decline. Is there a future for live donor liver transplant in the United States today? And if so, under what circumstances?

Response From R.W. Busuttil:

Although there is no question that patients with high MELD scores and acute illness do not do as well as patients with lower scores and less severe illness, they derive the greatest benefit as long as we avoid futile transplants. Regarding quality of life, we have found that patients with liver transplants are close to the general population in physical health and superior in mental outlook. However, we have not specifically looked at patients with MELD scores of 35 or greater. If we can get those patients through the first month or 2 after transplant, their long-term outcome is just as good as patients with lower MELD scores.

Regarding live donation, there is no doubt that although live donation was slowly increasing in the United States until the early 2000s, it has since declined, with a very slight resurgence over the last few years. The problem is that I am not convinced that live donation is the best treatment of patients with high MELD scores. There is no question that if you know how to do the operation, and can do it safely, you will have good outcomes. Furthermore, outcomes in recipients with low MELD scores are good. However, I doubt that anyone attempting to popularize live liver donation is going to take a partial live donor graft and place it in someone with a MELD score of 35, because these patients are usually on dialysis, intubated, and on vasopressors going into the operating room.

DISCUSSANTS

G.B. Klintmalm (Dallas, TX):

Busuttil has shown us the development of liver transplantation in the United States during the past 29 years. By doing so, he has driven development in the technical refinement of the procedure, pre- and postoperative care, and the surgical specialty of immunosuppression. His presentation focuses on the field before and after the adoption of the MELD system for organ allocation in 2002. It is gratifying that despite seeing the sickest patients, the results show that these patients derive the greatest benefit, as evidenced by improved short- and long-term survival. Of note, the 4% improvement in 1-year survival that has been achieved since the introduction of the MELD system is based on documentation of 10 years of follow-up. Thus, it is the surgery and perioperative care that have improved, not long-term immunosuppression.

I have 4 questions.

First, it is clear that you have intentionally decided to pursue older donors, donors with longer length of stay before donation, and a significant number of DCDs. Can you expand on how these factors have been counted in the execution of the transplants to achieve the outcomes you have shown us?

Second, vascular complications have decreased. How was this achieved? However, the biliary complications increased. Is this related to the DCD donors or some other factor?

Third, primary donor nonfunction is down by a third, to 6.8% which is an important achievement. How was this accomplished, especially in light of those marginal donors?

Finally, the length of stay has increased by almost 20%, from 29 to 34 days. In an era in which cost containment is paramount, how has this affected the bottom line? And how would you be able to continue in a grim financial future?

Response From R.W. Busuttil:

How have we dealt with older donors with longer lengths of stay and DCDs? First, we try to match donors to recipients if we have several patients for whom the organ is offered. Obviously, patients with higher MELD scores do best with nonextended criteria donors. However, because donor organs are often allocated to a specific recipient, in many cases it is difficult to achieve optimal donor/recipient matching. It is absolutely critical to keep the cold ischemia time and warm ischemia time to an absolute minimum, particularly when you have an extended-criteria donor.

Second, if there is any question about the steatotic content of the graft, you must biopsy the liver and not rely on an estimation of its fat content. In these very sick patients, you absolutely cannot use an organ that has greater than 30% macrosteatosis.

Third, in regard to the DCD donors, you must be even more selective and certain that the warm ischemia time is no longer than 20 minutes. The literature indicates 30 minutes, but I think 30 minutes is too long.

Regarding the vascular and increased biliary complications, we have made a slight modification in the handling of the recipient's hepatic artery; we do not ligate it. We place a vascular bulldog clamp on the common hepatic artery before we do any ligation, and that prevents intimal dissection. This procedure alone has decreased our incidence of conduits from 9% down to 2%. I think that it is also reflective of our lower incidence of hepatic artery thrombosis.

Biliary complications have increased because we are using more marginal donors and DCDs, and we have reduced our use of T-tubes. Recently, a randomized prospective trial compared use of T-tubes versus not using T-tubes. The study reported more biliary complications when T-tubes are not used. As a result, we are now using T-tubes more often, particularly in the sicker patients.

You wanted to know why the primary nonfunction rate has been decreased. As I mentioned, we try to keep cold ischemia time and warm ischemia time down to an absolute minimum.

The fourth question is more difficult. What do we do when length of hospital stay has increased by 20%? What do our hospital administrators tell us about that? First, they tell us that there is a fixed price for a liver transplant. The longer the patients stay in the hospital, the lower the margin, so we do everything we can to discharge those patients quickly. However, we will never sacrifice patient care to achieve an earlier discharge. If we do that, we are not going to be able to take on those patients who derive the most benefit from liver transplantation.

DISCUSSANTS

R. Pollack (Skokie, IL):

Would you comment on the recurrence rate of hepatic carcinoma after transplantation and the concurrent treatment using sorafenib and other similar drugs to perhaps cure this disorder?

Response From R.W. Busuttil:

As my data show, we have seen better results since we began using the Milan criteria. We are actually better when we use the University of California, San Francisco criteria than we were before that period. I did not discuss this, but we are spearheading a randomized prospective multicenter trial studying the use of sorafenib as adjuvant therapy in patients who have higher incidence of recurrence. That is determined by poor differentiation, lymphovascular invasion, and other factors seen on the explant. Therefore, I cannot say what effect sorafenib will have. As you know, the drug has a certain amount of toxicity. In the next year or 2, we may be able to present the results of that trial.

DISCUSSANTS

D. Cherqui (New York, NY):

In your multivariate analysis, you showed that MELD scores of more than 34 were associated with significantly more mortality. What is your upper limit for the sickest patients?

How do you deal with underserved patients, those with encephalopathy, ascites, and so forth? You said earlier that you thought that live donation was not a good solution for patients with high MELD scores. What about patients with low MELD scores, split donations for 2 adults, living donors, and extended-criteria donors?

Response From R.W. Busuttil:

I think for patients with lower MELD scores, we would use all of the following options: living donor grafts, split grafts, extended-criteria organs, domino transplants, and so forth.

Although a MELD score of more than 34 is a multivariate predictor of mortality, we still offer these patients transplants because if we look at our data in the post-MELD era, survival is better. Thus, we do not turn those patients down who have the potential to derive the greatest benefit.